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**).

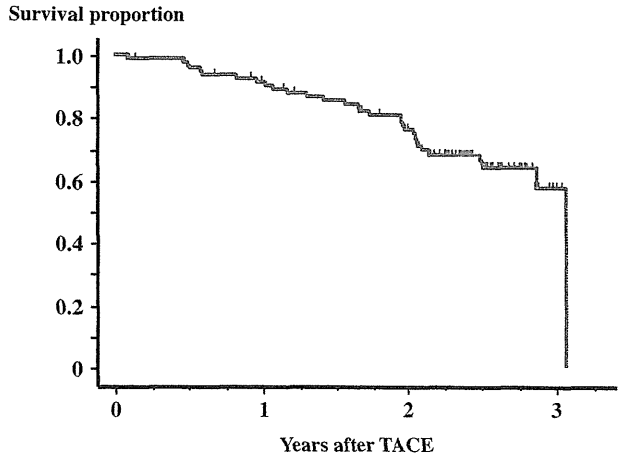

Figure 1. Overall survival and progression-free survival curves for 99 patients who underwent transcatheter arterial chemoembolization (TACE) for unresectable HCC. The tick marks indicate censored cases. (Available in color online at *www.jvir.org.*)

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.

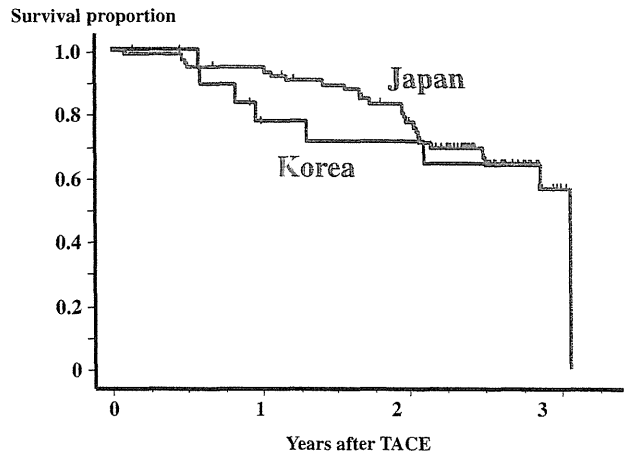

Figure 2. Comparison of overall survival curves between Japan (red line) and Korea (blue line). The tick marks indicate censored cases. TACE = transcatheter arterial chemoembolization. (Available in color online at *www.jvir.org.*)

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

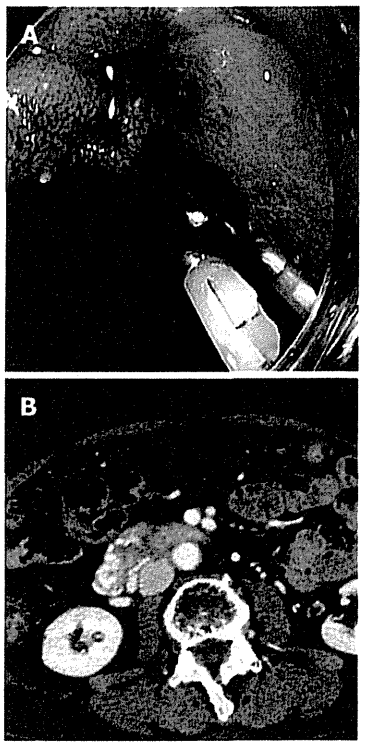

Figure 1 Endoscopy and computed tomography of the duodenum. A: Endoscopy demonstrates bleeding varices in the second portion of the duodenum; B: Contrast-enhanced computed tomography reveals markedly tortuous varices around the wall in the second and third portion of the duodenum.

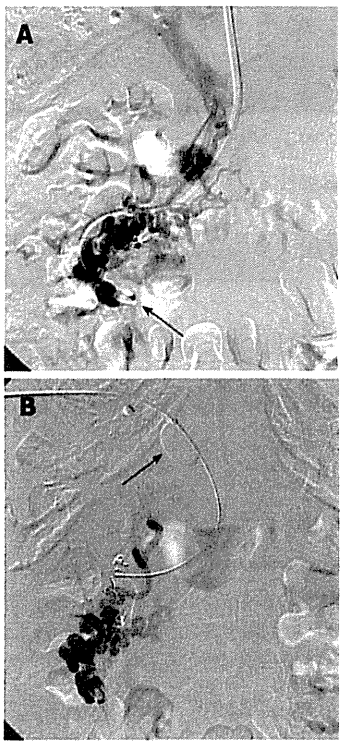

Figure 2 Balloon-occluded retrograde venography. A: Balloon-occluded retrograde venography (BRTV) shows the dilated efferent vein and the duodenal varices, but the contrast material quickly disappears through several afferent veins. Note that the balloon was inflated in the right ovarian vein (arrow); 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/μL; 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.

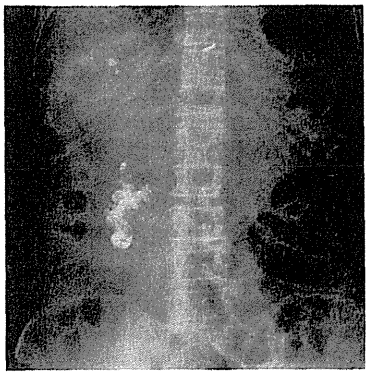

Figure 3 Radiograph after embolization of the duodenal varices demonstrates complete and adequate accumulation of the ethiodized oil in the varices.

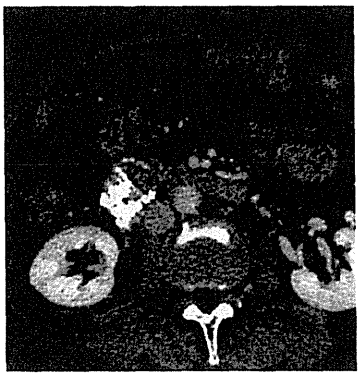

Figure 4 Contrast-enhanced computed tomography after embolization of the duodenal varices shows the complete accumulation of ethiodized oil in the varices.

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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ORIGINAL ARTICLE

Tumor response evaluation criteria for HCC (hepatocellular carcinoma) treated using TACE (transcatheter arterial chemoembolization): RECIST (response evaluation criteria in solid tumors) version 1.1 and mRECIST (modified RECIST): JIVROSG-0602

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Abstract

Background. Two standard sets of criteria are used to evaluate the tumor response of hepatocellular carcinoma (HCC): RECIST (Response Evaluation Criteria in Solid Tumors) and modified RECIST (mRECIST). The purpose was to compare two tumor response evaluation criteria, RECIST version 1.1 and mRECIST, for HCC treated using transcatheter arterial chemoembolization (TACE).

Methods. The radiological findings of patients who underwent TACE for HCCs in a multicenter clinical trial were examined. Sixty-five lesions in 21 patients treated with TACE without mixing iodized-oil were evaluated. The tumor size was evaluated by measuring the entire lesion, including the necrotic part, using RECIST version 1.1, whereas only the contrast-enhanced part observed during the arterial phase was measured using mRECIST. Five radiologists independently measured each lesion twice. To evaluate the inter-criteria reproducibility, the complete response (CR) rate, the response rate, the kappa statistics, and the proportion of agreement (PA) for response categories were calculated. The same analyses were conducted for inter- and intra-observer reproducibility.

Results. In the inter-criteria reproducibility study, the CR rate and the response rate obtained using mRECIST (56.9% and 79.7%) were higher than those obtained using RECIST version 1.1 (9.2% and 43.1%). In the inter- and intra-observer reproducibility study, mRECIST exhibited an 'almost perfect agreement', while RECIST version 1.1 exhibited a 'substantial agreement'.

Conclusions. Considerable differences in the CR rate and the response rate were observed. From the viewpoint of the high inter- and intra-observer reproducibility, mRECIST may be more suitable for tumor response criteria in clinical trials of TACE for HCC.

Key words: *Hepatocellular carcinoma, modified RECIST, RECIST version 1.1, reproducibility, tumor response*

Introduction

Two standard sets of criteria are used to evaluate the tumor response of hepatocellular carcinoma (HCC) treated using loco-regional therapy, such as transcatheter arterial embolization (TACE): RECIST (Response Evaluation Criteria in Solid Tumors) criteria (1) and modified RECIST (mRECIST) criteria (2).

RECIST criteria were published by the National Cancer Institute in 2000 with the objective of unifying

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the criteria used for response assessments. These criteria evaluate the unidimensional measurement of the longest diameter of the tumor lesions and have been used in most oncology trials. However, a number of questions and issues have arisen, leading to the development of revised RECIST (version 1.1) criteria (3). In the RECIST version 1.1 criteria, the major changes included the number of lesions to be assessed, the assessment of pathological lymph nodes, confirmation of a response, disease progression, and the necrotic tumor size (i.e. in cases where a lesion which was solid at baseline has become necrotic in the center, the longest diameter of the entire lesion should be followed).

In 2000, a panel of experts on HCC from the European Association for the Study of the Liver (EASL) agreed that estimating the reduction in viable tumor volume (as recognized using enhanced spiral computed tomography (CT)) should be considered the optimal method for assessing the local response to treatment in patients with HCC (4). Since then, most authors reporting the results of loco-regional therapy for HCC have evaluated tumor response according to this recommendation (5,6).

The aforementioned expert panel continued the concept of viable tumor endorsed by EASL and adapted the unidimensional measurement as a substitute for the bidimensional one in the determination of tumor response for target lesions in HCC (7). These amendments confirmed the American Association for the Study of Liver Disease (AASLD)–Journal of the National Cancer Institute (JNCI) guidelines and were defined as 'modified RECIST (mRECIST)' criteria (2). Therefore, mRECIST criteria were developed for loco-regional therapies to HCC. On the other hand, RECIST version 1.1 criteria were developed for systemic therapies; however, RECIST version 1.1 criteria are used in many oncology trials including loco-regional therapies for the treatment of HCC.

A study investigating the inter-criteria reproducibility between the older versions of criteria (RECIST version 1.0 and EASL) has been reported (8). Furthermore, a comparative study of tumor response by the updated criteria (RECIST version 1.1 and mRECIST) has been published (9). However, to the best of our knowledge, the inter- and intra-observer reproducibility between RECIST version 1.1 and mRECIST has not been investigated or reported.

Using these standardized criteria for evaluating tumor response in clinical trials, reproducible results should be obtained by all investigators. For a surrogate marker such as tumor response for therapy, both 'precision' (observer consistency study) and 'accuracy' (validation study comparing to gold standard) are evaluated. From the viewpoint of 'precision', we compared RECIST version 1.1 and mRECIST criteria by evaluating the inter- and intra-observer reproducibility.

The purpose of the present study was to clarify the differences in tumor response as evaluated using two updated sets of criteria (RECIST version 1.1 and mRECIST) by assessing the inter-criteria reproducibility. Moreover, another purpose of the present study was to investigate which set of criteria was superior for use as tumor response evaluation criteria in clinical trials of TACE for HCC by assessing the inter- and intra-observer reproducibility.

Materials and methods

We analyzed the radiological findings of patients who underwent pan-hepatic TACE for multiple HCCs in a multicenter clinical trial. In this trial, the eligibility criteria included patients with untreated, bilobar multiple HCCs, compensated Child–Pugh A or B cirrhosis, and the absence of vascular invasion or extrahepatic spread. TACE was performed using cisplatin (IA call, Nihon-Kayaku; 35–65 mg/m^2) and gelatin particles without mixing iodized-oil. The present study was conducted in accordance with the Helsinki Declaration, and the protocols were approved by the institutional review board. Informed written consent for the treatment protocols, including the secondary use of treatment-associated documents, was obtained from each patient. Twenty-one patients were entered from 19 July 2005 to 15 May 2007.

Image analysis

All patients underwent a dynamic study performed using a multi-slice CT scanner with non-ionic contrast medium. CT scans were obtained within two weeks before TACE and one month after TACE. Tumor assessments were made using a 5-mm interval, and axial images were obtained during the unenhanced phase, the arterial phase, and the portal venous or equilibrium phase.

Tumor response evaluation

Response was defined according to RECIST version 1.1 criteria measuring the entire lesion, including the necrotic part. On the other hand, mRECIST were used to evaluate the lesion taking tumor necrosis, recognized by the non-enhanced areas, into account. Both guidelines adopted the unidimensional measurement (Figure 1).

According to RECIST version 1.1 criteria, a complete response (CR) was defined as the disappearance

of all target lesions; a partial response (PR) was defined as at least a 30% decrease in the sum of the longest diameter of the target lesions; progressive disease (PD) was defined as at least a 20% increase in the sum of the longest diameter of the target lesions; and stable disease (SD) was defined as neither sufficient shrinkage to qualify for PR nor a sufficient increase to qualify for PD.

According to mRECIST criteria, CR was defined as the absence of enhanced tumor areas during the arterial phase, reflecting complete tissue necrosis; PR was defined as at least a 30% decrease, PD was defined as at least a 20% increase in the sum of the longest diameter in the enhanced tumor areas; and SD was defined using the same definition as that used in RECIST version 1.1 criteria.

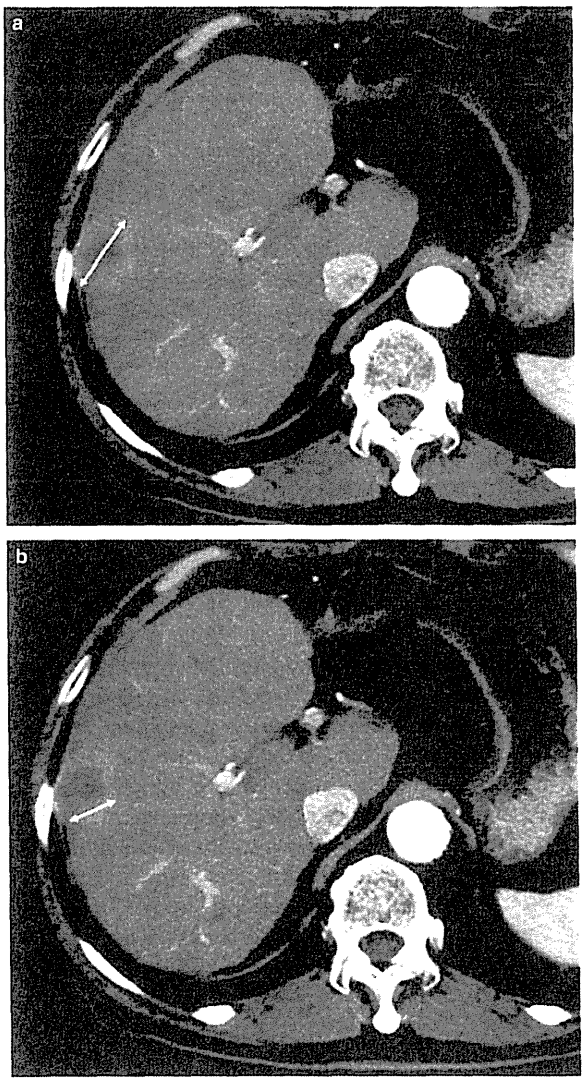

Figure 1. A: RECIST ver. 1.1: Response was defined according to a unidimensional measurement of the entire lesion, including the necrotic part. B: mRECIST: Response was defined according to a unidimensional measurement of the viable part, excluding the necrotic part.

Evaluation methods

Five observers measured 65 lesions in 21 patients independently. A total of 325 measurements were made for the first measurement. The second measurement was performed independently by the same five observers. The sum of the longest diameters for all the target lesions was calculated for baseline and post-treatment. The baseline sum was used as the reference from which the objective tumor response could be calculated. The percentage changes were calculated as the post-treatment value divided by the pre-treatment value. The percentage changes were then classified using RECIST version 1.1 and mRECIST tumor response classification systems. Tumor response was categorized as CR, PR, SD, or PD based on both sets of criteria. Furthermore, the CR rate and the response rate were also calculated.

All the images were collected from each institution and supplied to the Japan Interventional Radiology in Oncology Study Group (JIVROSG) Data Center using the WEB system.

Analysis of inter-criteria reproducibility

To examine the inter-criteria reproducibility between RECIST version 1.1 and mRECIST criteria, we estimated the kappa statistics and the proportion of agreement for the CR, PR, SD, and PD categories among the five observers. The data for the first measurements were analyzed to evaluate the inter-criteria reproducibility.

Analysis of inter-observer reproducibility

To examine the inter-observer reproducibility among the five observers, we estimated the kappa statistics and the proportion of agreement. Each pair yielded 10 pairs for comparison. The data for the first measurements were analyzed to evaluate the inter-observer reproducibility.

Analysis of intra-observer reproducibility

The data for the first and second measurements were compared to assess the intra-observer reproducibility for the same observer. The intra-observer reproducibility for the same observer yielded five pairs for comparison.

Statistics

Kappa statistics were performed to determine the concordance/agreement of the tumor response criteria. The potential kappa values ranged from −1.0 (complete disagreement) through 0 (chance agreement) to 1.0 (complete agreement). Interpretations of the strength of the agreement determined using the kappa values were given by adopting the criteria (9). The kappa values of the two agreements were compared for statistical significance using a paired *t* test. Comparisons between groups were done using the Fisher exact test. A conventional *P* value of 0.05 was considered statistically significant. All analyses were conducted using SPSS (version 17.0).

Results

Patient population

Sixty-five untreated lesions in 21 patients treated using pan-hepatic TACE were evaluated. The patients' characteristics were as follows (Table I), median age (range): 68 years (27–74 years); sex (male/female): 19/2; hepatitis C virus/hepatitis B virus/others: 12/3/6; Child–Pugh A/B: 20/1; total number of nodules (range): 65 nodules (1–5 nodules); mean tumor size (range): 20 mm (10–132 mm).

Inter-criteria reproducibility

The inter-criteria reproducibility using RECIST version 1.1 and mRECIST criteria is summarized in Tables II and III. Five observers measured 65 lesions independently, for a total of 325 measurements. According to RECIST version 1.1 criteria, the CR rate and the response rate were 9.2% and 43.1%, respectively; according to mRECIST criteria, the CR rate and the response rate were 56.9% and 79.7% (Table II).

Among the 185 CR lesions that were identified using mRECIST criteria, RECIST version 1.1 criteria classified the same responses as PR for 89 lesions, SD for 64 lesions, and PD for 2 lesions (Table III). The kappa value was 0.149 (95% CI 0.098–0.201), and the proportion of agreement was 35.5% (Table III).

Table I. Patients and characteristics.

No. of patients	21
Age, median (range)	68 (27–74)
Sex (male/female)	19/2
HCV/HBV/others	12/3/6
Child–Pugh A/B	20/1
No. of nodules, all (range)	65 (1–5)
Mean tumor size (range), mm	20 (10–132)

HCV = hepatitis C virus; HBV = hepatitis B virus.

Inter-observer reproducibility

The inter-observer reproducibility among the five observers was analyzed using the data for the first measurements, with each pair yielding 10 pairs for comparison. These 10 pairs for comparisons, or 650 measurements, are collectively shown in Table IV. For the inter-observer reproducibility for RECIST version 1.1, the kappa value was 0.628 (95% CI 0.571–0.684), and the proportion of agreement was 78.8%. For the inter-observer reproducibility for mRECIST, the kappa value was 0.829 (95% CI 0.792–0.866), and the proportion of agreement was 90.0%.

Intra-observer reproducibility

The intra-observer reproducibility was analyzed from the data for the first and second measurements, with each pair yielding five pairs for comparison. These five pairs for comparisons, or 325 measurements, are collectively shown in Table V. For the intra-observer reproducibility for RECIST version 1.1, the kappa value was 0.643 (95% CI 0.565–0.722), and the proportion of agreement was 79.4%. For the intra-observer reproducibility for mRECIST, the kappa value was 0.900 (95% CI 0.858–0.942), and the proportion of agreement was 94.2%.

Discussion

The inter-criteria reproducibility study between RECIST version 1.0 and EASL guidelines, and a comparative study of tumor response by RECIST and mRECIST have been reported (8,9). However, no information is available concerning the inter-observer reproducibility in those reports. In addition to performing an inter-criteria reproducibility study, we also estimated the inter- and intra-observer reproducibility to investigate which set of criteria (RECIST version 1.1 or mRECIST) is superior for performing tumor response evaluations in clinical trials of TACE for HCC.

Inter-criteria reproducibility

An evaluation of the tumor response according to RECIST version 1.0 and EASL guidelines after loco-regional therapies in patients with HCC has been reported. RECIST missed all the CRs obtained by

Table II. Inter-criteria reproducibility between RECIST version 1.1 and mRECIST criteria. Number of lesions (%).

Response category	Complete response	Partial response	Stable disease	Progressive disease	Overall response[a]
Response criteria					
RECIST	30 (9.2)	110 (33.8)	180 (55.4)	5 (1.5)	140 (43.1)
	$P < 0.001$				$P < 0.001$
mRECIST	185 (56.9)	74 (22.8)	65 (20)	1 (3)	259 (79.7)

[a]Complete response + partial response.
RECIST = Response Evaluation Criteria in Solid Tumors; mRECIST = modified RECIST.

Table III. Inter-criteria reproducibility between RECIST version 1.1 and mRECIST criteria: distribution chart.

		RECIST				
		Complete response	Partial response	Stable disease	Progressive disease	Total
mRECIST	Complete response	30	89	64	2	185
	Partial response	0	21	53	0	74
	Stable disease	0	0	63	2	65
	Progressive disease	0	0	0	1	1
Total		30	110	180	5	325

Proportion of agreement = 35.5%. Kappa = 0.149.

tumor necrosis and underestimated the extent of the partial tumor response because of tissue necrosis (8).

In our inter-criteria reproducibility study comparing RECIST version 1.1 and mRECIST criteria, similar results were obtained. The CR rate and the response rate obtained using mRECIST criteria were higher than those obtained using RECIST version 1.1 criteria (56.9% versus 9.2%, $P < 0.001$; 79.7% versus 43.1%, $P < 0.001$).

According to mRECIST criteria, if a tumor that was solid at baseline became entirely necrotic, all the tumors were evaluated as CR. On the other hand, using RECIST version 1.1 criteria, the necrotic tumor was evaluated as a non-CR based on the measurement of the entire lesion, leading to a different conclusion, such as PR, SD, or PD (Figure 2). Among 185 CR lesions that were identified using mRECIST criteria, 155 lesions (83.8%) were evaluated as non-CR using RECIST version 1.1 criteria. In particular, two lesions evaluated as CR using mRECIST criteria were categorized as PD using RECIST version 1.1 criteria; thus, two sets of criteria produced opposite conclusions (Table III). As the tumor size was very small and a 20% increase was thought to be within the range of measurement error, these two lesions were identified as PD using RECIST version 1.1 criteria. In some cases, this event might be caused by an increase in the necrotic tumor size secondary to chemoembolization. Therefore, the inter-criteria reproducibility between RECIST version 1.1 and mRECIST criteria for loco-regional therapy achieving complete tumor necrosis may have a low concordance.

The differences in the CR rate and the response rate between RECIST version 1.1 and mRECIST criteria indicate that the researchers should ascertain the presence or absence of 'm' (mRECIST? or RECIST?).

Table IV. Inter-observer reproducibility.

	Kappa	Proportion of agreement (%)
Inter-observer reproducibility		
RECIST	0.628 (95% CI 0.571–0.684)	78.8
mRECIST	0.829 (95% CI 0.792–0.866)	90.0

Inter- and intra-observer reproducibility

Standardized tumor response evaluation systems are considered to be reliable in clinical trials when they are reproducible among different observers. The importance of inter-observer reproducibility for any

Table V. Intra-observer reproducibility.

	Kappa	Proportion of agreement (%)
Intra-observer reproducibility		
RECIST	0.643 (95% CI 0.565–0.722)	79.4
mRECIST	0.900 (95% CI 0.858–0.942)	94.2

classification scheme has been discussed previously for other grading systems (10-14). Clinical investigators must take into account inter-observer reproducibility in tumor response evaluations, which can greatly affect the results of clinical trials.

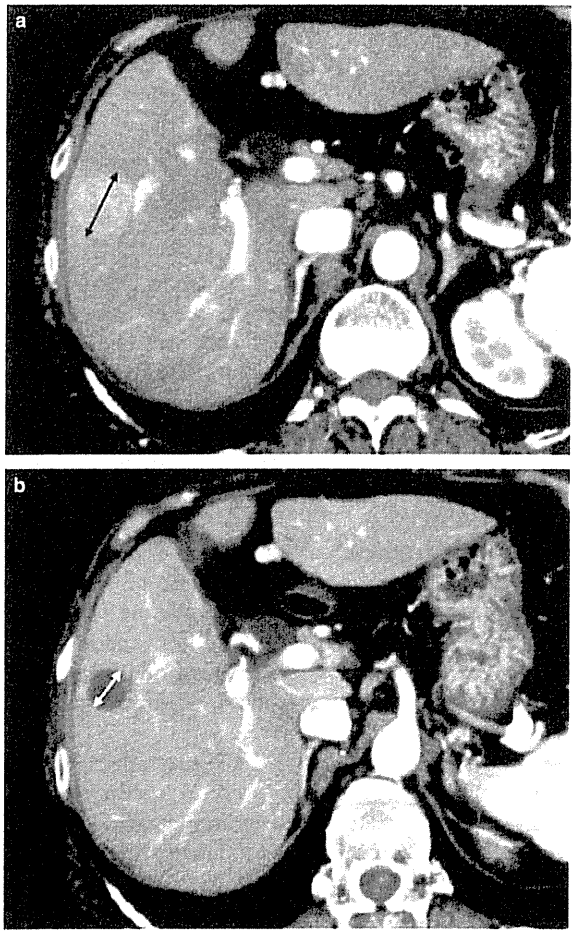

Figure 2. A: CT before TACE: Both criteria (RECIST version 1.1 and mRECIST) measured the longest diameter of the tumor. B: CT after TACE: The tumor had become entirely necrotic. The tumor response was evaluated as CR using mRECIST criteria (i.e. no measurement) and as non-CR using RECIST version 1.1 criteria (i.e. the measurement of the longest diameter of the entire tumor).

In our inter- and intra-observer reproducibility study, the kappa value and the proportion of agreement using mRECIST criteria ('almost perfect agreement') were higher than those for RECIST version 1.1 criteria ('substantial agreement'). In consideration of the high inter- and intra-observer reproducibility, mRECIST can be more recommended for use as tumor response criteria in clinical trials of TACE for HCC.

The present study had several limitations. The number of patients was relatively small, and the analyses were performed not on a per-patient basis, but on a per-lesion basis. To investigate which set of criteria was superior as tumor response criteria in clinical trials of TACE for HCC, the observer consistency study (inter- and intra-observer reproducibility between the two updated sets of criteria) were investigated in this study. A validation study comparing the updated criteria to the gold standard (i.e. overall survival) should be encouraged in future studies.

In conclusion, considering the differences in the CR rate and the response rate between RECIST version 1.1 and mRECIST criteria, close attention must be paid to the criteria used for a precise interpretation of the tumor response outcome. Furthermore, mRECIST criteria may be more suitable for tumor response criteria in clinical trials of TACE for HCC, compared with RECIST version 1.1 criteria, from the viewpoint of the high inter- and intra-observer reproducibility.

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Clinical Investigation: Pancreatic Cancer

A Multicenter Phase II Trial of S-1 With Concurrent Radiation Therapy for Locally Advanced Pancreatic Cancer

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Summary

S-1 is the first single anticancer agent to be judged non-inferior to gemcitabine in a large-scale, randomized, phase III trial for advanced pancreatic cancer, and it can also act as a radiosensitizer. S-1 with concurrent radiation therapy showed very favorable activity, with mild toxicity in patients with

Purpose: The aim of this trial was to evaluate the efficacy and toxicity of S-1 and concurrent radiation therapy for locally advanced pancreatic cancer (PC).

Methods and Materials: Locally advanced PC patients with histologically or cytologically confirmed adenocarcinoma or adenosquamous carcinoma, who had no previous therapy were enrolled. Radiation therapy was delivered through 3 or more fields at a total dose of 50.4 Gy in 28 fractions over 5.5 weeks. S-1 was administered orally at a dose of 80 mg/m^2 twice daily on the day of irradiation during radiation therapy. After a 2- to 8-week break, patients received a maintenance dose of S-1 (80 mg/m^2/day for 28 consecutive days, followed by a 14-day rest period) was then administered until the appearance of disease progression or unacceptable toxicity. The primary efficacy endpoint was survival, and the secondary efficacy endpoints were progression-free survival, response rate, and serum carbohydrate antigen 19-9 (CA19-9) response; the safety endpoint was toxicity.

Results: Of the 60 evaluable patients, 16 patients achieved a partial response (27%; 95% confidence interval [CI], 16%-40%). The median progression-free survival period, overall survival period, and 1-year survival rate of the evaluable patients were 9.7 months (95% CI, 6.9-11.6 months),

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locally advanced pancreatic cancer.

16.2 months (95% CI, 13.5-21.3 months), and 72% (95%CI, 59%-82%), respectively. Of the 42 patients with a pretreatment serum CA19-9 level of ≥100 U/ml, 34 (81%) patients showed a decrease of greater than 50%. Leukopenia (6 patients, 10%) and anorexia (4 patients, 7%) were the major grade 3-4 toxicities with chemoradiation therapy.

Conclusions: The effect of S-1 with concurrent radiation therapy in patients with locally advanced PC was found to be very favorable, with only mild toxicity. © 2013 Elsevier Inc.

Introduction

Pancreatic cancer (PC), one of the most lethal human cancers, has become the fifth most common cause of death due to cancer in Japan; it has been estimated that PC was responsible for 26,791 deaths in 2009, representing approximately 3% of all deaths. PC patients have a dismal prognosis, as their 5-year survival after diagnosis is less than 5%. Of all treatment modalities available for PC, only resection offers an opportunity for a cure. However, approximately half of patients already have metastases at the time of diagnosis, and approximately one-third of patients are diagnosed as having locally advanced disease, whereas only a small proportion of patients are eligible for surgery, as a result of the lack of effective screening. Concurrent chemoradiation therapy with external beam radiation therapy and chemotherapy using 5-fluorouracil (5-FU) is often used in patients who have unresectable PC due to vascular involvement that includes the celiac artery or supra-mesenteric artery, with no distant metastases on radiological examination, because it is generally accepted as a standard therapy for locally advanced PC (1-4). A variety of anticancer agents, including gemcitabine (5) and capecitabine (6), and various radiation schedules (7-8) have been examined in clinical trials, but survival has not been significantly improved.

S-1 is a new oral fluoropyrimidine derivative in which tegafur is combined with 2 5-chloro-2,4-dihydroxypyridine modulators and oteracil potassium, a potentiator of 5-FU's antitumor activity that also decreases gastrointestinal toxicity. A multi-institutional, late-phase II trial of S-1 involving metastatic PC patients reported a good tumor response rate (38%) and improved survival (median, 9.2 months) (9). A phase III trial compared therapy with S-1, with gemcitabine alone, and with gemcitabine plus S-1 in patients with unresectable PC in Japan and Taiwan, and S-1 therapy was found to provide efficacy and toxicity similar to gemcitabine when it was used as a first-line treatment for advanced PC (median survival: S-1, 9.7 months; gemcitabine, 8.8 months [hazard ratio, 0.96; non-inferiority P value <.001]); thus, S-1 was judged to be non-inferior to gemcitabine (10). S-1 also acts as a radiosensitizer, and preclinical and clinical studies have demonstrated the radiosensitizing potency of S-1 (11). Not only is S-1 a potent radiosensitizer that has been shown to have promising antitumor activity against advanced PC, but also, since it is active orally, it is also much more convenient for patients than intravenous 5-FU infusion. Thus, concurrent raditation therapy and oral S-1 instead of 5-FU infusion may be a more efficient treatment that also improves patients' quality of life. In a phase I trial conducted in one of our hospitals, the recommended S-1 dose with concurrent radiation therapy was found to be 80 mg/m^2/day on the day of irradiation; at this dose, S-1 was found to have excellent antitumor activity with mild toxicity (12). Consequently, a multi-institutional phase II study was conducted to clarify the efficacy and safety of concomitant radiation therapy with S-1 in patients with locally advanced PC.

Methods and Materials

Patients and eligibility

Patients eligible for study entry had locally advanced nonresectable clinical stage III (T4N0-1 and M0) PC, according to International Union Against Cancer criteria. Eligibility criteria were adenocarcinoma or adenosquamous carcinoma confirmed on cytology or histology; no previous chemotherapy for PC; a square (10 cm × 10 cm) radiation field could encompass all pancreatic lesions and lymph node metastases; age ≥20 years; Eastern Cooperative Oncology Group (ECOG) performance status of 0-2; adequate oral intake; satisfactory hematological functions (hemoglobin concentration, ≥9.0 g/dl; leukocyte count, ≥3500/mm^3; platelet count, ≥100,000/mm^3); adequate hepatic function (serum total bilirubin ≤2.0 times the upper normal limit [UNL] or ≤3.0 mg/dl with biliary drainage); aspartate aminotransferase [AST] and alanine aminotransferase [ALT] ≤2.5 times UNL or ≤5 times UNL with biliary drainage; serum albumin ≥3.0 g/dl; and normal renal function (serum creatinine ≤UNL). Written informed consent was obtained from all patients.

Exclusion criteria were active infection; active gastroduodenal ulcer; watery diarrhea; phenytoin, warfarin potassium, or flucytosine treatment; pleural effusion or ascites; severe complications such as cardiac or renal disease; psychiatric disorder; history of drug hypersensitivity; and active concomitant malignancy. In addition, pregnant and lactating women and women of childbearing age who were not using effective contraception were also excluded.

Pretreatment evaluation required a complete history and physical examination and baseline assessments of organ function. In addition, contrast medium-enhanced computed tomography (CT) or magnetic resonance imaging of the abdomen and X-ray or CT of the chest was performed for pretreatment staging to assess the local extension of the tumor and to exclude the presence of distant metastases. The criteria for local extension surrounding the pancreas included tumor invasion to the celiac trunk or superior mesenteric artery, or both, which corresponded to clinical stage III according to the International Union Against Cancer (6th edition). All patients with obstructive jaundice underwent percutaneous transhepatic or endoscopic retrograde biliary drainage before treatment. Laparoscopy and laparotomy to rule out occult peritoneal dissemination prior to study entry were not necessary.

Treatment schedule

The regimen consisted of S-1 with concurrent radiation therapy and maintenance S-1 chemotherapy.

S-1 with concurrent radiation therapy

Radiation therapy was delivered with >6-MV photons, using a multiple (three or more) field technique. A total dose of 50.4 Gy