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Endoscopic ultrasound-guided versus surgical pancreatic duct drainage after failed endoscopic retrograde pancreatography: a pilot comparative study

Jia-Su Li[1] · Kai-Lian Zheng[2] · Shun-Li Lv[1] · Xiao-Ju Su[1] · Kai-Xuan Wang[1] · Zhao-Shen Li[1] · Jie Chen[1] · Yan Chen[1]

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Abstract

Background Endoscopic ultrasound-guided pancreatic duct (PD) drainage (EUS-PDD) is being increasingly performed as an alternative method to surgical drainage to achieve PD decompression after failed endoscopic retrograde pancreatography (ERP). However, no directly study has compared EUS-PDD with surgical PD drainage after failed ERP in patients with chronic pancreatitis.

Methods Consecutive patients who underwent EUS-PDD or longitudinal pancreaticojejunostomy after failed ERP were retrospectively identified from our endoscopy and medical information systems. The primary end point was the Izbicki pain score. The secondary end points were pain relief at the end of follow-up, procedure outcomes, adverse events, readmission, and reintervention.

Results A total of 21 patients (11 EUS-PDD, 10 surgical drainages) were analyzed. There were no significant differences in mean Izbicki pain score (EUS-PDD, 13.6 ± 10.1 vs. surgical drainage 10.7 ± 7.9, $p = 0.483$) or complete/partial pain relief (60%/30% vs. 70%/30%, $p = 0.752$) at the end of follow-up of the two groups. The rates of overall adverse events (27.3% vs. 30.0%, $p = 0.893$) and readmission (63.6% vs. 40.0%, $p = 0.290$) were similar in the two treatment groups, while patients in EUS-PDD group required more reinterventions (45.5% vs. 0%, $p = 0.039$) compared with patients in the surgery group.

Conclusion EUS-PDD showed comparable pain relief and safety to surgical PD drainage after failed ERP, with a higher rate of reintervention. The selection of EUS-PDD or surgical drainage may be appropriate based on an individualized strategy.

Jia-Su Li, Kai-Lian Zheng, and Shun-Li Lv contributed equally to this work.

Yan Chen, Jie Chen, and Zhao-Shen Li share co-corresponding authorship.

✉ Zhao-Shen Li
zhs.li@hotmail.com

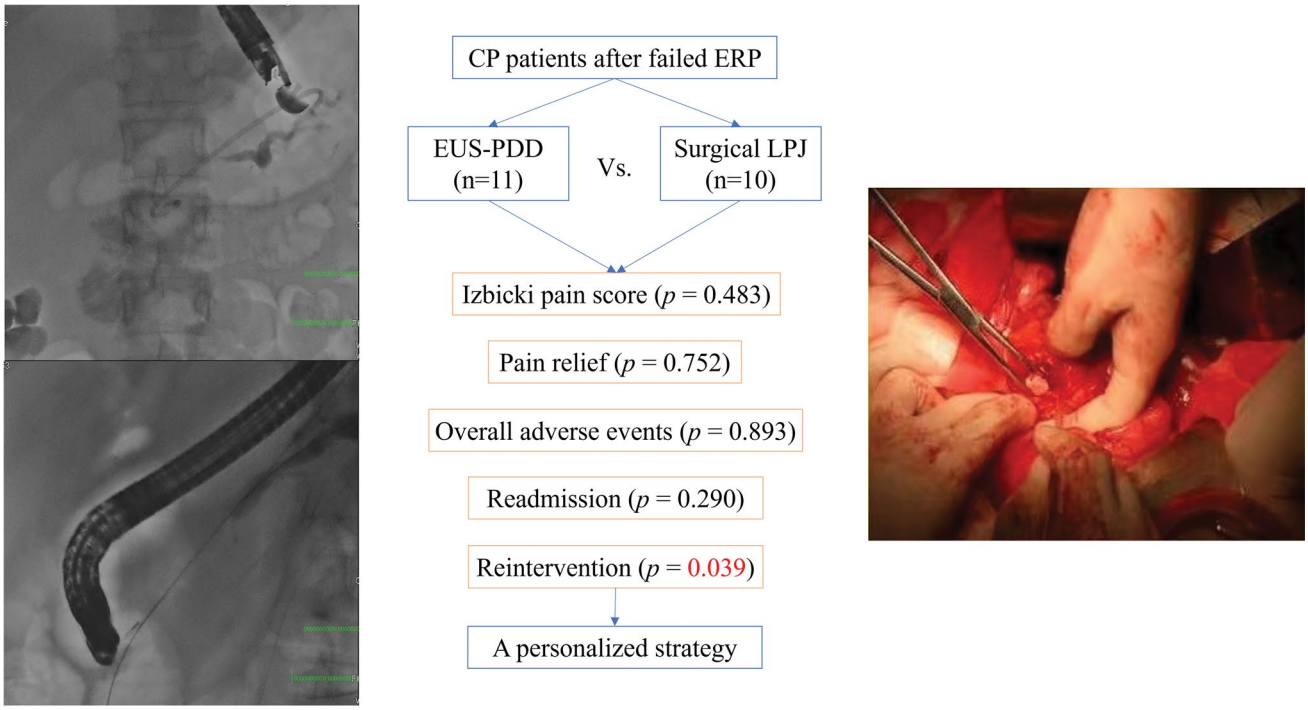
✉ Jie Chen
drchen021@163.com

✉ Yan Chen
medchenyan@126.com

[1] Department of Gastroenterology, Changhai Hospital, Naval Medical University, 168 Changhai Road, Shanghai 200433, China

[2] Department of Hepatobiliary Pancreatic Surgery, Changhai Hospital, Navy Medical University, Shanghai, China

Graphical abstract



Keywords Endoscopic ultrasound · Pancreaticojejunostomy · Pancreatic duct · Drainage · Endoscopic retrograde pancreatography

For patients with a symptomatic dilated pancreatic duct (PD) as a result of pancreatic stones and/or strictures, endoscopic retrograde pancreatography (ERP) with transpapillary drainage is considered the mainstay drainage modality for achieving pancreatic decompression and relieving intractable pain that is refractory to conservative management [1]. However, in as many as 10% of patients, ERP may not be possible due to a complete PD obstruction/disconnection or strictures [2].

Traditionally, surgery may be the last option to manage pain after failed ERP [3]. Compared to endoscopic transpapillary drainage, surgical drainage of the PD appears to be more effective in patients with obstruction of the PD due to chronic pancreatitis (CP), with better pain relief, fewer reintervention procedures, and similar complications [4–6]. It is worth noting that the systematic review and meta-analysis of endoscopy versus early surgery for the management of CP included not only drainage procedures such as lateral/longitudinal pancreaticojejunostomy (LPJ, also known as the modified Puestow procedure or Partington procedure) but also resectional procedures such as pancreatoduodenectomy, distal pancreatectomy, Beger and Frey procedures [6]. As the standard drainage procedure for CP, LPJ may be a fairer comparison to simple endoscopic drainage methods [7].

On the other hand, since it has been first reported approximately two decades ago [8, 9], endoscopic ultrasound-guided PD drainage (EUS-PDD) has been shown to be a minimally invasive, effective, and safe alternative to surgical PD drainage, and is recommended in patients with PD obstruction as a rescue procedure after failed ERP or in patients with surgically altered anatomy or duodenal stenosis where ERP is not possible [10, 11]. Two meta-analyses have demonstrated the efficacy and safety of EUS-PDD, with a pooled rate of technical success and overall adverse events (AEs) being 81.4–84.8% and 18.1–21.3%, respectively [12, 13].

However, there are currently no directly comparative studies of EUS-PDD versus surgical drainage for CP patients after failed ERP. The aim of this single-center, retrospective study was to compare the efficacy and safety of EUS-PDD with LPJ standard drainage procedure.

Methods

Study design and population

An approval from the institutional review board was obtained to conduct this retrospective observational cohort

study, and written informed consents for the procedures were obtained from all patients. This study was reported according the 'Strengthening the Reporting of Observational studies in Epidemiology' (STROBE) guidelines. It was conducted in accordance with the principles of the Declaration of Helsinki.

Between June 2019 and March 2023, patients with a symptomatic dilated PD who underwent EUS-PDD or surgical LPJ in our hospital were identified from our endoscopy and medical information system. All patients' pancreatic conditions were assessed and confirmed by computerized tomography (CT) scan and/or magnetic resonance cholangiopancreatography (MRCP) before executing the selected procedure. The inclusion criteria consisted of adult patients (age ≥ 18 years) who had undergone EUS-PDD or LPJ for intractable pain associated with CP, and had a history of unsuccessful ERP. The exclusion criteria were (1) patients who underwent EUS-PDD due to other indications (e.g., posttraumatic PD leak/fistula, postoperative anastomotic strictures); (2) patients who underwent resectional procedures due to other indications (e.g., an enlarged pancreatic head); and (3) patients with incomplete medical records to obtain sufficient data.

Procedural techniques

EUS-PDD was performed by experienced therapeutic endoscopists with the patient under conscious sedation in our center. Antibiotic prophylaxis was administered before the procedure. A therapeutic linear echoendoscope was inserted and the transgastric approach was used as the preferred approach. After successful PD puncture with a 19G needle, a pancreatogram was obtained and a 0.035 in. or 0.025 in. guidewire inserted. The decision to dilate the stricture and the selection of approach to achieve PD drainage (rendezvous technique, pancreaticogastrostomy, and antegrade drainage) [2, 10] were made according to the judgment of the endoscopist. The technical details and illustrations of the EUS-guided rendezvous technique or transmural stenting can be found in Fig. 1e and f of the European Society of Gastrointestinal Endoscopy technology review on therapeutic EUS [14].

LPJ was carried out by modified Puestow procedure for retrograde drainage of the PD [7, 15, 16]. In brief, the procedure included the exposure of the pancreas and PD location, opening the main PD, Roux-en-Y limb preparation, and pancreaticojejunostomy [16].

Clinical outcomes and study variables

The primary end point of this study was the Izbicki pain score, which is a validated pain score specifically designed for CP, including two subjective items [frequency of pain attacks and visual analogue scale (VAS)] and two objective items (use of analgesic medication and time of disease-related inability to work) [17]. The scale ranges from 0 to 100 points, where a higher score indicates more severe pain. The preoperative pain score was obtained at the time of admission, while the postoperative pain score was achieved during 6–12 months after discharge through outpatient service or telephone follow-up.

The secondary end points were pain relief (complete relief was defined as Izbicki pain score ≤ 10 points; partial relief was defined as Izbicki pain score > 10 points after a more than 50% decrease compared with the baseline scores), AEs of interventions, length of single hospital stay, single medical costs, readmission and reintervention. The definitions of AEs and the severity of the grading system were according to the Cotton's criteria for endoscopic AEs in the EUS-PDD arm [18] and the Clavien–Dindo classification for surgical complications in the LPJ arm [19], respectively. The decision to remove or exchange stents was based on the presence of discomfort symptoms and evidence of stent displacement or dysfunction during follow-up examinations.

Data specific to EUS-PDD included diameter of the main PD, technical success, drainage approach (rendezvous vs. transmural stenting), and the size and length of the stent inserted. Data specific to LPJ included the incision length of PD, operative time, intraoperative blood loss, and other simultaneous surgical procedures (e.g., choledocholithotomy).

Statistical analysis

Continuous variables were reported as mean ± standard deviation or median (range), and compared by using Student's *t* test or the Mann–Whitney *U* test. Categorical variables were presented as frequencies and proportions, and compared by using χ^2 testing or Fisher exact test where appropriate. A level of $p < 0.05$ was considered statistically significant. All the statistical analyses were conducted using SPSS Statistics software version 21.0 (IBM Corp., NY, USA).

Results

Patient characteristics

A total of 21 CP patients who received EUS-PDD or surgical LPJ drainage were enrolled in this study, including 11 patients who underwent EUS-PDD and 10 patients who underwent surgical LPJ drainage. Characteristics and outcomes of patients who underwent EUS-PDD or LPJ are summarized in Tables 1 and 2, respectively. The baseline patient characteristics in the two groups were similar (Table 3).

Table 1 Characteristics and outcomes of patients who underwent EUS-PDD

Case no	Age (years)	Gender (M/F)	BMI	Duration of symptoms (years)	Diameter of PD (cm)	EUS technique	Length of the stent (cm)	Diameter of the stent (Fr)	Technical success	Adverse events	Pain relief	Readmission	Reintervention
1	34	M	25.4	3	0.6	Rendezvous technique	7	7	Yes	No	Complete	Yes	No
2	34	M	21.2	2	0.6	Rendezvous technique	9	7	Yes	Duodenal ulcer (mild)	No	Yes	Yes
3	64	M	26.8	4	0.5	Rendezvous technique	7	7	Yes	No	Complete	Yes	No
4	26	F	17.3	12	0.5	Rendezvous technique	7	7	Yes	No	NA	NA	NA
5	52	F	21.0	0.5	0.6	Nasopancreatic drainage tube	–	–	Yes	No	Partial	No	No
6	36	F	17.3	8	2.3	–	–	–	No	Perforation (moderate)	Complete	No	No
7	36	M	19.3	8	0.7	–	–	–	No	Pancreatitis (moderate)	Partial	Yes	Yes
8	33	M	14.4	2	0.5	Transmural stenting	9	7	Yes	No	Complete	Yes	Yes
9	53	M	22.5	10	0.8	Rendezvous technique	7	8.5	Yes	No	Complete	No	No
10	37	M	23.0	1	0.7	Rendezvous technique	7	7	Yes	No	Partial	Yes	Yes
11	32	F	30.1	1.5	0.7	Transmural stenting	9	7	Yes	No	Complete	Yes	Yes

EUS-PDD endoscopic ultrasound-guided pancreatic duct drainage, *BMI* body mass index, *PD* pancreatic duct, *EUS* endoscopic ultrasound, *NA* not available

Table 2 Characteristics and outcomes of patients who underwent LPJ

Case no	Age (years)	Gender (M/F)	BMI	Duration of symptoms (years)	Incision length of PD (cm)	Technical success	Adverse events	Pain relief	Readmission	Reintervention
1	55	M	23.9	5	3	Yes	Infection (Grade II)	Complete	Yes	No
2	57	M	21.4	2	4	Yes	No	Complete	No	No
3	62	M	25.8	10	NA	Yes	Infection (Grade II)	Complete	No	No
4	24	M	24.8	2	5	Yes	No	Partial	Yes	No
5	36	F	26.1	0.2	3	Yes	No	Complete	No	No
6	56	M	24.2	1	8	Yes	No	Complete	No	No
7	28	F	16.9	2	5	Yes	No	Complete	Yes	No
8	26	M	26.0	7	4	Yes	No	Complete	No	No
9	54	M	18.2	12	10	Yes	No	Partial	Yes	No
10	52	M	27.2	5	5	Yes	Bleeding (Grade II)	Partial	No	No

LPJ longitudinal pancreaticojejunostomy, *BMI* body mass index, *PD* pancreatic duct, *NA* not available

EUS-PDD and surgical drainage

Technical outcomes are summarized in Table 4. In the EUS-PDD group, 11 patients underwent 13 sessions of EUS-PDD, of which 1 patient underwent EUS-PDD again after stent migration, and 1 patient underwent stent replacement. The mean diameter of the dilated PD was 0.8 ± 0.5 cm, with a total technical success rate of 84.6% (11/13, 81.8% per patient [9/11]). In two patients, the guidewire/stent could not be inserted through the duodenal papilla due to PD obstruction or stricture; one patient underwent follow-up with diet adjustment and conservative medication treatment, and the remaining one subsequently underwent two sessions of extracorporeal shock wave lithotripsy (ESWL) and two sessions of failed ERP during the follow-up period. The plastic stent was placed by a rendezvous procedure in 6 patients, and transmural drainage in the others (including one case with nasopancreatic drainage tube). The nasopancreatic drainage tube was cut under endoscopy at the patient's discharge and used as an internal drainage stent. The median length of the stent is 7 (7–9) cm, and the median diameter of the stent is 7 (7–8.5) Fr.

All surgical LPJ procedures were successful. The mean incision length of PD was 5.2 ± 2.3 cm, and the median intraoperative blood loss was 100 (10–200) ml. One patient concurrently underwent choledocholithotomy with T-tube drainage, and three patients underwent pancreatic biopsy.

Adverse events

The overall incidence of AEs per patient in EUS-PDD group was 27.3% (3/11), and 30% (3/10) in the surgical group ($p = 0.893$). There was no significant difference in the occurrence of postoperative pancreatitis ($p = 0.340$), bleeding ($p = 0.294$), and infection ($p = 0.128$) between groups (Table 4).

Three patients in the EUS-PDD group experienced AEs. The first patient developed postinterventional pancreatitis (9.1%). This case had the hydrophilic end of the guidewire cut off by the tip of the puncture needle during the procedure; the retained remnant remained and subsequently led to acute pancreatitis (moderate). The second case experienced postoperative abdominal pain, with CT scan showing multiple free gases in the abdominal cavity that suggests a possible gastrointestinal perforation, which is cured after a week of conservative treatment (moderate). The last patient developed duodenal ulcer due to the irritation of the end of the stent 2 months after the stent implantation (mild). There were no AEs such as bleeding, pancreatic fistula, and death.

In the surgical group, one patient had gastrointestinal bleeding, and two had infections. All three cases were Grade II complications. This bleeding patient experienced postoperative abdominal pain and had a red stool, who

Table 3 Baseline patient characteristics

Variable	EUS-PDD ($n=11$)	Surgical drainage ($n=10$)	p-value
Age (mean ± SD, years)	39.7 ± 11.4	45.0 ± 14.7	0.369
Gender (Male/Female)	7/4	8/2	0.418
Duration of symptoms (mean ± SD, years)	4.7 ± 4.0	4.6 ± 4.0	0.952
Body mass index (mean ± SD)	21.7 ± 4.6	23.5 ± 3.5	0.333
History of biliary and pancreatic surgery	3	1	0.326
Cholecystectomy	3	4	0.546
Extracorporeal shock wave lithotripsy	5	1	0.080
Diabetes mellitus	1	3	0.234
Alcohol consumption	3	2	0.703
Smoker	1	4	0.105
Painkiller use	7	3	0.081
Reasons for failed ERP			0.945
Failure of deep PD cannulation	11	9	
Inaccessibility to the papilla	/	1	

EUS-PDD endoscopic ultrasound-guided pancreatic duct drainage, *SD* standard deviation, *ERP* endoscopic retrograde pancreatography, *PD* pancreatic duct

Table 4 Technical outcomes

Variable	EUS-PDD ($n=11$)	Surgical drainage ($n=10$)	p-value
Technical success per patient	81.8% (9/11)	100% (10/10)	0.167
Diameter of pancreatic duct (mean ± SD, cm)	0.8 ± 0.5	–	
Incision length of pancreatic duct (mean ± SD, cm)	–	5.2 ± 2.3	
Preoperative VAS score	7.1 ± 1.9	7.8 ± 1.3	0.343
Postoperative VAS score	2.4 ± 2.3[a]	2.1 ± 0.9[a]	0.706
Preoperative Izbicki pain score	52.2 ± 12.6	45.0 ± 9.6	0.170
Postoperative Izbicki pain score	13.6 ± 10.1[a]	10.7 ± 7.9[a]	0.483
Pain relief			0.752
Complete	60% (6/10)	70% (7/10)	
Partial	30% (3/10)	30% (3/10)	
Total adverse events per patient	27.3% (3/11)	30% (3/10)	0.893
Acute pancreatitis	1 (Moderate)	0	0.340
Bleeding	0	1 (Grade II)	0.294
Infection	0	2 (Grade II)	0.128
Single hospital stay (median, range, days)	10 (4–19)	12 (10–24)	0.062
Single medical costs (mean ± SD, USD)	5487.7 ± 1734.4	6901.7 ± 3008.3	0.237
Readmission	63.6% (7/11)	40% (4/10)	0.290
Reintervention	45.5% (5/11)	0% (0/10)	0.039

EUS-PDD endoscopic ultrasound-guided pancreatic duct drainage, *SD* standard deviation, *VAS* visual analogue scale

[a]The postoperative pain scores of the two groups were significantly lower than the corresponding preoperative pain scores, respectively, all $p<0.001$

was considered to have bleeding at the anastomotic site and improved through blood transfusion and conservative drug treatment. One of the two infections developed respiratory alkalosis with fever after surgery, and aspergillus was detected in the drainage tube and treated with antibiotics. The remaining patient with abdominal pain was found to have fecal enterococci in the drainage fluid. There were no incidents of acute pancreatitis, pancreatic fistula, anastomotic leakage, or death in these surgical patients.

Hospital stay and costs

The median length of single hospital stay was 10 (4–19) days in the EUS-PDD group, and 12 (10–24) days in the surgical group ($p = 0.062$). Mean single medical costs were similar between the EUS-PDD group (5487.7 ± 1734.4 USD) and the surgical group (6901.7 ± 3008.3 USD, $p = 0.237$).

Pain relief

During the 6- to 12-month follow-up period, there was one patient lost to follow-up in the EUS-PDD group, while zero in the surgical group. Pairwise comparisons showed significant differences of pain relief before and after endoscopic and surgical interventions, respectively (p all < 0.001). In the EUS-PDD group, pain scores were obtained in 10 of 11 patients. The usage rate of painkillers before intervention was 70.0% (7/10). The mean preoperative VAS score was 7.1 ± 1.9 points, while the mean VAS score at the end of follow-up was 2.4 ± 2.3 points ($p < 0.001$). The mean preoperative Izbicki pain score was 52.2 ± 12.6 points, while the mean Izbicki pain score at the end of follow-up was 13.6 ± 10.1 points ($p < 0.001$).

In the surgical group, all the 10 patients with painful symptoms received pain scores, with a usage rate of painkillers before intervention being 30% (3/10). The mean preoperative VAS score was 7.8 ± 1.3 points, while the mean postoperative VAS score was 2.1 ± 0.9 points ($p < 0.001$); The mean preoperative Izbicki pain score was 45.0 ± 9.6 points, while the postoperative Izbicki pain score was 10.7 ± 7.9 points ($p < 0.001$).

The pain scores with regard to preoperative VAS score ($p = 0.343$), preoperative Izbicki pain score ($p = 0.170$), VAS score ($p = 0.706$), and Izbicki pain score ($p = 0.483$) at the end of follow-up were similar between the two groups, respectively. At the end of follow-up, complete and partial pain relief was achieved in 60% (6/10) and 30% (3/10) of patients in the EUS-PDD group, and in 70% (7/10) and 30% (3/10) of patients in the surgical group, respectively, which were not significant ($p = 0.752$).

In the EUS-PDD group, the remaining symptomatic patient suspected of having pancreatic divisum underwent two sessions of ERP transpapillary PD cleaning and stent replacement, as well as one time of EUS-guided fine-needle biopsy for pancreatic head mass. After no clear malignant lesions were detected, surgical pancreatectomy was ultimately performed.

Readmission and reintervention

The overall readmission rate was 63.6% (7/11) in the EUS-PDD group, and 40% (4/10) in the surgical group, which was comparable ($p = 0.290$). The EUS-PDD group also included two patients with concurrent common bile duct stones who underwent ERCP stone removal and biliary stent placement. In the surgical group, the four patients were all re-hospitalized with acute exacerbations of CP and improved after conservative treatment.

The reintervention rate was 45.5% (5/11) in the EUS-PDD group, and 0% (0/10) in the surgical group, which was significant ($p = 0.039$). In addition to the two patients mentioned above who underwent EUS-PDD again, and two cases of technical failure, the remaining seven technically successful patients underwent re-examination with the stent in place or without any discomfort symptoms, so no further intervention specifically targeting EUS-PDD stent was given and regular follow-up was continued. Other main reintervention reason for the EUS-PDD group was to try transforming EUS-PDD to transpapillary drainage, including two cases of ERP failed with deep PD cannulation (both the 2 patients also underwent ESWL). The remaining patient suspected of pancreatic divisum with painful symptoms, combined with pancreatic head mass and severe anxiety, ultimately chose surgical pancreatectomy. During the follow-up period, there was no reintervention treatment in the surgical group.

Discussion

To our knowledge, this pilot research is the first study to directly compare EUS-guided with surgical LPJ for PD drainage for CP patients after failed ERP. Our results revealed that EUS-PDD is minimally invasive, effective, and safe, with comparable pain relief and rate of overall AEs to that of standard surgical drainage. However, EUS-PDD was associated with higher rate of reintervention when compared with standard surgical drainage.

The clinical outcomes of EUS-PDD in the present study demonstrated high technical success rate of 84.6% (81.8% per patient) and acceptable rate of overall AEs of 27.3%, which are comparable to previous studies [12, 13]. EUS-PDD is technically challenging with a steep learning curve [20] and is often performed by experienced senior EUS endoscopists in our center, one of the top advanced endoscopy centers both domestically in China and internationally, to ensure its success rate and safety. By adding EUS-PDD to ERP, the success rate of endoscopic PD drainage will be improved, as some studies reporting that the technical success rate for endoscopic interventions for refractory PD strictures/obstructions was > 90% [21, 22].

In our study, 27.3% (3/11) of patients in the EUS-PDD group had a history of biliary and pancreatic surgery, which increased the difficulty of the procedure and also the risk of AEs. Furthermore, the majority of patients with PD stones did not achieve complete stone removal, and those with incomplete resolution of PD stricture experienced a higher

likelihood of requiring later reinterventions compared to surgical drainage ($p = 0.039$), highlighting a limitation of current endoscopic treatment. Fortunately, a recent study reported that peroral pancreatoscopy through the mature fistula created by EUS-guided pancreaticogastrostomy to diagnose and treat PD stricture/pancreato-jejunal anastomotic stricture achieved promising results [23]. The combination of laser, electrohydraulic lithotripsy, or other methods will further enhance the effectiveness of EUS-PDD-mediated treatment techniques in the near future.

We found EUS-PDD was comparable to surgical drainage with regard to pain relief ($p = 0.752$), AEs ($p = 0.893$), and single hospital stay ($p = 0.062$), with a higher rate of reintervention ($p = 0.039$), which were partly inconsistent with previous studies comparing endoscopic treatment with surgical procedures [4–6]. Previous studies suggested that surgical drainage of the PD was more effective in terms of pain scores than endoscopic treatment in patients with obstruction of the PD due to CP, with similar rates of complications, length of hospital stay, and changes in pancreatic function, but lower number of reinterventions [4–6]. The reasons for the differences may be as follows: (1) the pain score has a character of subjectivity, and there may be recall bias; (2) surgical procedures included not only drainage procedures such as LPJ but also resectional procedures such as pancreatoduodenectomy, distal pancreatectomy, Beger and Frey procedures [5, 6]; and LPJ as a comparison group for endoscopy in our study is more reasonable [7]; (3) endoscopic interventions performed in the endoscopy group in previous studies were pancreatic sphincterotomy, PD stenting, stone extraction, and ESWL, while EUS-PDD has not been compared with surgical drainage in the past [6]. Besides, patients in our surgical drainage group perhaps had mild and short-term pain symptoms, which may manifest as lower proportion of painkillers used (30% vs. 70%, $p = 0.081$), and patients with severe conditions in previous studies may choose further surgical methods for definitive treatment.

As a minimally invasive endoscopic technique, EUS-PDD has achieved promising clinical results [12, 13, 21], as also confirmed by this study. Further improvement in technical and clinical success rates, as well as safety, such as more reasonable patient selection, technological advancements, and an increase in endoscopists training experience, would further enhance the role of EUS-PDD in the treatment of PD-related diseases.

Our preliminary comparative study has a few limitations. First, this study was single-center retrospective design with small sample size and inevitable case selection bias, despite all cases being from one of the top endoscopy centers in a tertiary general hospital. Second, due to the incompleteness of relevant data, we were unable to evaluate changes in the diameter of PD, long-term stent-related AEs, and pancreatic endocrine and exocrine functions, which are important for the efficacy evaluation and would weaken the advantages of the results of the present study. Subsequent prospective study designs can incorporate these indicators. Third, although the single hospital costs and overall readmission rates of the two groups were comparable, the reintervention rate of the endoscopic group was significantly higher. Due to lack of the data availability, we were unable to compare the total medical expenses, which may underestimate the costs and total length of hospital stay of the endoscopic group. Therefore, further large, randomized, prospective comparative studies are needed to confirm our results.

Conclusion

Our study firstly showed that EUS-PDD had comparable efficacy in pain relief and safety to standard surgical PD drainage after failed ERP, with a higher rate of reintervention. The selection of EUS-PDD or surgical drainage may be more appropriate based on a personalized strategy including patient condition, physician expertise, and their individual preferences. Further larger prospective studies are warranted to confirm the results and the individualized strategy.

Author contributions Conception and design: YC, JC, and ZSL. Acquisition, analysis, and interpretation of data: JSL, KLZ, and SLL. Technical or material support: XJS and KXW. First draft of the manuscript: JSL. Critical revision and editing: All authors. Study supervision: YC, JC, and ZSL. Final approval: All authors.

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