This supplement contains the following items:

Effect of Primary Endoscopic Ultrasound-Guided Transmural Biliary Drainage for Malignant Distal Biliary Obstruction: A Multicenter Randomized Trial

Protocol version 1.2

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1. Protocol abstract

Title: Effect of Primary Endoscopic Ultrasound-Guided Transmural Biliary Drainage for Malignant Distal Biliary Obstruction: A Multicenter Randomized Trial

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Backgrounds

ERCP is an established therapeutic procedure for the palliation of obstructive jaundice.[1] However, a wide array of complications stemming from the procedure, including pancreatitis, cholangitis, and stent dysfunction resulting in untimely reintervention, has continued to pose a significant challenge.[2, 3]

The success rate of endoscopic retrograde biliary drainage (ERBD) with ERCP in patients with malignant biliary obstruction is 90%-95%,[2] however, selective biliary cannulation is still challenging in some cases and conventional ERCP may not be possible in patients with tumor invasion of the duodenum or major papilla, surgically altered anatomy (e.g., Roux-en-Y anastomosis), or complex hilar biliary strictures.[4-6] Traditionally in such cases, percutaneous transhepatic biliary drainage (PTBD) is an useful alternative. However, PTBD had various complications up to 33% and the presence of an external drainage catheter would also have a cosmetic problem related to the external drainage and an adverse impact on quality of life (QOL) of terminally ill patients.[7, 8]

Since endoscopic ultrasound-guided bile duct puncture was described in 1996, sporadic reports of EUS-guided biliary drainage (EUS-BD) suggested that it was a feasible and

effective alternative in patients with failed conventional ERCP stenting.[9-19] A recent meta-analysis reported EUS-BD to be a viable alternative to transpapillary approach in relieving biliary obstruction when performed at institutions with procedural expertise.[20] Some theoretical advantages of EUS-BD over ERBD include 1) avoidance of traumatic papillary manipulation that can lead to acute pancreatitis, 2) ability to access bile duct even when ampulla cannot be approached endoscopically and 3) no need to place the stent thorough the biliary stricture.[21, 22]

To date, only a small volume of retrospective studies comparing EUS-BD with conventional ERBD exists, lacking a well-designed prospective randomized study with robust data. Therefore, we aimed to evaluate the noninferiority of EUS-BD compared to ERBD as a primary palliation method in relieving malignant distal biliary obstruction.

Study protocol

Objective

The primary objective of this trial is to evaluate the noninferiority of technical success between EUS-BD and ERBD for primary paillation of malignant distal biliary obstruction.

Primary endpoint: The primary end point is technical success of EUS-BD and ERBD. Secondary endpoint: The secondary end points are clinical success, adverse events, stent patency, re-intervention rate, and QOL.

Design and settings

This study is a multicenter, open label, prospective, randomized, noninferiority trial to compare the technical outcomes of EUS-BD and ERBD with primary palliation of cholestasis in malignant distal biliary obstruction. An informed consent will be obtained before study enrollement. Patients will be prospectively enrolled from all four academic institutions, where surgery and radiology back-up were available to help manage failed procedures and/or procedure-related adverse events. The patients with unresectable malignant distal biliary obstruction will be randomized in a 1:1 ratio to EUS-BD or ERBD without risk stratification. Each hospital's Institutional Review Board approved the study protocol.

Entry criteria

Inclusion criteria

1) Presence of unresectable malignant distal biliary obstruction (i.e., pancreatic cancer, common bile duct cancer, ampulla of Vater cancer, gallbladder cancer, duodenal cancer, and metastatic biliary obstruction)

2) Histologic or radiologicdiagnosis of malignancy prior to endoscopic intervention

3) A Karnofsky index of ≧30%

4) No serious or uncontrolled medical illness

6) Provided informed consent

Exclusion criteria

1) Patient age of less than 18 years

2) Uncorrectable coagulopathy

3) History of allergy to radiocontrast agents

4) Hilar biliary obstruction

5) Refusal to participate in this study

Measurements

1) Technical success

2) Clinical success

3) Procedure time

4) Procedure-related complications

5) Re-intervention rate

6) Stent patency

7) Overall survival

8) Mortality

9) Hospital stay

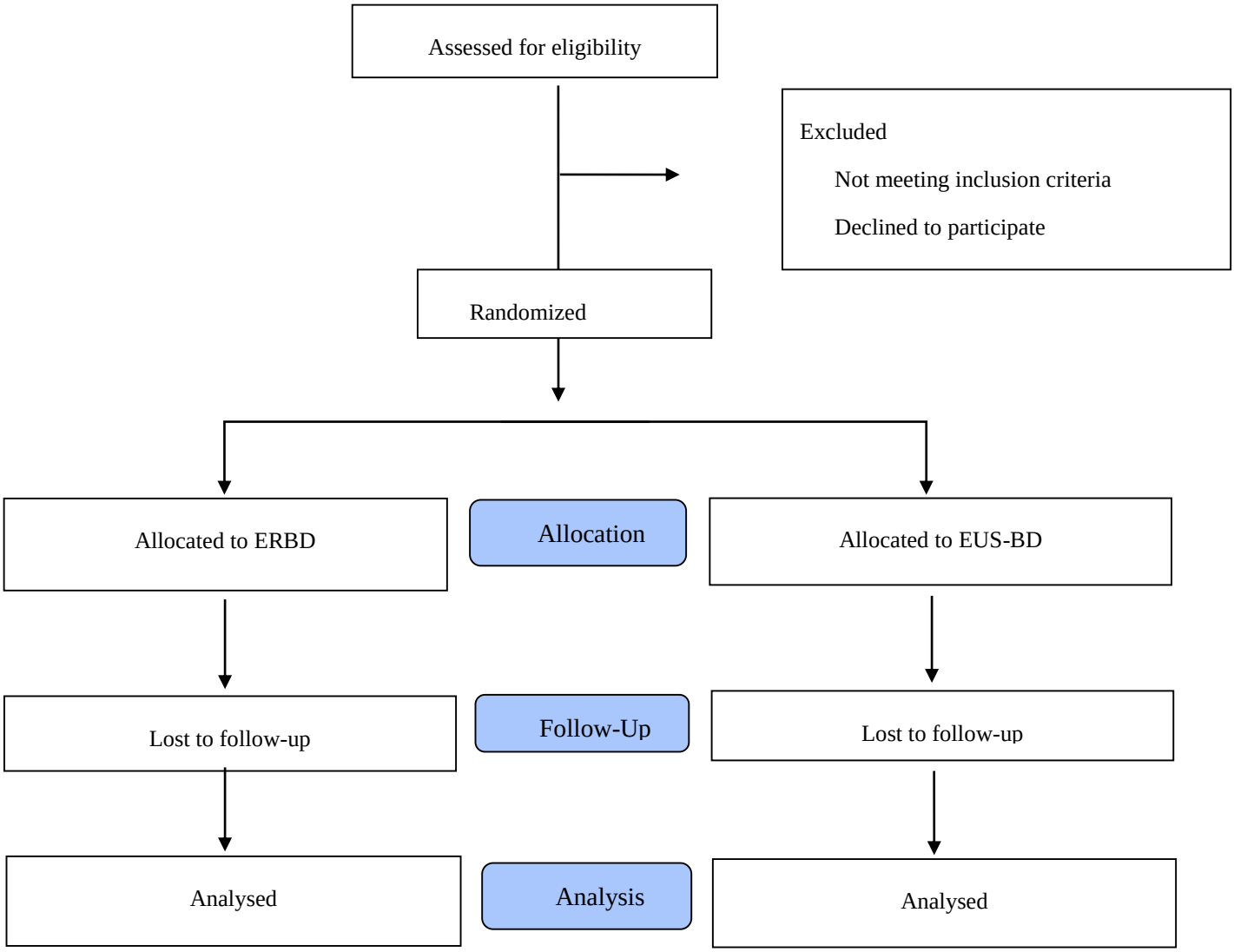
10) QOL

Statistical analysis

The primary analysis was a noninferiority comparison between transpapillary and transmural stenting for technical success rates. The assumed technical success rate for transpapillary approach was 95%.[2] We set a margin of noninferiority for a technical success rate between transpapillary and transmural stenting as 10% according to the results of a pooled analysis.[23] To achieve a statistical power of 80%

with the assumption of a 1-sided type I error rate of 5%, a total of (59 per group) was calculated. Considering a 5% of drop-out rate, we calculated a final sample size of 124 of patients (62 per group). Sample size and power were calculated using the PASS 12 program (NCSS, Kaysville, UT). The noninferiority hypothesis for primary outcome is assessed using the Z-test with a 95% one-sided confidence interval of the difference in the technical success rate and the margin of noninferiority. The characteristics of the study groups will be compared using Student *t* tests for continuous variables and a Pearson chi-square test or the Fisher exact test for categorical variables. Overall survival and stent patency will be calculated by the Kaplan-Meier method with use of the log-rank test. The QOL score analysis will be performed with a Student *t* test for comparison of difference of the score between baseline and 4 or 12 weeks. A P value of less than 0.05 is considered statistically significant.

2. Study flow chart



	1st Admission	Post procedure			Follow-up
		After 24 hours	After 1 week	After 1 month	Admission for managing complication or per 1 months
Demographics	▲				
Chemical test	▲	▲	▲	▲	▲
CT (tumor response)	▲				△
Histologic test	▲				
Inclusion/exclusion criteria	▲				
EUS-BD or ERBD	▲				
Procedure-related adverse events and unscheduled re-intervnetion	▲	▲	▲	▲	▲
Bile duct decompression (EUS-BD, ERBD)	▲	▲	▲	▲	▲
EORTC-OLQ-30	▲			▲	▲
Mortality		▲	▲	▲	▲

* ▲ = prerequisite data, △ = optional data

3. List of abbreviation

Acronym	Definition
ERCP	Endoscopic Retrograde Cholangiopancreatogram
ERBD	Endoscopic Retrograde Biliary Drainage
EUS-BD	Endoscopic ultrasonography guided biliary drainage
EUS-CD	Endoscopic ultrasonography guided choledochoduodenostomy
EUS-HG	Endoscopic ultrasonography guided hepaticogastrostomy
PTBD	Percutaneous Transhepatic Biliary Drainage

4. Quality control and quality assurance

4.1 Ethics and Responsibility

This study will be conducted in compliance with the protocol, the Sponsors' standard operating procedures and local regulations where applicable, the International Conference on Harmonization (ICH) GCP guidelines and the Declaration of Helsinki.

4.2 Confidentiality

All information generated in this study must be considered highly confidential and must not be disclosed to any persons not directly concerned with the study without written prior permission from the Sponsor. However, authorized regulatory officials and Sponsor personnel will be allowed full access to the records.

Only initials and unique patient numbers in case report forms will identify patients. All medications provided and patient bodily fluids and/or other materials collected specifically for this trial shall be used solely in accordance with this protocol, unless otherwise agreed to in writing by the Sponsor.

5. Background

Transpapillary stent placement with endoscopic retrograde cholangiopancreatography (ERCP) has been the preferred treatment for the palliation of malignant distal biliary obstruction.[1, 24, 25] However, after the procedure, acute pancreatitis, cholangitis, stent occlusion or migration, and cholecystitis account for substantial morbidity and are not preventable.[2, 3] The overall adverse event rate related to transpapillary stenting range from 28% to 36%.[21, 26, 27] Acute pancreatitis is the most common and feared adverse event after transpapillary approach, with reported rates ranged from 2% to 18%.[2, 21, 26, 27] Moreover, duodenal stricture is often accompanied with malignant distal biliary obstruction, making transpapillary approach technically difficult or impossible.[2]

Transmural stent placement under endoscopic ultrasound (EUS) guidance has emerged as an alternative procedure to percutaneous transhepatic biliary drainage after failed transpapillary stenting.[10, 20] Recent meta-analysis showed that transmural stenting is an effective alternative procedure for relieving biliary obstruction when performed in expert centers with appropriate training and skill.[20] Theoretically, transmural stenting has some advantages compared to transpapillary stenting: 1) no need to traverse the papilla, 2) available even if the ampulla is inaccessible with endoscopy, and 3) no need to place the stent thorough the biliary stricture.[21, 22] However, there is a dearth of clinical study about a primary palliation of cholestasis with EUS-guided transmural stenting. Moreover, there is no prospective comparative study between transpapillary and transmural stent placement. Therefore, we aimed to evaluate the noninferiority of transmural stenting compared to transpapillary stenting as a primary palliation of malignant distal biliary obstruction.

6. Trial Objectives and Hypotheses

The primary objective of this trial is to evaluate the technical success of EUS-BD compared with ERBD in unresectable malingnant distal biliary obstruction. The alternative hypothesis is that the EUS-BD is not inferior to the conventional ERBD.

6.1 Primary endpoint:

The primary end point is technical success of EUS-BD and ERBD.

6.2 Secondary endpoint

The secondary end points are functional success, re-intervention rate, cost-effectiveness, and complications.

7. Trial Design

This study is a multicenter, open label, prospective, non-inferiority, randomized trial to compare the efficacy of EUS-BD with ERBD for patients with unresectable malignant distal biliary obstruction

8. Subjective & methods

8.1 Study protocol

This study is a multicenter, open label, prospective, randomized, noninferiority trial to compare the technical outcomes of EUS-BD and ERBD with malignant distal biliary obstruction.

Eligible patients will be randomized 1:1 ratio to (1) EUS-BD, (2) ERBD.

Each hospital's Institutional Review Board approved the study protocol and we obtained specific informed consents for EUS-BDS or ERBD from each patient before the each procedure.

Four tertiary academic referral centers in South Korea performed ERCPs to relieve malignant obstructive jaundice.

- Asan Medical Center, Seoul

- SoonChunHyang University Cheonan Hospital, Cheonan

- Inje University Ilsan Paik Hospital, Goyang

- Dankook University Hospital, Cheonan

8.2 Endpoints

The primary end point is primary technical success of EUS-BD and ERBD.

The secondary end points are functional success, re-intervention rate, cost-effectiveness and complications.

8.3 Study timeline

Overall study will require 12 months between May 2015 and June 2016.

8.4 Inclusion criteria

1) Presence of unresectable malignant distal biliary obstruction (i.e., pancreatic cancer, cholangiocarcinoma, ampulla of Vater cancer, gallbladder cancer, duodenal cancer, and metastatic biliary obstruction)

2) Histologic or radiologic diagnosis of malignancy prior to endoscopic intervention

3) A Karnofsky index of ≧30%

4) No serious or uncontrolled medical illness

5) Provided informed consent

8.5 Exclusion criteria

1) Patient age of less than 18 years

2) Uncorrectable coagulopathy

3) History of allergy to radiocontrast agents

4) Hilar biliary obstruction

5) Refusal to participate in this study

9. Randomization

Eligible patients are randomly assigned to EUS-BD or ERBD in a one-to-one ratio without risk stratification. We obtained sequentially numbered, opaque, sealed envelopes with computer-generated random numbers using a block randomization (block size of 4) from a statistician. The randomization assignment was opened by one of the attending nurses, and the allocation sequence was concealed from all patients and operators before procedure in the endoscopic suite.

10. Protocol Procedures

10.1 EUS-guided biliary drainage (EUS-BD)

We administered broad spectrum prophylactic antibiotics directed against gram positive and gram negative organisms before the procedure to minimize the risk of sepsis and abscess formation. EUS-BD was performed using a linear-array echoendoscope (GF-UCT 240-AL 10 or AL 5, Olympus Medical Systems, Tokyo, Japan) at the same place on the same time. EUS-BD was performed by EUS-guided hepaticogastrostomy (EUS-HG) or EUS-guided choledocoduodeostomy (EUS-CD) according to the specific situations. EUS-HG was performed in patients with hilar stricture or altered anatomy such as

subtotal gastrectomy with Billroth II anastomosis or Roux-en-Y anastomosis, and EUS-CD was attempted in patients with mid to distal extrahepatic bile duct obstructions. We usually access the dilated ducts of segment 2 or 3 with the echoendoscope placed at the cardia or lesser curvature of the stomach and the dilated extrahepatic duct with the endoscope position in the duodenal bulb. The initial puncture was performed under real-time ultrasound and color doppler guidance, to avoid intervening blood vessels. We punctured the bile duct using a 19-gauge fine needle aspiration needle (EUSN-19-T, Cook Endoscopy, Winston-Salem, NC) and aspirated bile to confirm position followed by cholangiography to delineate the dilated bile duct and stricture. Next, we inserted a 0.025-inch guidewire (VisiGlide, Olympus Medical Systems, Tokyo, Japan) through the EUS-guided 19-G needle and coiled it into the bile duct lumen for transluminal stent placement. EUS-BD was performed according to the direction that the guidewire was inserted into the CBD and IHD. Without using a graded dilation catheter, bougie, or needle-knife cautery, the delivery system was directly inserted and the preloaded metallic stent within the catheter then sequentially deployed over the guidewire.

The newly modified delivery introducer (Standard Sci Tech Inc., Seoul, South Korea) which is advanced from animal study, has 3F catheter with 4F smooth tapered metal tip for simple puncture of the intestinal wall and liver parenchyma without the need of graded dilation devices. The outer sheath of the delivery catheter is size 7F, which provides good pushability and adequate resistance.[28] A self-expandable metal stent, consisting of both uncovered and nitinol-covered portions, was preloaded into the catheter. The uncovered proximal end of the stent (8 mm in diameter and 15 mm in length), which is funnel shaped to prevent small-branched bile duct obstruction and distal migration, was placed into the bile duct. The body and distal portions of the stent were covered with a silicone membrane (6 mm in diameter and 35 or 45 mm in length) for the prevention of bile leaks, and the distal end was equipped with four flaps for the prevention of inward stent migration.[28]

10.2 Endoscopic retrograde biliary drainage (ERBD)

ERBD was performed in randomly selected patients with unresectable malignant distal biliary obstruction. Prophylactic antibiotics was administered before the start of the intervention. ERBD was performed using a standard duodenoscope or cap-assisted forward scope when patients had surgically altered anatomy as Billroth II anastomosis with the patient under conscious sedation with midazolam and meperidine. After biliary cannulation, contrast media was injected to obtain cholangiogram. Then, a guidewire was passed through the stricture, and sphincterotomy was done. Finally, self-expandable metal stent was placed across the papilla

11. Post Procedure Management: Follow-up phase

All patients will be evaluated before the ERCP, 24 hours, 1 week, and 1-month after EUS-BD or ERBD. Then liver function test will be assessed every one month. We followed up the patients for one year after the procedures or until death. If previously placed metal stents show an early clogging, stent revision or additional PTBD was considered for biliary decompression. All parameters were recorded by study coordinators and monitored by a data and safety monitoring board (Division of Hepatobiliary and Pancreatic Surgery, Jae Hoon Lee, and Division of Gastroenterology and Asan Medical Center, Ji Yong Ahn).

12. Statistical analysis

12.1 Sample size calculation

The primary analysis was a noninferiority comparison between transpapillary and transmural stenting for technical success rates . The assumed technical success rate for transpapillary approach was 95%.[2] We set a margin of noninferiority for a technical success rate between trans

papillary and transmural stenting as 10% according to the results of a pooled analysis and after a discussion with the contributing physicians, who stated that this noninferiority margin of 10% would be clinically relevant.. To achieve a statistical power of 80% with the assumption of a 1-sided type I error rate of 5%, a total of (59 per group) was calculated. Assuming there is a 5% drop-out rate, we calculated a final sample size of 124 patients (62 per group). Sample size was calculated using the PASS 12 program (NCSS, Kaysville, UT) by a statistical expert.

12.2 Data from study sites

Categorical parameters were compared by a chi-square test and Fisher's exact test, and continuous variables were compared by Student's t-test. Cumulative patency duration was estimated using the Kaplan-Meier technique and compared by using the log-rank test. All statistical analyses were performed using SAS software (version 9.4; SAS Institute, Cary, NC), with results considered significant at P-value <0.05.

13 Adverse Events/Serious Adverse Events

13.1 Adverse Event

For the purpose of this trial, an adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation subject enrolled in a device clinical study and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom or disease temporally associated with the study procedures, whether or not considered related to the investigational device or procedure.

Grade refers to the relationship of the adverse event.

a. definitely not related

a. probably related

b. possibly related

c. definitely related

Grade refers to the severity of the adverse event.

a. Mild; asymptomatic or mild symptoms

b. Moderate; local or noninvasive intervention indicated; limiting

c. Severe; Medically significant, hospitalization or prolongation of hospitalization indicated

Grade refers to the intervention for the adverse event

a. None

b. Medicated therapeutic drug

c. Hopitalization

13.2 Serious Adverse Event (SAE)

An adverse event is considered serious for this trial if it meets one or more of the following criteria and is device-related:

Results in death

Is life-threatening, *i.e.*, the patient was, in the opinion of the Investigator, at immediate risk of death from the event as it occurred *(It does not include an event that, had it occurred in a more severe form, might have caused death.)*

Results in persistent or significant disability (significant, persistent or permanent change or disruption in patient's body function/structure, physical activity or quality of life

Requires in-patient hospitalization or prolongs hospitalization

13.3 Notification of adverse event

All events meeting the AE/SAE criteria must be reported to the Safety committee and IRB within 24 hours of becoming aware of the events.

Adverse events	Date	Severity of the adverse event	Relationship	Intervention	Others
Symptom/ sign	(yr/m/d)	1. Mild; asymptomatic or mild symptoms 2. Moderate; local or noninvasive intervention indicated; limiting 3. Medically significant, hospitalization or prolongation of hospitalization indicated	1. Definitely not related 2. Probably related 3. Possibly related 4. Definitely related	1. None 2. Dosage change or stop 3. Medicated therapeutic drug 4. Hopitalization 5. Withdrawal	
Events		① ② ③	① ② ③ ④	① ② ③ ④ ⑤	
	□ Unknown				
		① ② ③	① ② ③ ④	① ② ③ ④ ⑤	
	□ Unknown				
		① ② ③	① ② ③ ④	① ② ③ ④ ⑤	

Definition of adverse events

Based on the timing, procedure (EUS-BD and ERBD)-related adverse events was defined as intra-procedure if it occurred during procedure or in recovery area, or post-procedure within in 14 days after procedure.[15, 16] Procedure-related adverse events were also described using the Common Technology

Criteria for Adverse Events (CTCAE) v 3.0 and 4.0. Severity of adverse events was graded as mild, moderate, severe and fatal according to the ASGE classification.[29] Procedure-related adverse events were defined as mild or moderate if patients required less than 4 nights or between 4 to 10 nights of hospitalization respectively. They were classified as severe if unplanned or prolonged hospitalization was required for more than 10 nights or required intensive care unit or surgery.[29] Bile leak was defined as cholangiographic evidence of contrast leaking from the opacified bile ducts during procedure without post-procedure peritoneal irritation. Bile peritonitis was defined as bile leakage with signs of peritoneal irritation. Self-limited pneumoperitoneum was defined as intraperitoneal air on radiologic imaging without peritoneal irritation.

Biliary re-intervention was defined as any type of scheduled or unscheduled endoscopic, percutaneous, or surgical procedure that was required to improve biliary drainage after EUS-BD or ERBD.[17] Stent occlusion was defined as the recurrence of jaundice and cholestasis, and/or evidence of a dilated biliary system on ultrasound or computed tomography (CT) with a direct view of the upper endoscope, requiring biliary intervention.[17]

14. Investigational Agreement

I have read and understand the protocol (including the Investigator's Brochure) and agree that it contains all the ethical, legal and scientific information necessary to conduct this Trial. I will personally conduct the study as described.

I will provide copies of the protocol to all physicians, nurses and other professional personnel responsible

to me who will participate in the study. I will discuss the protocol with them to assure myself that they are sufficiently informed regarding the devices used in the study, the concurrent medications, the efficacy and safety parameters and the conduct of the study in general. I am aware that this protocol must be approved by the Institutional Review Board (IRB) responsible for such matters in the Clinical Study Facility where the device and drug will be tested, prior to commencement of this study. I agree to adhere strictly to the attached protocol. I understand that this IRB approved protocol will be submitted to the authorities by the Sponsor, as appropriate. I agree that clinical data entered on case report forms by me and my staff will be utilized by the Sponsor in various ways such as for submission to governmental regulatory authorities and/or in combination with clinical data gathered from other research sites, whenever applicable. I agree to allow Sponsor monitors and auditors as well as inspectors from regulatory authorities, full access to all medical records at the research facility for patients screened or randomized in the study.

I agree to provide all patients with informed consent forms, as required by government and ICH regulations.

I further agree to report to the Sponsor any adverse experiences in accordance with the terms of this protocol, KFDA regulation, and ICH guideline.

Principal Investigator (print)

Do Hyun Park

Principal Investigator (signature) Date 5/1/2015

Institution Name/Location

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Protocol version 3.4

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1. Protocol abstract

Title: Effect of Primary Endoscopic Ultrasound-Guided Transmural Biliary Drainage for Malignant Distal Biliary Obstruction: A Multicenter Randomized Trial
Principal investigator: Do Hyun Park, MD, PhD. Department of Medicine, Asan Medical Center, University of Ulsan College of Medicine
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Backgrounds ERCP is an established therapeutic procedure for the palliation of obstructive jaundice.[1] However, a wide array of complications stemming from the procedure, including pancreatitis, cholangitis, and stent dysfunction resulting in untimely reintervention, has continued to pose a significant challenge.[2, 3] The success rate of endoscopic retrograde biliary drainage (ERBD) with ERCP in patients with malignant biliary obstruction is 90%-95%,[2] however, selective biliary cannulation is still challenging in some cases and conventional ERCP may not be possible in patients with tumor invasion of the duodenum or major papilla, surgically altered anatomy (e.g., Roux-en-Y anastomosis), or complex hilar biliary strictures.[4-6] Traditionally in such cases, percutaneous transhepatic biliary drainage (PTBD) is an useful alternative. However, PTBD had various

complications up to 33% and the presence of an external drainage catheter would also have a cosmetic problem related to the external drainage and an adverse impact on quality of life (QOL) of terminally ill patients.[7, 8]

Since endoscopic ultrasound-guided bile duct puncture was described in 1996, sporadic reports of EUS-guided biliary drainage (EUS-BD) suggested that it was a feasible and effective alternative in patients with failed conventional ERCP stenting.[9-19] A recent meta-analysis reported EUS-BD to be a viable alternative to transpapillary approach in relieving biliary obstruction when performed at institutions with procedural expertise.[20] Some theoretical advantages of EUS-BD over ERBD include 1) avoidance of traumatic papillary manipulation that can lead to acute pancreatitis, 2) ability to access bile duct even when ampulla cannot be approached endoscopically and 3) no need to place the stent thorough the biliary stricture.[21, 22]

To date, only a small volume of retrospective studies comparing EUS-BD with conventional ERBD exists, lacking a well-designed prospective randomized study with robust data. Therefore, we aimed to evaluate the noninferiority of EUS-BD compared to ERBD as a primary palliation method in relieving malignant distal biliary obstruction.

Study protocol

Objective

The primary objective of this trial is to evaluate the noninferiority of technical success

between EUS-BD and ERBD for primary paillation of malignant distal biliary obstruction.

Primary endpoint: The primary end point is technical success of EUS-BD and ERBD. Secondary endpoint: The secondary end points are clinical success, adverse events, stent patency, re-intervention rate, and QOL.

Design and settings

This study is a multicenter, open label, prospective, randomized, noninferiority trial to compare the technical outcomes of EUS-BD and ERBD with primary palliation of cholestasis in malignant distal biliary obstruction. An informed consent will be obtained before study enrollement. Patients will be prospectively enrolled from all four academic institutions, where surgery and radiology back-up were available to help manage failed procedures and/or procedure-related adverse events. The patients with unresectable malignant distal biliary obstruction will be randomized in a 1:1 ratio to EUS-BD or ERBD without risk stratification. Each hospital's Institutional Review Board approved the study protocol.

Entry criteria

Inclusion criteria

1) Presence of unresectable malignant distal biliary obstruction (i.e., pancreatic cancer, common bile duct cancer, ampulla of Vater cancer, gallbladder cancer, duodenal cancer, and metastatic biliary obstruction)

2) Histologic or radiologicdiagnosis of malignancy prior to endoscopic intervention

3) A Karnofsky index of ≧30%

4) No serious or uncontrolled medical illness

6) Provided informed consent

Exclusion criteria

1) Patient age of less than 18 years

2) Uncorrectable coagulopathy

3) History of allergy to radiocontrast agents

4) Hilar biliary obstruction

5) Refusal to participate in this study

Measurements

1) Technical success

2) Clinical success

3) Procedure time

4) Procedure-related complications

5) Re-intervention rate

6) Stent patency

7) Overall survival

8) Mortality

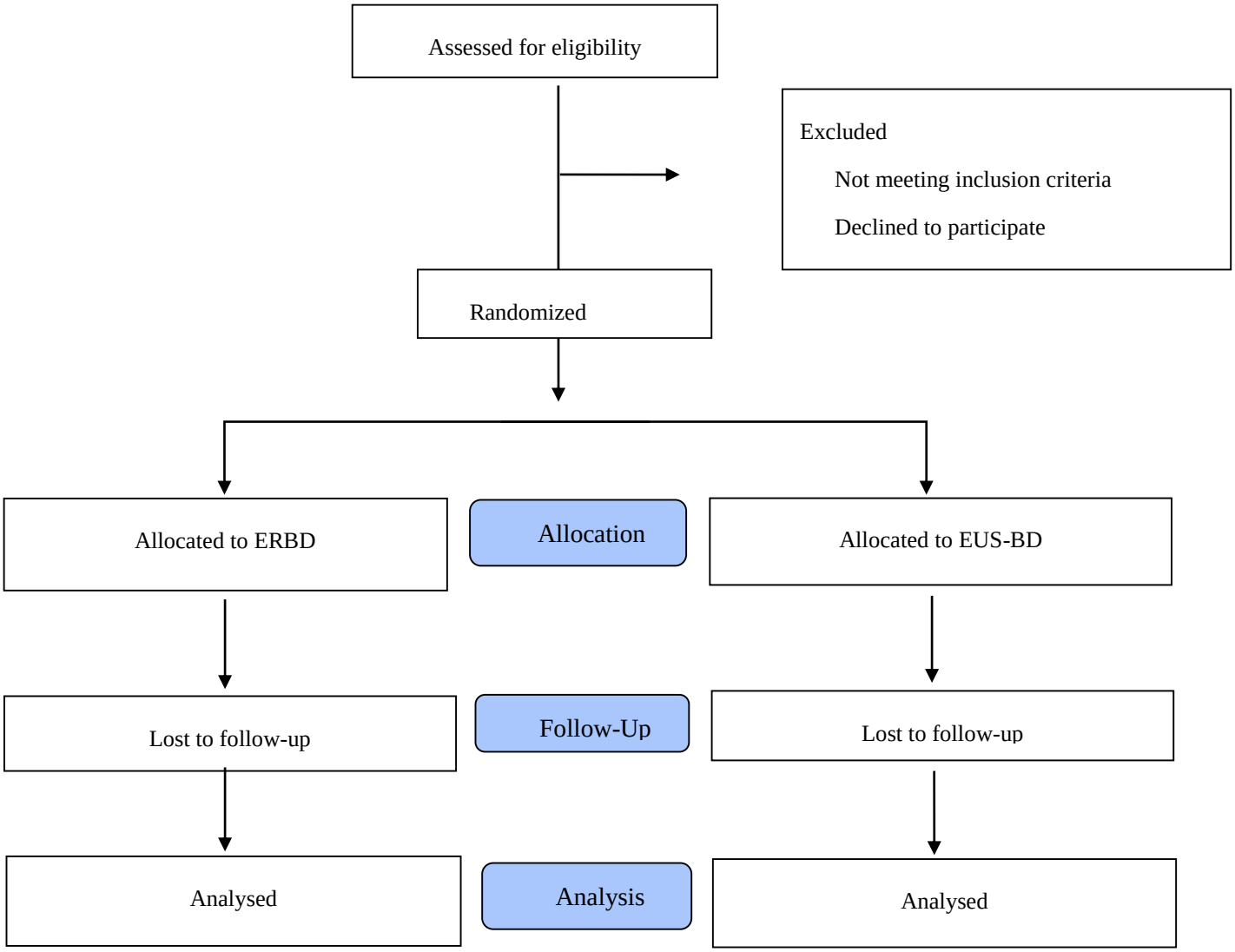
9) Hospital stay

10) QOL

Statistical analysis

The primary analysis was a noninferiority comparison between transpapillary and transmural stenting for technical success rates. The assumed technical success rate for transpapillary approach was 95%.[2] We set a margin of noninferiority for a technical success rate between transpapillary and transmural stenting as 10% according to the results of a pooled analysis.[23] To achieve a statistical power of 80% with the assumption of a 1-sided type I error rate of 5%, a total of (59 per group) was calculated. Considering a 5% of drop-out rate, we calculated a final sample size of 124 of patients (62 per group). Sample size and power were calculated using the PASS 12 program (NCSS, Kaysville, UT). The noninferiority hypothesis for primary outcome is assessed using the Z-test with a 95% one-sided confidence interval of the difference in the technical success rate and the margin of noninferiority. The characteristics of the study groups will be compared using Student *t* tests for continuous variables and a Pearson chi-square test or the Fisher exact test for categorical variables. Overall survival and stent patency will be calculated by the Kaplan-Meier method with use of the log-rank test. The QOL score analysis will be performed with a Student *t* test for comparison of difference of the score between baseline and 4 or 12 weeks. A P value of less than 0.05 is considered statistically significant.

2. Study flow chart



	1st Admission	Post procedure			Follow-up
		After 24 hours	After 1 week	After 1 month	Admission for managing complication or per 1 months
Demographics	▲				
Chemical test	▲	▲	▲	▲	▲
CT (tumor response)	▲				△
Histologic test	▲				
Inclusion/exclusion criteria	▲				
EUS-BD or ERBD	▲				
Procedure-related adverse events and unscheduled re-intervnetion	▲	▲	▲	▲	▲
Bile duct decompression (EUS-BD, ERBD)	▲	▲	▲	▲	▲
EORTC-OLQ-30	▲			▲	▲
Mortality		▲	▲	▲	▲

* ▲ = prerequisite data, △ = optional data

3. List of abbreviation

Acronym	Definition
ERCP	Endoscopic Retrograde Cholangiopancreatogram
ERBD	Endoscopic Retrograde Biliary Drainage
EUS-BD	Endoscopic ultrasonography guided biliary drainage
EUS-CD	Endoscopic ultrasonography guided choledochoduodenostomy
EUS-HG	Endoscopic ultrasonography guided hepaticogastrostomy
PTBD	Percutaneous Transhepatic Biliary Drainage

4. Quality control and quality assurance

4.1 Ethics and Responsibility

This study will be conducted in compliance with the protocol, the Sponsors' standard operating procedures and local regulations where applicable, the International Conference on Harmonization (ICH) GCP guidelines and the Declaration of Helsinki.

4.2 Confidentiality

All information generated in this study must be considered highly confidential and must not be disclosed to any persons not directly concerned with the study without written prior permission from the Sponsor. However, authorized regulatory officials and Sponsor personnel will be allowed full access to the records.

Only initials and unique patient numbers in case report forms will identify patients. All medications provided and patient bodily fluids and/or other materials collected specifically for this trial shall be used solely in accordance with this protocol, unless otherwise agreed to in writing by the Sponsor.

5. Background

Transpapillary stent placement with endoscopic retrograde cholangiopancreatography (ERCP) has been the preferred treatment for the palliation of malignant distal biliary obstruction.[1, 24, 25] However, after the procedure, acute pancreatitis, cholangitis, stent occlusion or migration, and cholecystitis account for substantial morbidity and are not preventable.[2, 3] The overall adverse event rate related to transpapillary stenting range from 28% to 36%.[21, 26, 27] Acute pancreatitis is the most common and feared adverse event after transpapillary approach, with reported rates ranged from 2% to 18%.[2, 21, 26, 27] Moreover, duodenal stricture is often accompanied with malignant distal biliary obstruction, making transpapillary approach technically difficult or impossible.[2]

Transmural stent placement under endoscopic ultrasound (EUS) guidance has emerged as an alternative procedure to percutaneous transhepatic biliary drainage after failed transpapillary stenting.[10, 20] Recent meta-analysis showed that transmural stenting is an effective alternative procedure for relieving biliary obstruction when performed in expert centers with appropriate training and skill.[20] Theoretically, transmural stenting has some advantages compared to transpapillary stenting: 1) no need to traverse the papilla, 2) available even if the ampulla is inaccessible with endoscopy, and 3) no need to place the stent thorough the biliary stricture.[21, 22] However, there is a dearth of clinical study about a primary palliation of cholestasis with EUS-guided transmural stenting. Moreover, there is no prospective comparative study between transpapillary and transmural stent placement. Therefore, we aimed to evaluate the noninferiority of transmural stenting compared to transpapillary stenting as a primary palliation of malignant distal biliary obstruction.

6. Trial Objectives and Hypotheses

The primary objective of this trial is to evaluate the technical success of EUS-BD compared with ERBD in unresectable malingnant distal biliary obstruction. The alternative hypothesis is that the EUS-BD is not inferior to the conventional ERBD.

6.1 Primary endpoint:

The primary end point is technical success of EUS-BD and ERBD.

6.2 Secondary endpoint

The secondary end points are functional success, re-intervention rate, cost-effectiveness, and complications.

7. Trial Design

This study is a multicenter, open label, prospective, non-inferiority, randomized trial to compare the efficacy of EUS-BD with ERBD for patients with unresectable malignant distal biliary obstruction

8. Subjective & methods

8.1 Study protocol

This study is a multicenter, open label, prospective, randomized, noninferiority trial to compare the technical outcomes of EUS-BD and ERBD with malignant distal biliary obstruction.

Eligible patients will be randomized 1:1 ratio to (1) EUS-BD, (2) ERBD.

Each hospital's Institutional Review Board approved the study protocol and we obtained specific informed consents for EUS-BDS or ERBD from each patient before the each procedure.

Four tertiary academic referral centers in South Korea performed ERCPs to relieve malignant obstructive jaundice.

- Asan Medical Center, Seoul

- SoonChunHyang University Cheonan Hospital, Cheonan

- Inje University Ilsan Paik Hospital, Goyang

- Dankook University Hospital, Cheonan

8.2 Endpoints

The primary end point is primary technical success of EUS-BD and ERBD.

The secondary end points are functional success, re-intervention rate, cost-effectiveness and complications.

8.3 Study timeline

Overall study will require 12 months between May 2015 and June 2017.

8.4 Inclusion criteria

1) Presence of unresectable malignant distal biliary obstruction (i.e., pancreatic cancer, cholangiocarcinoma, ampulla of Vater cancer, gallbladder cancer, duodenal cancer, and metastatic biliary obstruction)

2) Histologic or radiologic diagnosis of malignancy prior to endoscopic intervention

3) A Karnofsky index of ≧30%

4) No serious or uncontrolled medical illness

5) Provided informed consent

8.5 Exclusion criteria

1) Patient age of less than 18 years

2) Uncorrectable coagulopathy

3) History of allergy to radiocontrast agents

4) Hilar biliary obstruction

5) Refusal to participate in this study

9. Randomization

Eligible patients are randomly assigned to EUS-BD or ERBD in a one-to-one ratio without risk stratification. We obtained sequentially numbered, opaque, sealed envelopes with computer-generated random numbers using a block randomization (block size of 4) from a statistician. The randomization assignment was opened by one of the attending nurses, and the allocation sequence was concealed from all patients and operators before procedure in the endoscopic suite.

10. Protocol Procedures

10.1 EUS-guided biliary drainage (EUS-BD)

We administered broad spectrum prophylactic antibiotics directed against gram positive and gram negative organisms before the procedure to minimize the risk of sepsis and abscess formation. EUS-BD was performed using a linear-array echoendoscope (GF-UCT 240-AL 10 or AL 5, Olympus Medical Systems, Tokyo, Japan) at the same place on the same time. EUS-BD was performed by EUS-guided hepaticogastrostomy (EUS-HG) or EUS-guided choledocoduodeostomy (EUS-CD) according to the specific situations. EUS-HG was performed in patients with hilar stricture or altered anatomy such as

subtotal gastrectomy with Billroth II anastomosis or Roux-en-Y anastomosis, and EUS-CD was attempted in patients with mid to distal extrahepatic bile duct obstructions. We usually access the dilated ducts of segment 2 or 3 with the echoendoscope placed at the cardia or lesser curvature of the stomach and the dilated extrahepatic duct with the endoscope position in the duodenal bulb. The initial puncture was performed under real-time ultrasound and color doppler guidance, to avoid intervening blood vessels. We punctured the bile duct using a 19-gauge fine needle aspiration needle (EUSN-19-T, Cook Endoscopy, Winston-Salem, NC) and aspirated bile to confirm position followed by cholangiography to delineate the dilated bile duct and stricture. Next, we inserted a 0.025-inch guidewire (VisiGlide, Olympus Medical Systems, Tokyo, Japan) through the EUS-guided 19-G needle and coiled it into the bile duct lumen for transluminal stent placement. EUS-BD was performed according to the direction that the guidewire was inserted into the CBD and IHD. Without using a graded dilation catheter, bougie, or needle-knife cautery, the delivery system was directly inserted and the preloaded metallic stent within the catheter then sequentially deployed over the guidewire.

The newly modified delivery introducer (Standard Sci Tech Inc., Seoul, South Korea) which is advanced from animal study, has 3F catheter with 4F smooth tapered metal tip for simple puncture of the intestinal wall and liver parenchyma without the need of graded dilation devices. The outer sheath of the delivery catheter is size 7F, which provides good pushability and adequate resistance.[28] A self-expandable metal stent, consisting of both uncovered and nitinol-covered portions, was preloaded into the catheter. The uncovered proximal end of the stent (8 mm in diameter and 15 mm in length), which is funnel shaped to prevent small-branched bile duct obstruction and distal migration, was placed into the bile duct. The body and distal portions of the stent were covered with a silicone membrane (6 mm in diameter and 35 or 45 mm in length) for the prevention of bile leaks, and the distal end was equipped with four flaps for the prevention of inward stent migration.[28]

10.2 Endoscopic retrograde biliary drainage (ERBD)

ERBD was performed in randomly selected patients with unresectable malignant distal biliary obstruction. Prophylactic antibiotics was administered before the start of the intervention. ERBD was performed using a standard duodenoscope or cap-assisted forward scope when patients had surgically altered anatomy as Billroth II anastomosis with the patient under conscious sedation with midazolam and meperidine. After biliary cannulation, contrast media was injected to obtain cholangiogram. Then, a guidewire was passed through the stricture, and sphincterotomy was done. Finally, self-expandable metal stent was placed across the papilla

11. Post Procedure Management: Follow-up phase

All patients will be evaluated before the ERCP, 24 hours, 1 week, and 1-month after EUS-BD or ERBD. Then liver function test will be assessed every one month. We followed up the patients for one year after the procedures or until death. If previously placed metal stents show an early clogging, stent revision or additional PTBD was considered for biliary decompression. All parameters were recorded by study coordinators and monitored by a data and safety monitoring board (Division of Hepatobiliary and Pancreatic Surgery, Jae Hoon Lee, and Division of Gastroenterology and Asan Medical Center, Ji Yong Ahn).

12. Statistical analysis

12.1 Sample size calculation

The primary analysis was a noninferiority comparison between transpapillary and transmural stenting for technical success rates . The assumed technical success rate for transpapillary approach was 95%.[2] We set a margin of noninferiority for a technical success rate between transpapillary and transmural stenting as 10%

according to the results of a pooled analysis and after a discussion with the contributing physicians, who stated that this noninferiority margin of 10% would be clinically relevant. To achieve a statistical power of 80% with the assumption of a 1-sided type I error rate of 5%, a total of (59 per group) was calculated. Assuming there is a 5% drop-out rate, we calculated a final sample size of 124 patients (62 per group). Sample size was calculated using the PASS 12 program (NCSS, Kaysville, UT) by a statistical expert.

12.2 Data from study sites

Idependent data management survice (Clinical Trial Center [CTC] in Asan Medical Center) contracted to manage multi-center study data. Electronic (web-based) submission of de-identified subject data approved by institutional review board (IRB).

Categorical parameters were compared by a chi-square test and Fisher's exact test, and continuous variables were compared by Student's t-test. Cumulative patency duration was estimated using the Kaplan-Meier technique and compared by using the log-rank test. All statistical analyses were performed using SAS software (version 9.4; SAS Institute, Cary, NC), with results considered significant at P-value <0.05.

13 Adverse Events/Serious Adverse Events

13.1 Adverse Event

For the purpose of this trial, an adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation subject enrolled in a device clinical study and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom or disease temporally associated with the study procedures, whether or not considered related to the investigational device or procedure.

Grade refers to the relationship of the adverse event.

a. definitely not related

a. probably related

b. possibly related

c. definitely related

Grade refers to the severity of the adverse event.

a. Mild; asymptomatic or mild symptoms

b. Moderate; local or noninvasive intervention indicated; limiting

c. Severe; Medically significant, hospitalization or prolongation of hospitalization indicated

Grade refers to the intervention for the adverse event

a. None

b. Medicated therapeutic drug

c. Hopitalization

13.2 Serious Adverse Event (SAE)

An adverse event is considered serious for this trial if it meets one or more of the following criteria and is device-related:

Results in death

Is life-threatening, *i.e.*, the patient was, in the opinion of the Investigator, at immediate risk of death from the event as it occurred *(It does not include an event that, had it occurred in a more severe form, might have caused death.)*

Results in persistent or significant disability (significant, persistent or permanent change or disruption in patient's body function/structure, physical activity or quality of life

Requires in-patient hospitalization or prolongs hospitalization

13.3 Notification of adverse event

All events meeting the AE/SAE criteria must be reported to the Safety committee and IRB within 24 hours of becoming aware of the events.

Adverse events	Date	Severity of the adverse event	Relationship	Intervention	Others
Symptom/ sign	(yr/m/d)	1. Mild; asymptomatic or mild symptoms 2. Moderate; local or noninvasive intervention indicated; limiting 3. Medically significant, hospitalization or prolongation of hospitalization indicated	1. Definitely not related 2. Probably related 3. Possibly related 4. Definitely related	1. None 2. Dosage change or stop 3. Medicated therapeutic drug 4. Hopitalization 5. Withdrawal	
Events		① ② ③	① ② ③ ④	① ② ③ ④ ⑤	
	□ Unknown				
		① ② ③	① ② ③ ④	① ② ③ ④ ⑤	
	□ Unknown				
		① ② ③	① ② ③ ④	① ② ③ ④ ⑤	

Definition of adverse events

Based on the timing, procedure (EUS-BD and ERBD)-related adverse events was defined as intra-

procedure if it occurred during procedure or in recovery area, or post-procedure within in 14 days after procedure.[15, 16] Procedure-related adverse events were also described using the Common Technology Criteria for Adverse Events (CTCAE) v 3.0 and 4.0. Severity of adverse events was graded as mild, moderate, severe and fatal according to the ASGE classification.[29] Procedure-related adverse events were defined as mild or moderate if patients required less than 4 nights or between 4 to 10 nights of hospitalization respectively. They were classified as severe if unplanned or prolonged hospitalization was required for more than 10 nights or required intensive care unit or surgery.[29] Bile leak was defined as cholangiographic evidence of contrast leaking from the opacified bile ducts during procedure without post-procedure peritoneal irritation. Bile peritonitis was defined as bile leakage with signs of peritoneal irritation. Self-limited pneumoperitoneum was defined as intraperitoneal air on radiologic imaging without peritoneal irritation.

Biliary re-intervention was defined as any type of scheduled or unscheduled endoscopic, percutaneous, or surgical procedure that was required to improve biliary drainage after EUS-BD or ERBD.[17] Stent occlusion was defined as the recurrence of jaundice and cholestasis, and/or evidence of a dilated biliary system on ultrasound or computed tomography (CT) with a direct view of the upper endoscope, requiring biliary intervention.[17]

14. Investigational Agreement

I have read and understand the protocol (including the Investigator's Brochure) and agree that it contains all the ethical, legal and scientific information necessary to conduct this Trial. I will personally conduct the

study as described.

I will provide copies of the protocol to all physicians, nurses and other professional personnel responsible to me who will participate in the study. I will discuss the protocol with them to assure myself that they are sufficiently informed regarding the devices used in the study, the concurrent medications, the efficacy and safety parameters and the conduct of the study in general. I am aware that this protocol must be approved by the Institutional Review Board (IRB) responsible for such matters in the Clinical Study Facility where the device and drug will be tested, prior to commencement of this study. I agree to adhere strictly to the attached protocol. I understand that this IRB approved protocol will be submitted to the authorities by the Sponsor, as appropriate. I agree that clinical data entered on case report forms by me and my staff will be utilized by the Sponsor in various ways such as for submission to governmental regulatory authorities and/or in combination with clinical data gathered from other research sites, whenever applicable. I agree to allow Sponsor monitors and auditors as well as inspectors from regulatory authorities, full access to all medical records at the research facility for patients screened or randomized in the study.

I agree to provide all patients with informed consent forms, as required by government and ICH regulations.

I further agree to report to the Sponsor any adverse experiences in accordance with the terms of this protocol, KFDA regulation, and ICH guideline.

Principal Investigator (print)

Do Hyun Park

Principal Investigator (signature) Date 8/7/2017

Institution Name/Location

Asan Medical Center/Seoul

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List of Committees and Participating Centers

	Centers	Investigators
Sponsor	Health and Welfare Administation	Do Hyun Park, MD
Executive Committee	Asan Medical Center	Do Hyun Park, MD

Data Safety Monitoring Board	Asan Medical Center	Jae Hoon Lee, MD Ji Yong Ahn, MD
Data Coordinating Center	Asan Medical Center (Web-based data management, Medrio)	Hye Ran Kang, Hye Sun Hwang, Sun Hyung Hur, Ji Seon Lee
Participating Centers 1	Asan Medical Center, Seoul	Do Hyun Park, MD
2	SoonChunHyang University Cheonan Hospital	Tae Hoon Lee, MD
3	Inje University Ilsan Paik Hospital	Woo Hyun Paik, MD
4	Dankook University Hospital	Jun-Ho Choi, MD

Case report form (CRF)

Title: **Effect of Primary Endoscopic Ultrasound-Guided Transmural Biliary Drainage for Malignant Distal Biliary Obstruction: A Multicenter Randomized Trial**

Institute No.	

Principal investigator	
Case No	
Patient initial	

I. Basic information

Hospital Name:

Sex/Age:

ASA class:

Underlying disease:

1) pancreatic cancer, 2) common bile duct cancer, 4) ampullary cancer,

5) gallbladder cancer, 6) hepatocellular carcinoma, 7) duodenal cancer, 8) metastatic malignancy,

9) Others:

Dilated CBD diameter:_____/_____mm

Laboratory findings:

Date		Pre-intervention	Post-intervention, 24hr	Post-intervention, 1 week	1 month later
Hematology	Hemoglobin				
	Leukocyte				
	Platelet				
Chemistry	Total bilirubin				
	AST				
	ALT				
	ALP				
	r-GT				
	Amylase				
	Lipase				

II. Technical results

Intervention: date (yy/mm/dd): (/ /)

If, EUS-BD: Stent type; diameter (mm)/ length (cm); /

Additional dilatation method: (Y/N)

Group

☐ EUS-BD ☐ ERCP

[Check if EUS-BD]

Drainage Method

☐ EUS-CD ☐ EUS-Choledochoantrostomy ☐ EUS-HG

IHD Diameter(##)

_____ mm

Surgically Altered Anatomy Type

☐ B-II ☐ Roux-en-Y op.

==========

Technical Success

Date of Biliary Drainage

month _____ day _____ year _____

Technical Success

(Intention-To-Treat)

☐ No ☐ Yes

Reasons of Technical Failure

☐ Duodenal Bulb Deformity

☐ Portal Vein Collaterals

☐ Transmural Fistula Dilation Failure

☐ Duodenal Bulb Obstruction

☐ Failed Guide Wire Manipulation to Proximal Bile Duct

☐ Insufficient Intrahepatic Ductal Dilatation

☐ Periampullary Tumor Infiltration with Duodenal Invasion

☐ Surgically Altered Anatomy

Cross-Over

☐ EUS-BD Fail로 ERCP

☐ EUS-BD Fail로 PTBD

☐ ERCP Fail로 EUS-BD

☐ ERCP Fail로 PTBD

Procedure Time (###)

(Time from biliary cannulation to stent placement in transpapillary stenting group, and time from needle puncture of the dilated bile duct to stent placement in transmural stenting group)

_____ min

Stent Length (cm)

☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10

[Check if ERCP]

Precutting

☐ No ☐ Yes

Stent Type

☐ Covered ☐ Uncovered

==========

Tract Dilatation

Tract Dilatation

☐ No ☐ Yes

Type

- ☐ Bougie
- ☐ Needle Knife
- ☐ Cystotome
- ☐ Hurricane Balloon

III. Complications

Early complication (within 14 days): / date (/ /)

Late complication: / date (/ /)

Post-procedure Complications	□ **Y** □ **N**
Pancreatitis (Cotton criteria) **Abdominal pain, only**	□ **Y** □ **N** **If, yes**, grade:mild/mode/severe □ **Y** □ **N**
Bleeding **Treatment** **Treatment result**	□ **Y** (minor/major) □ **N** □ observation □ clip □ APC □ epinephrine injection □ complete hemostasis □ angiographic embolization □ operation
Perforation/self-limited pneumoperitoneum **Treatment** **Treatment result**	□ **Y/Y** □ **N/N** □ observation □ clipping □ operation □ self-sealed □ endoscopic closure □ surgical closed □ fail
Cholangitis	□ **Y** □ **N**
Cholecystitis	□ **Y** □ **N**
Bile leak	□ **Y** □ **N**
Biloma or bile peritonitis	□ **Y/Y** □ **N/N**
Sepsis	□ **Y** □ **N**
Hemobilia	□ **Y** (venous/arterial) □ **N** □ conservative □ angiographic embolization □ operation
Stent malfunction	□ **Y** □ **N** **If yes,** 1) occlusion by tumor ingrowth or overgrowth 2) clogging by sludge or food materials 3) migration, distal ( )/ proximal ( )
Mortality (cause)	□ **Y** □ **N** **( )**
Other complications	

IV.

Outcomes

Stent patency (time to recurrent biliary obstruction; patients were censored at surgery, last follow-up, or death):

Day

Stent malfunction cause: tumor ingrowth/overgrowth, stent migration (proxi/distal), clogging, others ( )

Revision, date (/ /) (_____day from stent placement)

Revision method: transpapillary/transmural/PTBD,

Bilateral, right or left, CBD

Result- Success or Fail

Last follow-up date:

Survival: _____day, alive/death

V. Pain Score modified from C30/PAN26

Pre and Post-procedure pain score (before intervention/ past one week; 0~10): (/)

Follow up

Visit	Visit 1 Intervention	Visit 1 24 hrs	Visit 2 4 wks	Visit 3 8 wks	Visit 4 12 wks	Visit 5 ( ) wks
Exclusion criteria	X					
Basic information	X					
Past history	X					
Randomization	X					
EUS-BD/ ERBD	X					
Laboratory data	X	X	X	X	X	X
Complications		X	X	X	X	X
Outcomes		X	X	X	X	X
Informed consent	X					

agreement						
Serious adverse events		X	X	X	X	X

Admission . . .

YY MM DD

[Informed Consent]

Agree with informed consent ☐ Yes ☐ No

동의일 . . .

YY MM DD

[Demographic Data]

Age years Gender ☐ Male ☐ Female

[Diagnosis]

Diagnosis	☐ Pancreatic cancer ☐ Common bile duct cancer ☐ Gallbladder cancer ☐ Ampulla of Vater cancer ☐ Metastatic lymph nodes ☐ Others (_____)
Duodenal Obstruction	☐ No ☐ Yes
Type	☐ Type 1 ☐ Type 2 ☐ Type 3
Date of Duodenal Stent Insertion	month _____ day _____ year _____
Duodenal Stent Patency	_____ 일

[Chemistry]

. . .

YY MM DD

Contents	Level	Units
WBC		/mm^3
Amylase/Lipase		IU/L
CA 19-9		U/mL
Total bilirubin		mg/dL
Direct bilirubin		mg/dL
Alkaline phosphatase		IU/L
AST		IU/L
ALT		IU/L
GGT		IU/L

[Randomization]

Randomization ☐ Yes ☐ No

Code number ☐

. . .

Investigator's signature _____ Date

YY MM DD

[Procedure]

Randomized procedure ? ☐ Yes ☐ No

Procedure ☐ ERBD ☐ EUS-BD

Technical success ☐ Yes ☐ No

Date . . .

YY MM DD

Stent length:_____ cm

. . .

Investigator's signature _____ Date

YY MM DD

[Adverse Events]

☐ No

Adverse events	Start YY/MM/DD End YY/MM/DD	Seriousness 0= Not serious 1= Serious	Severity 1=Mild 2=Moderate 3=Severe 4=life threatening	Relation 0= not related 1 = related	Outcome 0=recovery 1=persist

Investigator's signature _____ Date . . .
년YY 월MM 일DD

End of Study

End of Study

Date

month _____ day _____ year _____

Completion of study

☐ No ☐ Yes

Reason for suspension of clinical trial

☐ Severe adverse event
☐ Decision by the investigator
☐ Follow up loss
☐ Others

Comment

_____

Appendix C. EORTC QLQ-C30 (3판) Korean version

귀하와 귀하의 건강 상태에 대하여 몇 가지 조사하고자 합니다. 모든 질문에 대한 응답은 귀하 스스로 해주시고, 각 문항마다 귀하와 가장 가깝다고 생각되는 부분에 동그라미 표시를 해 주시기 바랍니다. 본 질의서에 게재되어 있는 질문에는 정답이나 오답이 정해져 있지 않으며 귀하가 제공하는 모든 정보에 대한 비밀은 엄격히 보호됩니다.

귀하의 성명을 적어 주십시오(　　)

생년월일 : _____년 _____월 _____일

작 성 일 : _____년 _____월 _____일

1 전혀 아니다 / 2 약간 그렇다/ 3 꽤 그렇다 / 4 매우 그렇다

1 무거운 쇼핑 백이나 가방을 옮길 때처럼 힘을 쓰는 일을

할 때 곤란을 느끼십니까? 1 2 3 4

2 오래 걷는 것이 힘이 드십니까? 1 2 3 4

3 집 밖에서 잠깐 걷는 것이 힘이 드십니까? 1 2 3 4

4 낮 시간 중에 자리(침대)에 눕거나 의자에 기대고 싶습니까? 1 2 3 4

5 식사 도중 혹은 옷을 입는 동안, 세면을 할 때나 화장실 이용할 때 누군가의 도움이 필요합니까? 1 2 3 4

* 지난 한 주를 기준으로 답변하여 주십시오.

1 전혀 아니다 / 2 약간 그렇다/ 3 꽤 그렇다 / 4 매우 그렇다

6 일을 하거나 기타 일상생활을 영위하는데 한계를 느낀 적이 있습니까? 1 2 3 4

7 취미생활이나 여가활동을 하는데 있어 한계를 느낀 적이 있습니까? 1 2 3 4

8 숨이 가쁜 적이 있습니까? 1 2 3 4

9 통증을 느껴 본 적이 있습니까? 1 2 3 4

10 휴식이 필요하다고 생각한 적이 있습니까? 1 2 3 4

11 숙면을 취하는데 곤란을 느낀 적이 있습니까? 1 2 3 4

12 몸이 허하다고 느낀 적이 있습니까? 1 2 3 4

13 식욕이 감퇴하셨습니까? 1 2 3 4

14 속이 메스꺼운 적이 있습니까? 1 2 3 4

15 구토를 하신 적이 있습니까? 1 2 3 4

다음 페이지로 가십시오

* 지난 한 주를 기준으로 답변하여 주십시오.

1 전혀 아니다 / 2 약간 그렇다/ 3 꽤 그렇다 / 4 매우 그렇다

16 변비 증세를 경험한 적이 있습니까? 1 2 3 4

17 설사를 한 적이 있습니까? 1 2 3 4

18 피로를 느끼셨습니까? 1 2 3 4

19 통증으로 인해 일상생활을 영위하는데 지장을 받은 경험이 있습니까? 1 2 3 4

20 신문을 읽거나 텔레비전을 시청할 때 집중하는 데 곤란을 겪은 경험이 있습니까? 1 2 3 4

21 긴장감을 느끼셨습니까? 1 2 3 4

22 걱정에 시달리셨습니까? 1 2 3 4

23 짜증을 느끼셨습니까? 1 2 3 4

24 우울함을 느끼셨습니까? 1 2 3 4

25 기억력 감퇴를 느끼셨습니까? 1 2 3 4

26 귀하의 건강상태나 의약치료가 귀하의 가정 생활에 어떤 곤란을 야기 했습니까? 1 2 3 4

27 귀하의 건강상태나 의약치료가 귀하의 사회 생활에 어떤 곤란을 야기 했습니까? 1 2 3 4

28 귀하의 건강상태나 의약치료로 인하여 경제적인 어려움을 겪으셨습니까? 1 2 3 4

* 다음 문항을 읽고 1에서 7까지 번호 중 귀하와 가장 가깝다고 생각되는 번호에 동그라미 표시를 해 주시기 바랍니다.

29. 지난 한 주간의 전반적인 귀하의 건강 상태를 평가하신다면 다음 중 어디에 해당합니까?

1 2 3 4 5 6 7

매우 나쁨 아주 좋음

30. 지난 한 주간의 전반적인 귀하의 삶의 질을 평가하신다면 다음 중 어디에 해당합니까?

1 2 3 4 5 6 7

매우 나쁨 아주 좋음

Summary of changes (amendments) in protocol

4/5/2016

1.Study coordinator was changed (from Hye Ran Kang to Hye Sun Hwang).

6/2/2016

1. Study period was extended due to slow enrollement of patients until June 2017.

8/3/2016

1.Idependent data management service (Clinical Trial Center [CTC] in Asan Medical Center) contracted to manage multi-center study data.

2.Electronic (web-based) submission of de-identified subject data approved by institutional review board (IRB).

Final Statistical Analytic Plan

The primary analysis was a noninferiority comparison between transpapillary and transmural stenting for technical success rates. The assumed technical success rate for transpapillary approach was 95%. We set a margin of noninferiority for a technical success rate between transpapillary and transmural stenting as 10% according to the results of a pooled analysis and after a discussion with the contributing physicians, who stated that this noninferiority margin of 10% would be clinically relevant. To achieve a statistical power of 80% with the assumption of a 1-sided type I error rate of 5%, a total of (59 per group) was calculated. Assuming there is a 5% drop-out rate, we calculated a final sample size of 124 patients (62 per group). Sample size was calculated using the PASS 12 program (NCSS, Kaysville, UT) by a statistical expert (S.O.K.).

Summary of changes

8/7/2017

1.Statistical expert for data analysis was changed from Ji Sung Lee (Soonchunhyang University) to Seon-Ok Kim (Asan Medical Center) due to the carrer change of Ji Sung Lee to other university.