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# Early and long-term clinical outcomes of endoscopic interventions for benign pancreatic duct stricture/obstruction-the possibility of additional clinical effects of endoscopic ultrasonography-guided pancreatic drainage-

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ABSTRACT

*Objectives:* For benign pancreatic duct strictures/obstructions (BPDS/O), endoscopic ultrasonography-guided pancreatic drainage (EUS-PD) is performed when endoscopic transpapillary pancreatic drainage (ETPD) fails. We clarified the clinical outcomes for patients with BPDS/O who underwent endoscopic interventions through the era where EUS-PD was available.
*Methods:* Forty-five patients with BPDS/O who underwent ETPD/EUS-PD were included. We retrospectively investigated overall technical and clinical success rates for endoscopic interventions, adverse events, and clinical outcomes after successful endoscopic interventions.
*Results:* The technical success rates for ETPD and EUS-PD were 77% (35/45) and 80% (8/10), respectively, and the overall technical success rate using two drainage procedures was 91% (41/45). Among the 41 patients who underwent successful endoscopic procedures, the clinical success rates were 97% for the symptomatic patients (35/36). The rates of procedure-related pancreatitis after ETPD and EUS-PD were 13% and 30%, respectively. After successful endoscopic interventions, the cumulative 3-year rate of developing recurrent symptoms/pancreatitis was calculated to be 27%, and only two patients finally needed surgery. Continuous smoking after endoscopic interventions was shown to be a risk factor for developing recurrent symptoms/pancreatitis.
*Conclusions:* By adding EUS-PD to ETPD, the technical success rate for endoscopic interventions for BPDS/O was more than 90%, and the clinical success rate was nearly 100%. Due to the low rate of surgery after endoscopic interventions, including EUS-PD, for patients with BPDS/O, EUS-PD may contribute to their good clinical courses as a salvage treatment for refractory BPDS/O.


## 1. Introduction

Pancreatic diseases with benign main pancreatic duct (MPD) strictures/obstructions (BPDS/O), including chronic pancreatitis, often cause paroxysmal or persistent abdominal pain due to an increase in the internal pressure of the MPD [1]. For symptomatic patients with BPDS/O, their symptoms are usually improved with treatments for reducing the internal pressure of the MPD. From the results of three randomized controlled trials for symptomatic patients with chronic pancreatitis, surgical treatments are better than endoscopic interventions from a comparison of the rates of symptom recovery [2–4] and the long-term clinical outcomes [2,5]. However, in the guidelines for the management of symptomatic

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chronic pancreatitis, endoscopic therapy and/or extracorporeal shock wave lithotripsy (ESWL) are recommended as the first -line of therapy for painful chronic pancreatitis in terms of its invasiveness and its applicability toward the elderly and patients with several co-morbidities [1,6]. Thus, surgical treatments should be considered if endoscopic interventions appear unsatisfactory for pain relief [1,6].

Endoscopic transpapillary pancreatic drainage (ETPD) with/without ESWL is considered as a first-line endoscopic therapy for BPDS/O [5,6]. For BPDS/O with pancreatic stones likely to prevent ETPD, ESWL facilitates the endoscopic extraction of pancreatic stones and increases the success rate of pancreatic duct drainage [7,8]. On the other hand, it is sometimes difficult to perform ETPD when patients have a completely obstructed MPD, a meandering MPD, large pancreatic stones, or altered anatomy [9–13]. We have recently performed endoscopic ultrasound-guided pancreatic duct drainage (EUS-PD) for patients with BPDS/O for whom ETPD was unsuccessful. In recent studies involving EUS-PD, relatively good technical success rates (50%–100%) have been reported, but the rates of adverse events (7%–55%) are relatively high [10–20].

At the same time, the additional effects of EUS-PD on the overall outcomes of endoscopic interventions have not been studied yet, and reports on the long-term clinical outcomes after EUS-PD for the BPDS/O are lacking. Therefore, we sought to clarify the above-mentioned issues, which are associated with the clinical implications of EUS-PD as a salvage treatment for patients with BPDS/O, by retrospectively investigating the results of endoscopic monotherapy for the BPDS/O after EUS-PD became available in our hospital.

## 2. Patients and methods

### 2.1. Inclusion and exclusion criteria

This study was approved by the ethic committee at the Sendai City Medical Center (registration number: 2019–0032). In this study, we included the patients who underwent endoscopic monotherapy, including EUS-PD, due to 1) having symptomatic BPDS/O or 2) asymptomatic BPDS/O caused by pancreatic diseases apart from chronic pancreatitis and involved with progression of upstream MPD dilation which possibly may have caused pancreatic exocrine and endocrine insufficiency after EUS-PD became available in our hospital. On the other hand, we excluded patients with BPDS/O involving the pancreatic stones with the sizes of $\geq$5 mm because they were possibly indicated for ESWL.

### 2.2. Treatment strategy for BPDS/O

Indications for endoscopic interventions for patients with BPDS/O were as follows: 1) symptomatic patients with chronic pancreatitis [21] and 2) patients with pancreatic diseases apart from chronic pancreatitis who had clinical problems, such as abdominal symptoms and progressive upstream MPD dilation.

For the patients indicated for endoscopic interventions, we firstly perform transpapillary or transanastomotic endoscopic approach. If pancreatic stones prevent endoscopic interventions for BPDS/O, we endoscopically remove them. When ETPD does not work, we generally perform EUS-PD as a secondary treatment. For patients with the BPDS/O of pancreaticojejuno anastomosis after pancreatoduodenectomy, for which ETPD appears difficult in consideration of the previous reports [11,22,23], EUS-PD is recently allowed to be undertaken as an initial endoscopic intervention. If all endoscopic procedures fail or uncontrolled symptoms/pancreatitis occurs after endoscopic interventions, surgical treatment is used to control the patients' clinical conditions.

### 2.3. Outcome measurements

We retrospectively investigated the following by using the clinical databases of our medical center: 1) overall technical success rates of endoscopic interventions, 2) overall clinical success rates of endoscopic interventions, 3) adverse events related to the endoscopic procedures, and 4) long-term clinical outcomes during surveillance after successful endoscopic interventions.

### 2.4. Definitions

Technical success was determined when endoscopic stenting or adequate balloon dilation for BPDS/O could be performed. When pancreatic stones prevented successful endoscopic interventions for BPDS/O, technical success was needed to achieve the remove of pancreatic stones.

Regarding clinical success, abdominal symptoms were evaluated by using the following pain scoring system: no abdominal pain, 0; controllable abdominal pain without medication, 1; controllable abdominal pain with medication, 2; uncontrollable abdominal pain with medication, 3. For symptomatic patients, clinical success was defined as a decrease in the pain score of $\geq$1 point after endoscopic interventions. In addition, the change in the upstream MPD diameter determined by using contrast enhanced computed tomography or magnetic resonance cholangiopancreatography was investigated as a supplementary evaluation for clinical success.

### 2.5. Endoscopic procedures for ETPD

A duodenoscope (TJF-260V: Olympus Co., Tokyo, Japan) or balloon-assisted enteroscope (SIF TYPE Q260: Olympus Co.) was used to perform ETPD. During the performance of endoscopic retrograde pancreatography (ERP) with a cannula, the degree/length of BPDS/O and whether or not there are pancreatic stones in the MPD likely to prevent ETPD were evaluated. After a 0.025-inch guidewire could be passed through the BPDS/O, we performed endoscopic pancreatic sphincterotomy and then dilated the BPDS/O with 7 Fr dilators and/or 4–6 mm balloon catheters. When the adequate dilation of the BPDS/O was not obtained by using these devises, the use of 8–10 Fr dilators and/or 8 mm balloon was considered. Although pancreatic stenting was usually carried out for the dilated BPDS/O, patients did not undergo pancreatic stenting only when the BPDS/O was confirmed to be completely dilated by using pancreatography for the BPDS/O. For endoscopic pancreatic stenting, a 7 Fr straight type or single pigtail type plastic stent was firstly used. When pancreatic stones prevented ETPD, we tried to remove them using a basket catheter.

In case of patients who underwent pancreatic stenting, a plastic stent placed over the BPDS/O was regularly exchanged for one with a larger diameter (8.5–10 Fr) every three months, and the BPDS/O was determined to be free of stenting if shown to be dilated up to the same diameter as a 10 Fr pancreatic stent approximately one year after initial ETPD.

### 2.6. Endoscopic procedures for EUS-PD

An endosonoscope (GF-UCT260, Olympus Co.) was used to visualize dilated MPD via the stomach. EUS-PD was carried out using a 19-gauge needle (Expect™: Boston Scientific Co., Marlborough, USA; EZ shot 3 plus: Olympus Co.). After the tip of the needle was confirmed to be inside the MPD by injecting contrast medium into the MPD, a 0.025-inch guidewire was carefully advanced into the inside of the MPD via the needle, and then advanced beyond the BPDS/O if possible. When the guidewire

could be passed through the BPDS/O, both an EUS-PD route, namely pancreaticogastrostomy, and the BPDS/O were dilated with a 7-Fr hard-type dilator (ES Dilator: Zeon Medical, Tokyo, Japan) and/or 4 mm balloon catheter (Max Force Biliary Balloon Dilation Catheter: Boston Scientific Japan). When the BPDS/O could be dilated, a 7-Fr straight type plastic stent was usually placed over the BPDS/O by the antegrade or rendezvous method, and then a 7-Fr straight type plastic stent was placed to maintain a pancreaticogastrostomy route. For patients with pancreatic diseases apart from chronic pancreatitis, when the BPDS/O was completely dilated, pancreatic stenting for the dilated BPDS/O was not performed. If the guidewire could be not passed through the BPDS/O, a plastic stent was deployed across the pancreaticogastrostomy route for the purpose of pancreatic drainage.

### 2.7. Adverse events related to endoscopic procedures

We evaluated the following adverse events which occurred during endoscopic procedures or within two weeks after endoscopic interventions: 1) abdominal pain or pancreatitis, 2) bleeding, 3) perforation, 4) cardiopulmonary adverse events and 5) death. Post-endoscopic retrograde cholangiopancreatography pancreatitis (PEP) was evaluated on the basis of the criteria proposed by Cotton et al. [24].

### 2.8. Statistical analyses

Pearson's $\chi 2$ test or Fisher's exact test was used for categorical variables. Student's t-test or the Mann-Whitney *U* test was used for continuous variables. To analyze risk factors for developing symptoms/acute pancreatitis after successful endoscopic interventions, multivariate analysis was performed for the possible risk factors with p-values $< 0.2$ by using univariate analysis with a log-rank test. The Cox proportional hazard model was used for the multivariate analysis. A p-value of $<0.05$ was considered to be statistically significant. SPSS software (version 12; IBM Japan, Ltd., Tokyo, Japan) was used for all analyses in the study.

## 3. Results

### 3.1. Baseline characteristics of the patients

Of the consecutive 52 patients who were diagnosed to have BPDS/O indicated for endoscopic interventions after EUS-PD became available in our hospital (from January 2004 to August 2017), 45 patients were included in this study, and the remaining 7 patients were excluded due to the pancreatic stone with the sizes of $\geq$5 mm or pancreatic stones involving multiple pancreatic duct strictures, and these patients were referred to another hospital for the further treatments using ESWL.

Baseline characteristics of the 45 patients are shown in Table 1. The median age was 54 years (IQR: 45–60), and 33 were male. Underlying diseases causing the BPDS/O were chronic pancreatitis for 34, stricture/obstruction of the pancreaticojejuno anastomosis for 5, stricture/obstruction of the pancreatic duct orifice after endoscopic papillectomy for 3, and other benign pancreatic diseases for 3 patients. Of the 45 patients, 40 (89%) were symptomatic just before initial endoscopic pancreatic interventions. Although the remaining 5 patients were asymptomatic just before endotherapy, 2 patients had abdominal symptoms which originated in chronic pancreatitis during approximately 1–2 years before initial endotherapy in addition to having the BPDS/O involving a progressive upstream MPD dilation, and 3 patients had the BPDS/O with a progressive upstream MPD dilation caused by other pancreatic diseases.

### 3.2. Technical success rate of endoscopic procedures for BPDS/O

A flowchart of the endoscopic procedures for 45 patients with BPDS/O is shown in Fig. 1. Of the 45 patients, 43 underwent ETPD, and the remaining 2 underwent EUS-PD as an initial endoscopic intervention for BPDS/O. The technical success rate of ETPD was 77% (33/43). Among the 10 patients with failed ETPD, the guidewire could not be passed through the BPDS/O for 7 patients and the orifice at the enteric site of the pancreaticojejuno anastomosis could not be found endoscopically for 3 patients. Endoscopic procedures for patients with successful ETPD (n = 33) included pancreatic duct stenting for 21 (64%) and endoscopic dilation for the BPDS/O without pancreatic duct stenting for 12 patients. In addition, for 18 of the 33 patients with successful ETPD (55%), the removal of pancreatic stones was carried out. For the 10 patients for whom ETPD failed, 8 underwent EUS-PD as a secondary endoscopic procedure and the remaining 2 underwent no additional endoscopic interventions.

EUS-PD was performed for a total of 10 patients (initial intervention, n = 2; secondary, n = 8; the detail of the 10 patients is shown in Table 2), and the technical success rate was 80% (8/10) (EUS-guided pancreatic transluminal stenting without pancreatic stent placement for BPDS/O, n = 4; only antegrade balloon dilation for BPDS/O, n = 2; endoscopic pancreatic duct stenting for BPDS/O by using the rendezvous technique, n = 2). For 2 patients with failed EUS-PD, as the guidewire placed in the MPD was accidently deviated during the procedure, re-puncture for the MPD could not be performed due to the collapse of the MPD. Thus, for 6 of 8 patients with successful EUS-PD (75%), pancreatic stent placement was performed for an EUS-PD route and/or BPDS/O. In addition, the technical success rates of EUS-PD for each of underlying cause of BPDS/O were 75% (3/4) for chronic pancreatitis, 80% (4/5) for the stricture/obstruction of the pancreaticojejuno anastomosis, and 100% (1/1) for the stricture/obstruction of the pancreatic duct orifice after endoscopic papillectomy.

When adding the results of EUS-PD, the overall technical success rate of endoscopic procedures for the BPDS/O increased from 77% (33/43) to 91% (41/45). Of the 41 patients who underwent successful endoscopic procedures for BPDS/O, 27 underwent pancreatic stent placement for the BPDS/O or EUS-PD route and the remaining 14 underwent only endoscopic dilation, including the removal of pancreatic stones, for the BPDS/O. Regarding each of underlying cause of BPDS/O, the technical success rates of endoscopic procedures improved from 82% (28/34) to 91% (31/34) for chronic pancreatitis, 0% (0/3) to 80% (4/5) for the stricture/obstruction of the pancreaticojejuno anastomosis, and 67% (2/3) to 100% (3/3) for the stricture/obstruction of the pancreatic duct orifice after endoscopic papillectomy. For the remaining 4 patients with unsuccessful endoscopic interventions, including 2 patients who did not want to undergo EUS-PD after failed ETPD and 2 patients for whom EUS-PD failed, conservative management without additional endoscopic interventions was carried out when abdominal symptom or acute pancreatitis related to the BPDS/O developed during surveillance after the last endoscopic interventions.

### 3.3. Clinical success rate of endoscopic procedures for the BPDS/O

Of the 41 patients, 36 had symptomatic BPDS/O, and nearly all of their symptoms improved after endoscopic pancreatic interventions (35/36, 97%). Moreover, compared with a mean pretreatment score, their mean pain scores significantly improved 1, 6, and 12 month after successful endoscopic interventions, respectively (Fig. 2A).

With regard to the detail of endoscopic procedures for 36 symptomatic patients, 23 (64%) underwent pancreatic stent

**Table 1**
Baseline characteristics of 45 patients.

| | |
|---|---|
| Age, median (IQR) | 54 (45–60) |
| Sex (Male/Female) | 33/12 |
| Drinking habit, n (%) | |
| Continuous drinking before endoscopic interventions | 26 (58%) |
| Continuous drinking after endoscopic interventions | 24 (53%) |
| Smoking habit, n (%) | |
| Continuous smoking before endoscopic interventions | 16 (36%) |
| Continuous smoking after endoscopic interventions | 13 (29%) |
| Brinkman index on patients with a habit of smoking, median (IQR) | 585 (450–760) |
| Underlying pancreatic diseases, n(%) | |
| Chronic pancreatitis | 34 (76%) |
| BPDS/O of pancreatojejuno anastomosis | 5 (11%) |
| BPDS/O after endoscopic papillectomy | 3 (7%) |
| Other | 3 (7%) |
| Reasons for performing endoscopic treatments, n (%) | |
| Symptomatic BPDS/O just before initial pancreatic endotherapy | 40 (89%) |
| BPDS/O involving a progressive upstream MPD dilation | 5 (11%) |
| Imaging findings on admission | |
| Location of BPDS/O, Ph/Pb/Pt | 40/5/0 |
| MPD diameter, mm, median (IQR) | 7.0 (5.0–8.9) |
| Pancreatic stone, n (%) | 22 (49%) |
| Laboratory data on admission | |
| WBC (count/μl), median (IQR) | 5670 (4390–6590) |
| CRP (mg/ml), median (IQR) | 0.5 (0.2–1.8) |
| Amylase (IU/l), median (IQR) | 96 (81–168) |
| Lipase (IU/l), median (IQR) | 76 (35–206) |

**Abbreviations**: IQR, interquartile range; BPDS/O, benign main pancreatic duct stricture/obstruction; MPD, main pancreatic duct; Ph, pancreatic head; Pb, pancreatic body; Pt, pancreatic tail; WBC, serum white blood cell level; CRP, serum C-reactive protein level; Amylase, serum amylase level; Lipase, serum lipase level.

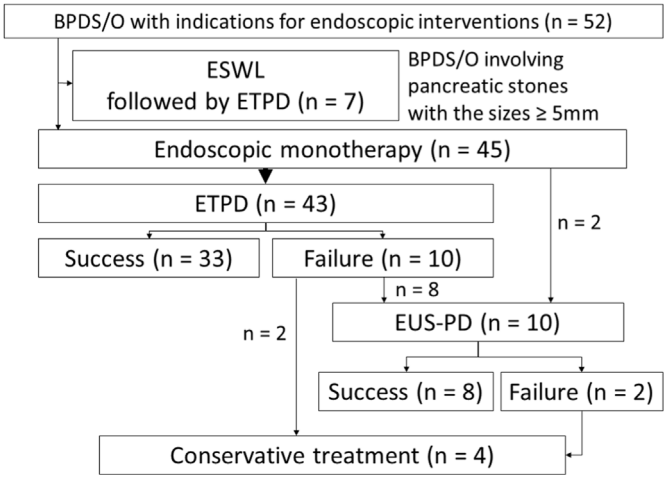


**Fig. 1. Flowchart for the clinical management for patients with BPDS/O**
BPDS/O, benign main pancreatic duct stricture/obstruction; ESWL, extracorporeal shock wave lithotripsy; ETPD, endoscopic transpapillary pancreatic drainage; EUS-PD, endoscopic ultrasound-guided pancreatic duct drainage.

replacement for the BPDS/O and/or EUS-PD route. Of the 23 patients with pancreatic stent replacement, 16 patients (Group A) underwent surveillance without pancreatic stenting after a median surveillance period of 4.4 months from initial pancreatic stenting (periodic pancreatic stent exchanges were carried out one or more times during this period for 50% of those). The remaining 7 patients (Group B) continued to have pancreatic stents in the BPDS/O or EUS-PD route by undergoing periodic pancreatic stent exchanges during surveillance after initial endoscopic interventions. On the other hand, 13 of the 36 symptomatic BPDS/O patients with successful endoscopic pancreatic interventions (Group C) underwent surveillance without pancreatic stenting after only the endoscopic dilation for the BPDS/O. Fig. 2B shows that mean pain scores in the above-mentioned groups A, B, and C equally improved between the clinical conditions before and approximately 12 months after initial endoscopic interventions. For the 41 patients with successful initial endoscopic interventions, their upstream MPD diameters decreased from 8.1 ± 4.1 to 5.2 ± 3.5 mm one month after initial endoscopic interventions.

**Table 2**
Details of EUS-PD

| Age | Sex | Pancreatic diseases | Pain | Endoscopic procedures | Dilation | Stent | AE | Rec |
|---|---|---|---|---|---|---|---|---|
| 54 | M | CP | − | EUS-guided pancreaticogastrostomy | − | + | − | + |
| 27 | M | CP | + | Failure | NE | NE | − | − |
| 58 | M | CP | + | EUS-guided pancreaticogastrostomy | + | + | − | − |
| 50 | M | CP | − | EPS by using the rendezvous technique | + | + | − | − |
| 80 | F | BPDS/O of PA | − | Antegrade balloon dilation | + | − | + | − |
| 69 | M | BPDS/O of PA | + | EUS-guided pancreaticogastrostomy | + | + | − | − |
| 60 | M | BPDS/O of PA | − | Failure | NE | NE | − | − |
| 55 | F | BPDS/O of PA | + | Antegrade balloon dilation | + | − | + | − |
| 59 | M | BPDS/O of PA | + | EUS-guided pancreaticogastrostomy | + | + | − | + |
| 82 | F | BPDS/O after EP | + | EPS by using the rendezvous technique | − | + | + | − |

**Abbreviation**: BPDS/O, benign pancreatic duct stricture/obstruction; CP, chronic pancreatitis; PA, pancreatojejuno anastmosis; EP, endoscopic papillectomy; EUS, endoscopic ultrasonography; EPS, endoscopic pancreatic duct stenting; AE, adverse event; Rec, Recurrence; NE, not evaluable.

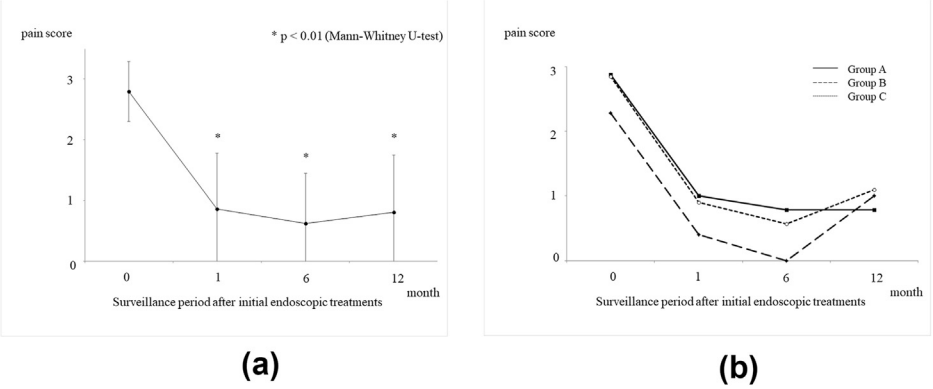


**Fig. 2. Changes in the pain score after initial successful endoscopic treatments**
Fig. 2A shows the significant decrease in the mean pain score of the 36 patients after initial endoscopic interventions. Of the 36 symptomatic patients with successful endoscopic interventions, 23(64%) underwent pancreatic stent placement for the benign main pancreatic duct stricture/obstruction (BPDS/O) or endoscopic ultrasound-guided pancreatic duct drainage (EUS-PD) route. Of those, 16 patients (Group A) underwent surveillance without pancreatic stenting after a median surveillance period of 4.4 months from initial pancreatic stenting and the remaining 7 patients (Group B) continued to have pancreatic stents in the BPDS/O or EUS-PD route by undergoing periodic pancreatic stent exchanges. On the other hand, 13 of the 36 symptomatic patients (Group C) underwent surveillance without pancreatic stenting after only the endoscopic dilation for the BPDS/O. Fig.2B shows that symptoms improved equally for the above-mentioned groups A, B, and C during approximately 12 months after initial pancreatic endoscopic interventions.

### *3.4. Adverse events related to endoscopic procedures*

The percentages of patients who developed PEP after ETPD and EUS-PD were 14% (6/43; mild PEP, 6) and 30% (3/10; mild PEP, 2; severe PEP, 1), respectively, and all patients with PEP including severe PEP improved with conservative treatments. Other adverse events related to the endoscopic procedures did not occur.

### *3.5. Clinical outcomes during surveillance after successful endoscopic interventions*

Recurrent symptoms/pancreatitis occurred for 11 of 41 patients after successful endoscopic procedures (median observation period, 23 months [range: 1–137]); Fig. 3), and the cumulative 3-year rate of developing symptoms/pancreatitis calculated by using the Kaplan-Meier method was 27% (Fig. 4A). These 11 patients

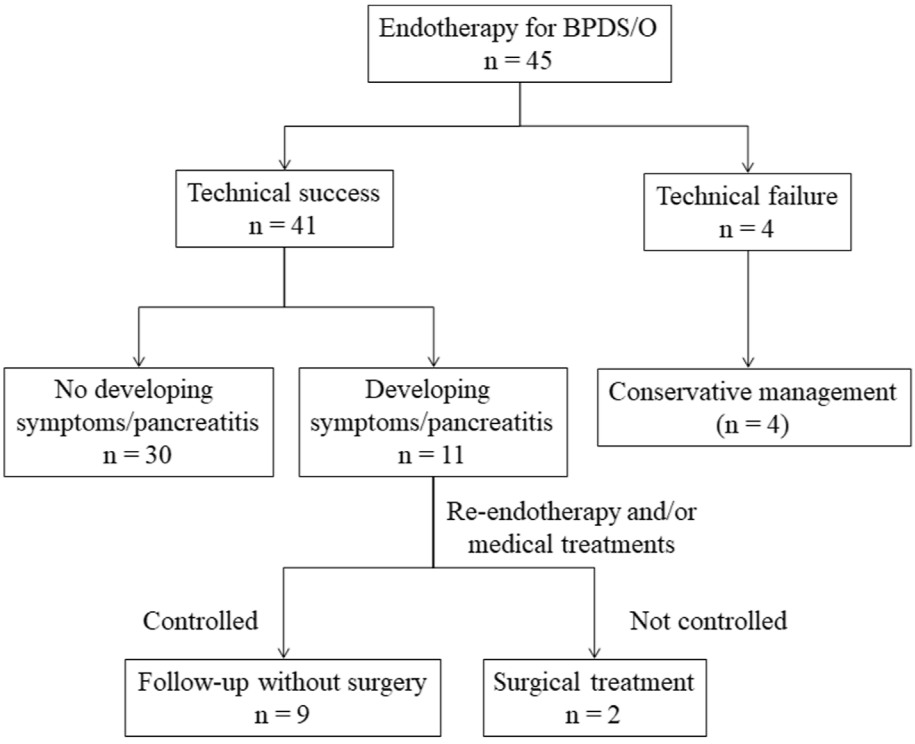


**Fig. 3. Clinical course after endoscopic interventions**
ESWL, extracorporeal shock wave lithotripsy; ETPD, endoscopic transpapillary pancreatic drainage.

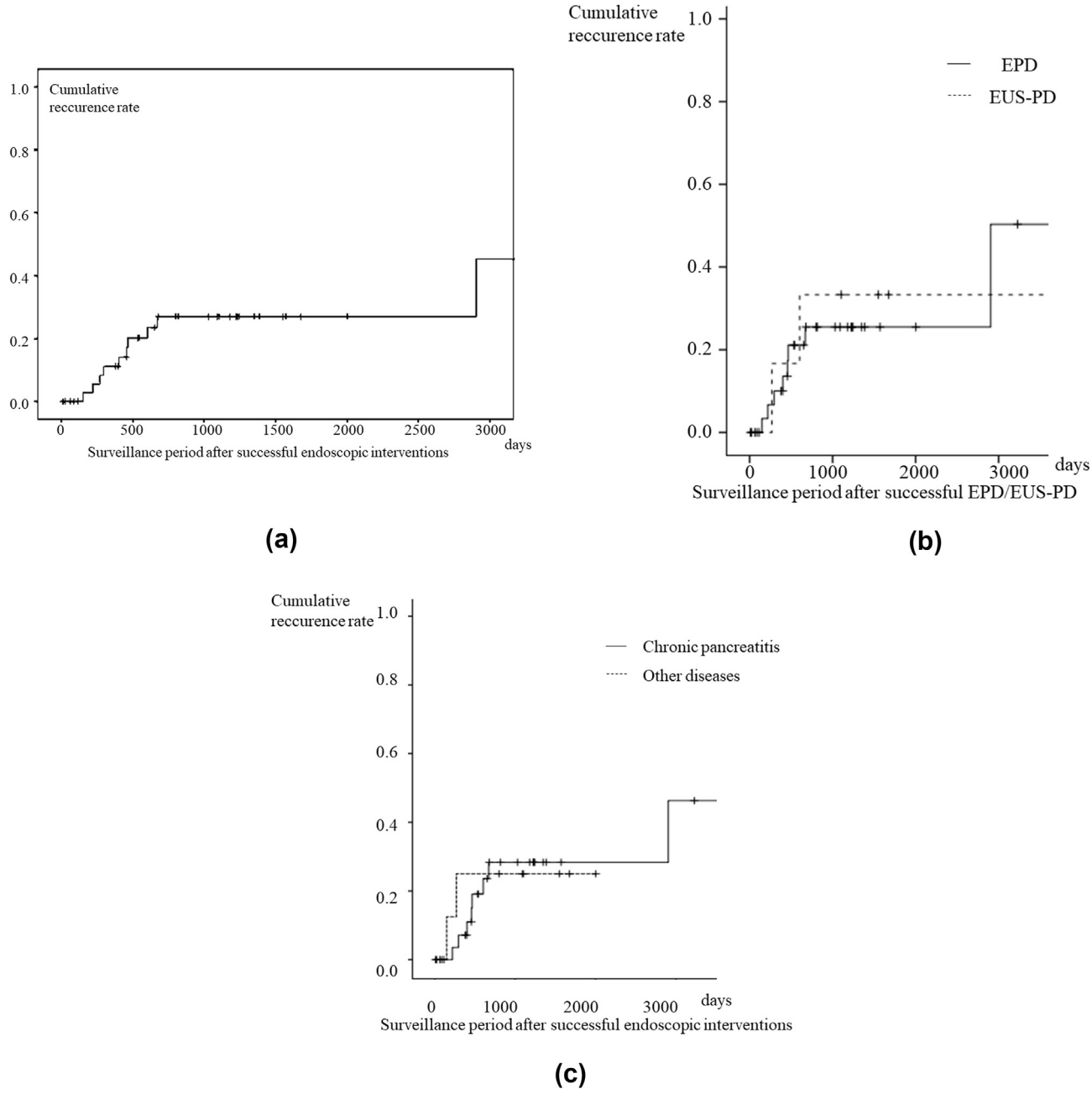


**Fig. 4. Cumulative rate of recurrent pancreatitis/symptoms related to benign main pancreatic duct stricture/obstruction (BPDS/O) after successful endoscopic interventions**
A: This rate for all 41patients. Median observation period after successful endoscopic interventions was 23 months (range 1–137) and the cumulative 3-year recurrence rate was 27%. B: This rate for 33 patients with successful endoscopic transpapillary pancreatic drainage (ETPD) and 8 patients with successful endoscopic ultrasound-guided pancreatic duct drainage (EUS-PD). There were no significant differences in this rate between the two groups ($p = 0.894$). C: This rate for 31 patients with chronic pancreatitis and 10 patients with other diseases. There were also no significant differences in this rate between the two groups ($p = 0.980$).

underwent conservative treatments and/or endoscopic reinterventions for their symptoms/pancreatitis (the median number of endoscopic reinterventions, 1; range, 0–2), and their clinical conditions could be controlled for 9 of the 11 patients. However, the remaining 2 patients finally underwent surgery (lateral side-to-side pancreaticojejunostomy) due to their uncontrollable symptoms/pancreatitis after 363 and 3018 days from initial endoscopic procedures. The cumulative 3-year rates of developing symptoms/pancreatitis for patients with successful ETPD ($n = 33$) and those with successful EUS-PD ($n = 8$) were 26% and 33%, respectively (Fig. 4B). In addition, those for patients with chronic pancreatitis ($n = 31$) and other diseases ($n = 10$) were 28% and 25%, respectively (Fig. 4C).

To clarify the risk factors for developing symptoms/pancreatitis after successful endoscopic interventions, 15 possible risk factors were used for univariate/multivariate analyses (Table 3). The following three possible risk factors with P-values < 0.2 by using the log-rank test were used in the multivariate analysis: continuous drinking ($p = 0.15$), continuous smoking ($p = 0.01$) and balloon dilation ($p = 0.19$). By using the Cox proportional hazard model, continuous smoking was shown to be a significant risk factor for developing symptoms/pancreatitis after successful endoscopic

**Table 3**
Risk factors for developing symptoms/acute pancreatitis after endoscopic interventions.

| Factors related to the clinical background and course | Univariate (p value) | Multivariate (p value) | OR | 95% CI |
|---|---|---|---|---|
| Sex: male | 0.74 | | | |
| Age: <70 | 0.31 | | | |
| Chronic pancrteatitis: Present | 0.98 | | | |
| Pancreatic stone: Present | 0.49 | | | |
| Abdonimal pain: Present | 0.82 | | | |
| Continuous drinking: Yes | 0.15 | 0.662 | | |
| Continious smoking: Yes | 0.01 | 0.019 | 5.101 | 1.306–19.924 |
| BMI: ≤18.5, ≥25 | 0.68 | | | |
| EUS-PD: Yes | 0.89 | | | |
| EPST: Yes | 0.99 | | | |
| Balloon dilation: Yes | 0.19 | 0.229 | | |
| Pancreatic stone removal: Yes | 0.58 | | | |
| Pancreatic duct stenting: Yes | 0.5 | | | |
| Adverse events related to endoscopic procedure: Present | 0.9 | | | |
| Decrease in the upstream MPD diameter ≥20% | 0.4 | | | |

**Abbreviation**: BMI, body mass index; EUS-PD, endoscopic ultrasound-guided pancreatic duct drainage; EPST, endoscopic pancreatic sphincterotomy; OR, odds ratio; CI, confidence interval.

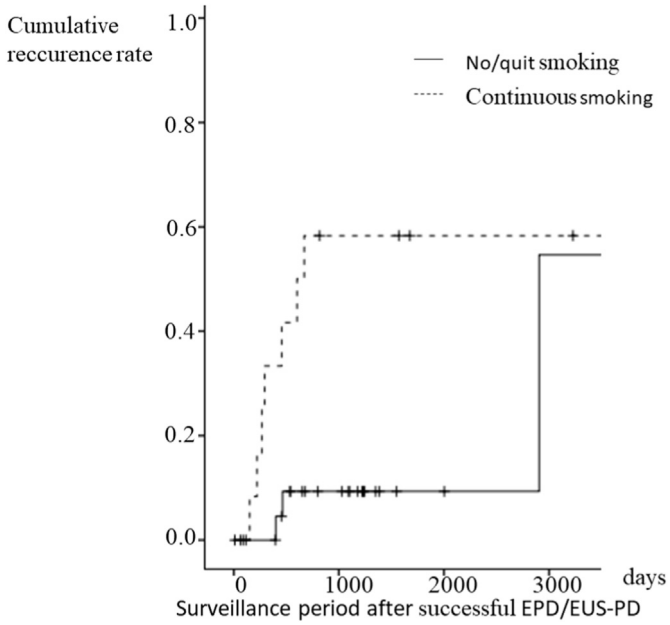


**Fig. 5. Difference in the cumulative rates of recurrent pancreatitis/symptoms related to BPDS/O after successful endoscopic interventions between "no-smoking/smoking cessation" and "continuous smoking" group**There was a significant difference in the cumulative rate of recurrent pancreatitis/symptoms related to BPDS/O between patients who did not smoke ("no-smoking/smoking cessation" group) and those who smoked continuously ("continuous smoking" group) after endoscopic interventions ($p = 0.008$). Their cumulative 3-year recurrence rates of pancreatitis/symptoms related to BPDS/O were 9% and 58%, respectively.

interventions ($p = 0.019$; 95% confidence interval, 1.3–19.9; odds ratio, 5.1). The cumulative 3-year recurrence rates of symptoms/pancreatitis in the "no-smoking/smoking cessation" and "continuous smoking" groups were 9% and 58%, respectively (Fig. 5).

## 4. Discussion

This study examined the results of endoscopic interventions for BPDS/O without pancreatic stones ≥5 mm in the era where EUS-PD is available. Although the technical success rate of ETPD was 77%, it increased to 91% when EUS-PD was used as a salvage method for unsuccessful ETPD. In addition, from this study, the following data was obtained: 1) 98% of patients with technical successes clinically improved; 2) 73% of patients with technical successes followed good clinical courses during a median surveillance period of 23 months; and 3) only 2% of patients finally underwent surgery after successful endoscopic interventions. From this results, the BPDS/O with pancreatic stones of <5 mm or that without pancreatic stones is a good indication for endoscopic interventions without ESWL, and it is of great significance that most of the patients undergoing endoscopic interventions, including EUS-PD, could avoid surgery during an intermediate-term surveillance.

Pancreatic endoscopic interventions are shown to be effective for symptomatic pancreatic diseases caused by an increased internal pressure of the MPD, such as chronic pancreatitis [21], the stricture of pancreatoenteric anastomosis [25], and pancreatic divisum [26]. On the other hand, with regard to chronic pancreatitis, surgery is shown to be superior to endoscopic interventions in term of long-term pain relief [27], although international consensus guidelines recommend interventional endoscopy with/without ESWL as a first-line therapy for pain relief [6,21]. In this study, the relatively low rates of recurrent pain/pancreatitis (27% per 3-years) and surgery (5% per 3-years) were shown through the investigation using patients who had BPDS/O with/without pancreatic stones <5 mm. This may indicate that most of patients with symptomatic BPDS/O involving no pancreatic stones or small ones can obtain relatively long-term pain relief by using only endoscopic endotherapy. In addition, when the BPDS/O is considered to be caused by chronic pancreatitis, indications for pancreatic endotherapy should be limited to symptomatic patients [21]. On the other hand, for the BPDS/O caused by pancreatic diseases apart from chronic pancreatitis, appropriate indications for pancreatic endotherapy have not been established. Although this study included 3 asymptomatic patients with BPDS/O caused by pancreatic diseases apart from chronic pancreatitis, the clinical value of pancreatic endotherapy for those patients should be investigated using large-scare population in the future.

In this study, EUS-PD was used mainly as a salvage method for patients with BPDS/O for whom ETPD was initially unsuccessful, and the results of EUS-PD were relatively good (technical success rate: 80%) and are similar to those of the previous reports [11–20]. However, EUS-PD may be effective as the first endoscopic intervention for some kinds of BPDS/O for which ETPD is likely to fail, such as pancreatojejunostomy stenosis. From a recent international multicenter study, EUS-PD has been reported to have an advantage over enteroscopy-assisted ERP for patients with a stricture of the

pancreaticojejunostomy after Whipple surgery [25]. In fact, two recent patients with pancreaticojejunostomy strictures in this study successfully underwent EUS-PD as a first endoscopic intervention. In the future, the optimal timing for EUS-PD must be determined, with a focus on the differences in the success rate of ETPD for each underlying pancreatic disease which cause BPDS/O.

Although EUS-PD is a promising alternative to surgery after failed ETPD for the BPDS/O, the rate of adverse events related to EUS-PD in this study was relatively high (30%), similar to published data on EUS-PD [11–20]. In a recent paper on EUS-PD, it has been reported that the risk of adverse events depend on whether or not EUS-PD is technically successful [11]. To improve the rate of technical success of EUS-PD with a decrease in the rate of adverse events, procedural standardization of EUS-PD and development of dedicated devices for EUS-PD is necessary.

In regard to the clinical outcomes after successful endoscopic interventions, the cumulative 3-year rate of developing symptoms/pancreatitis was 27% (i.e., the cumulative 3-year rate of symptom-free status was 73%). From a meta-analysis on endoscopic interventions for BPDS/O, the rate of patients with long-term pain relief was estimated to be 67.5% [28], which is similar to that of patients with endoscopic technical success in this study. From the multivariate analysis in this study, the rate of developing symptom/pancreatitis after successful endoscopic interventions did not depend on the endoscopic procedures, and only continuous smoking was found to be a risk factor for developing symptom/pancreatitis after successful endoscopic interventions. In a recent paper on recurrent pancreatitis, smoking is reported to be an independent risk factor for recurrent pancreatitis in addition to etiology of pancreatitis (alcoholic/idiopathic) and necrotizing pancreatitis [29]. In addition, as is the case with our study, smoking is shown to be a risk factor for acute pancreatitis after endoscopic pancreatic interventions [30]. Thus, lifestyle modifications, including smoking cessation, may contribute to a decrease in the rate of developing symptom/pancreatitis after successful endoscopic interventions.

There are some limitations in this study. First, this study was retrospectively conducted at a single center with a relatively small sample size. Especially, the number of patients who underwent EUS-PD may be relatively low to evaluate the clinical value of EUS-PD. Therefore, the results of this study need to be verified by using a multicenter, large-sample validation cohort. Second, the pain scoring system for patients with BPDS/O used in this study is not common. The Izbicki pain score was not used in this study because it is exclusively used for scoring the degree of pain related to chronic pancreatitis [31] and because this study included patients with BPDS/O derived from etiologies other than chronic pancreatitis. Third, a median period of pancreatic stent placement for the 16 patients of Group A was short (4.4 months), although pancreatic stent placement for the BPDS/O is supposed to be continued for over one year in our hospital. In fact, the early removement of pancreatic stent was carried out for some patients in clinical practice when the BPDS/O was judged to be adequately dilated within one year after initial endoscopic interventions. Fourth, the results of this study may have limited application because patients who had pancreatic stones with sizes $\geq$5 mm were not included in this study. Although further investigations are needed to clarify whether or not EUS-PD is effective for BPDS/O involving pancreatic stones with sizes $\geq$5 mm, it is worthy of note that EUS-PD increased the endoscopic success rate from 77% to 91% and may have decreased the need for surgical treatment for BPDS/O in this study population.

In conclusion, EUS-PD increased the total technical success rate of endoscopic interventions for BPDS/O to more than 90% and may have contributed to a decrease in the number of patients needing surgery after ETPD for BPDS/O failed. Therefore, EUS-PD can act as a salvage endoscopic procedure for BPDS/O when ETPD fails, although careful attention should be paid to the relatively high rate of adverse events.

## Declaration of competing interest

Authors declare no conflict of interest for this article.

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