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Impact of long-term transmural plastic stents on recurrence after endoscopic treatment of walled-off pancreatic necrosis

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Abstract:

Background and study aims:
Endoscopic transmural drainage (ETD) using double pigtail stents (DPS) is a well-established treatment for walled-off pancreatic necrosis (WON). This study aimed to compare outcomes in patients undergoing ETD with DPS left indwelling versus those where stents were removed or migrated.

Patients and methods:
This retrospective, multicenter cohort study included patients with WON who underwent ETD using DPS between July 2001 and December 2019. The primary outcome was recurrence of a pancreatic fluid collection (PFC). Secondary outcomes were long term complications and recurrence-associated factors. Competing risk regression analysis considered DPS removal or migration as time-varying covariate.

Results:
Among 320 patients (median age 58, 36% female), DPS were removed in 153 (47.8%), migrated spontaneously in 27 (8.4%), and remained indwelling in 140 (43.8%). PFC recurrence was observed in 57 patients (17.8%): after removal in 39 (25.5%), after migration in 4 (14.8%) and in patients with indwelling DPS in 14 patients (10%). In 25 patients (7.8%) drainage of recurrent PFC was indicated. Risk factors for recurrence were DPS removal or migration (HR: 3.45, 95%CI: 1.37–8.70) and presence of a disconnected pancreatic duct (HR: 3.45, 95%CI: 1.84–14.0).

Conclusions:
Among patients who undergo ETD of WON, leaving DPS in situ seems to lower the risk on recurrent fluid collections, without any long term DPS-related complications. These results suggest that DPS should not be routinely removed and can be safely left indwelling indefinitely.

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ABSTRACT

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ABBREVIATIONS

ANP	Acute necrotizing pancreatitis
CP	Chronic Pancreatitis
DMII	Type II Diabetes Mellitus
DPDS	Disconnected Pancreatic Duct Syndrome
DPS	Double pigtail Stents
ERCP	Endoscopic retrograde cholangiopancreatography
ESGE	European Society of Gastrointestinal Endoscopy
ETD	Endoscopic Transmural Drainage
IQR	Interquartile Range
PFC	Peri-pancreatic fluid collection
WON	Walled-off pancreatic necrosis

Introduction

Acute pancreatitis can result in walled-off pancreatic necrosis (WON) in about 20% of patients [1]. Invasive intervention can be indicated for patients with acute necrotizing pancreatitis (ANP) and clinically suspected or proven infected necrosis, in line with the European Society of Gastrointestinal Endoscopy (ESGE) guideline recommendations [2]. Other indications of invasive treatment may be organ compression or abdominal compartment syndrome. Infected pancreatic necrosis is a serious condition associated with a prolonged and severe disease course, with mortality rates reported to be as high as 40% [3]. Furthermore, the loss of viable pancreatic parenchyma can cause disruption or disconnection of the pancreatic duct, resulting in disconnected pancreatic duct syndrome (DPDS) [4]. This condition can lead to ongoing formation of peri-pancreatic fluid collections (PFCs) and pancreatic fistula [5].

The ESGE recommends a step-up approach for the treatment of ANP, with percutaneous or endoscopic transmural drainage (ETD) as a first step, followed by necrosectomy if necessary [2]. If technically feasible the endoscopic approach is preferred [6, 7]. Prospective comparative studies show no differences in short term outcome between either placement of double-pigtail stents (DPS) or lumen apposing metal stents (LAMS) [8-10]. However, the guidelines do not provide a recommendation on the duration of DPS to remain in situ in for both patients with and for those without DPDS. Studies have shown varying rates (0-38%) of PFC recurrence and complications associated with DPS removal or leaving DPS indwelling [2, 11-14].

Our current study aims to investigate the rate of PFC recurrence in patients undergoing ETD for treatment of WON using DPS, both for patients in whom these were removed electively or migrated spontaneously, and in patients in whom these were left long-term indwelling. In addition, possible risk factors associated with recurrence of PFC are evaluated.

Material and methods

Study design and patient selection

A multicenter, retrospective cohort study was conducted at three Dutch tertiary referral centers for pancreaticobiliary diseases, on patients who underwent ETD for the treatment of WON between July 2001 and December 2019. The patients were identified from the local endoscopy database (Endobase or Clinical Assistant), in which all endoscopic procedures and reports are prospectively registered. WON was defined according to the revised Atlanta guidelines 2018 as a mature, encapsulated collection of pancreatic and/or peri-pancreatic necrosis that has developed a well-defined inflammatory wall [2]. As terminology of PFCs has changed over time, we retrospectively checked these criteria for all patients in consultation with an experienced gastroenterologist and radiologist experienced in hepatico-pancreato-biliary imaging, for all diagnostic imaging studies that were performed. Patients with ETD for cysts other than WON, such as pseudocysts, were excluded from this study. Initial drainage by LAMS was not an exclusion criteria, as long as DPS were placed after LAMS removal. This study was conducted in accordance to the guidelines of the Helsinki Declaration and was approved by the ethics committee of all participating centers (MEC-2019-0116).

Intervention

Initially, ETD was performed, with step-up endoscopic necrosectomy if clinically indicated. Endoscopic Ultrasound (EUS) was performed to visualize the WON, and the gastric or duodenal wall was punctured to create a fistulous tract using a cystotome or balloon dilatation. Subsequently DPS were placed under fluoroscopic guidance. The number, length, and diameter of the DPS were left to the discretion of the treating physician. If the WON contained a significant amount of solid necrotic tissue, a nasocystic catheter was routinely placed to irrigate and stimulate liquefaction of necrosis. Necrosectomy was performed during the first ETD if indicated or after the initial ETD, depending on whether the patient improved clinically or whether an infection of the WON was diagnosed. During a necrosectomy the fistulous tract was dilated to allow for endoscope access with a therapeutic gastroscope and necrotic tissue was removed.

Data collection

Using electronic patient records, data were collected on demographic factors (i.e. sex and age), medical history, etiology of the pancreatitis, size of WON, number of DPS placed, and number of endoscopic, radiological or surgical interventions for treatment of WON. WON size was measured using length, width and height. Length was defined as the longest length in the axial plane in centimeters (cm). In the same axial plane, the longest width (in cm) was measured perpendicular on the longest length. In addition, in the frontal plane the longest height (in cm) was measured.

In addition, long term complications, including chronic pancreatitis (CP), exocrine and/or exocrine insufficiency or type II Diabetes Mellitus (DMII), pancreatic fistula, or chronic pancreatic pain syndrome (>30 days after DPS placement) were recorded. Complications related to DPS, such as migration and/or perforation, were also recorded. Time to migration was based on the date of imaging confirming migration. Finally, the number of patients diagnosed with DPDS was recorded. For all patients, the maximum follow-up time was based on data availability in individual medical records; i.e. last moment of outpatient contact or death.

Cross-sectional imaging during follow up

After endoscopic treatment of WON, cross-sectional imaging was not routinely performed in every patient. Follow up imaging after endoscopic treatment of WON was performed in case of suspicion of PFC related symptoms or for diagnostic reasons other than detection of PFCs (for example, CAT scan for pseudo-aneurysm). When cross-sectional imaging or upper gastrointestinal endoscopy was performed during follow-up, this provided additional information on the status of DPS; i.e. whether they were still left indwelling or had migrated.

Study outcomes

The study's primary endpoint was the recurrence of PFC. As imaging to confirm WON resolution was not routinely performed, time to recurrence was calculated as time from last intervention to date of recurrence of PFC. Recurrence was defined as a PFC on imaging studies after initial successful treatment of WON,

and further classified as a true recurrent PFC in case of detection at the initial site of endoscopic drainage, or a new PFC in case of detection not at the initial site of endoscopic drainage.

The secondary endpoints were factors associated with PFC recurrence. Presence of DPDS was diagnosed at magnetic resonance cholangio-pancreatography, computed tomography (CT) scan or ERCP, and defined as a complete or incomplete disruption of the pancreatic duct as judged by an experienced radiologist in HPB imaging.

Statistical analysis

The statistical analysis included descriptive statistics using mean and standard deviation for normally distributed variables, and median and interquartile range (IQR) for non-normally distributed continuous variables. Categorical and dichotomous variables were described using frequencies and proportions (%). Competing risk analysis, using cause-specific hazard regression, was performed to assess the association between several variables and PFC recurrence. In addition, a sensitivity analysis for symptomatic PFC recurrence was performed. Variables included in these analyses were based on current literature or expert opinion. Variables included in multivariable regression were based on the statistical significance of the regression coefficients in the univariate model. In line with cause-specific hazard regression, all patients who died without a recurrence of PFC were treated as censored. DPS removal or migration of all DPS was treated as a combined time-varying covariate. Whenever migration of DPS occurred, but at least one DPS remained in situ, this was defined as indwelling. Outcomes were presented as a Hazard Ratio's (HR) using 95% confidence intervals (CI). A 2-sided p-value of <0.05 was considered statistically significant. Statistical analyses were performed using R software, version 4.2.2.

Results

Baseline characteristics

During the study period, 320 patients underwent ETD for symptomatic WON (114 (35.6%) female, median age 58 years [IQR: 48.0 – 68.0]). ANP was diagnosed in 306 patients (95.6%) and acute-on-chronic pancreatitis in 14 (4.4%). Biliary stones were the most common cause of ANP, occurring in 126 patients (39.4%). In 74% of patients the WON was infected prior to initial ETD. Baseline characteristics are presented in Table 1.

Endoscopic drainage procedures

ETD was performed via trans-gastric route in the majority of patients (n = 291 (90.9%)). A median of two DPS were placed. In 29 patients (9.1%) LAMS were exchanged to DPS and in three patients (0.9%) a LAMS was additionally placed in a different WON. Following initial ETD, a nasocystic drain was inserted in 249 patients (77.8%). An additional necrosectomy was performed in 169 patients (52.8%), with a median of three necrosectomy procedures [IQR: 2 – 4] in these patients. In 33 patients (10.3%) percutaneous drainage was performed after ETD and in 13 patients (4.1%) a surgical debridement was performed. Additional details on the ETD procedures and any additional procedures are presented in Table 2.

Stents and long term follow-up

Cross-sectional follow-up imaging was performed in 297 (92.8%) patients. During a median follow up of 23 months [IQR: 5.5 – 66.3], a total of 57 patients (17.8%) were diagnosed with a recurrence of a PFC after initial resolution of ETD treated WON. In patients with a recurrent PFC, resolution of initial WON was confirmed in all patients on cross-sectional imaging prior to date of diagnosis of a recurrent PFC. In 40/57 (70.2%) patients these were detected at the same location as the initially drained WON. Of all detected recurrences, 36 (63.2%) were symptomatic, mostly due to infection related complaints. In 24 symptomatic and one asymptomatic recurrence, additional intervention was indicated, most of the patients underwent ETD. The remaining PFC recurrences were managed conservatively.

Recurrence rates were different among subgroups of patients in which DPS were removed electively, DPS had migrated spontaneously, or were left indwelling. During follow-up, 153 of 320 (47.8%) patients had their DPS removed after a median period of 3.4 months [IQR: 1.6 – 7.0]. The median follow-up period after stents were removed was 27.1 months [IQR: 4.9 – 79.6]. Recurrence occurred in 39/153 patients (25.5%). In 27 of 320 patients (8.4%), spontaneous migration of all DPS was documented after a median follow-up of 7.4 months [IQR: 3.5 – 12.1]. Migration of all DPS was detected by cross-sectional imaging in all 27 patients. In 4 patients a gastroscopy was performed prior to electively remove the DPS, but upon inspection the DPS had already migrated spontaneously, after which cross-sectional imaging confirmed this finding. The median follow-up period after stents migration was 24.7 months [IQR: 5.7 – 48.2]. Recurrence after spontaneous migration of the stents occurred in 4/27 patients (14.8%). In the remaining 140 patients (43.8%), DPS were left in situ until end of follow-up or death (Figure 1), with a median follow-up of 8.2 months [IQR: 0.6 – 33.8]. Recurrence occurred in 14/140 patients (10%).

Recurrence and associated factors

In multivariate competing risk regression analysis, both presence of DPDS (HR: 5.08, 95%CI: 1.84 – 14.0) and DPS no longer in situ [HR 3.45, 95%CI: 1.37 – 8.70] were significantly and independently associated with recurrence of PFC after resolution of WON. Sensitivity analysis for only symptomatic recurrences showed consistent results, as shown in Supplementary Table 1.

DPS related complications

In 28 patients all DPS seemed to have migrated spontaneously, including one patient with recurrence diagnosed 22.7 months prior. In another 28 patients at least one DPS remained in situ after migration of one or multiple DPS. In one (1.8%) patient, DPS migrated through the WON and resulted in a perforation of the colon which was located outside the ETD fistula. The patient was treated conservatively by stent removal and antibiotics. This was diagnosed 9 days after last ETD. No DPS-related complications, such as occlusion or bleeding after DPS erosion, occurred in the patients with indwelling DPS.

Discussion

In this large, retrospective multicenter study of WON patients, leaving DPS indwelling after successful ETD is associated with a significantly lower recurrence rate of PFC than after removal or migration of the DPS. Severe DPS-related complications are rare. These results, in line with recent literature, suggest that DPS can considered to be left indwelling to reduce the number of PFC recurrences.

We found an overall recurrence rate of PFC after successful ETD of 17.8%, of which most were located at the initial site of WON drainage. In recent literature, these recurrence rates vary widely 0 – 37% [14-27]. Arvanitakis *et al.* compared stent retrieval versus leaving the stents indwelling, and found that retrieval was associated with higher recurrence rates, with no recurrences in the indwelling group [16]. However, only 46 patients were included of all types of PFC, and not WON specifically. Bang *et al.* reported similar findings in all types of PFC [11]. A study from 2013 reported that long-term indwelling stents are safe and effective with minimal complications [19]. In five patients (16.6%) migration of DPS occurred, resulting in recurrence of PFC in one patient. In the remaining 25 patients, no recurrence was diagnosed. All of the abovementioned studies are limited by the small sample size, the relatively short follow-up and competing risks such as death were not accounted for.

The study of Chavan *et al*., however, improved on many of these aspects [14]. After successful ETD and PFC resolution, the large caliber metal stent was removed and patients diagnosed with DPDS were randomized between DPS placement or no DPS. In the 104 patients after one year of follow-up, almost 20% of patients presented with a recurrence of PFC. This was not significantly associated with plastic stents replacement in both intention-to-treat analyses and per-protocol analyses. The trial has some limitations however, as postulated in three letters to the editor [28-30]. Firstly, the follow-up period stopped after one year, potentially missing an important part of follow-up as previous studies have shown that PFC recurrence mostly occurred in the first two years. Secondly, the per-protocol analyses was hampered by significant differential attrition bias. Thirdly, the protocol of the study was to place a DPS four weeks after initial LAMS placement, but complete resolution of the WON was not confirmed.

Several other studies have investigated potential risk factors for recurrence of PFC after initial resolution. We found DPS removal and/or migration as well as DPDS diagnosis to be significantly associated with PFC recurrence. Although severely limited by the small cohort of 35 patients, Rana *et al.* found removal of stents and/or diagnosis of DPDS were independent risk factors for recurrence [31], which was in line with other recent studies. [11, 16, 26]. Gkolfakis *et al*. found stent migration, CP, and the length of the first DPS >6 cm to be independent risk factors for recurrence [32]. However, they included all types of fluid collections and did not routinely remove stents lacking a clear comparison group. The major limitation of all of these studies is the fact that they have not taken into account competing risks, such as death, and removal or migration of the stent as a time-varying covariate. However, in the current study we have performed these exact analyses and have confirmed that DPDS diagnosis and removal or migration of the DPS are both independently and significantly associated with increased risk of PFC recurrence.

While recent studies on WON mainly focus on LAMS [33, 34], a recent systematic review and meta-analysis showed that LAMS and DPS have equal clinical outcomes and adverse events [35]. Recent prospective studies have shown no significant differences [8-10]. Therefore, more studies are needed focusing on DPS replacement after WON resolution by LAMS. The need to leave DPS indwelling may even favor DPS compared to LAMS.

As compared to the aforementioned studies, our study has several strengths. To the best of our knowledge, this is the largest study evaluating the clinical outcome of patients after endoscopic treatment of WON, with regard to the removal of DPS of leaving them in situ. Firstly, patients were included from three expert treatment centers and thereby including a large number of patients ensuring a high enough number of events to facilitate multivariable regression analysis. Secondly, with the use of competing risk analysis the competing event of mortality can be taken into account. Thirdly, time-varying covariates are more suited for complex situations in patient in which the status of the stent changes over time then stratification based on what happened in the follow-up. However, with its retrospective design some inherent limitations are worth noting. Long-term follow-up was not available in several patients as patients were referred back to another hospital or died shortly after. We took these factors partially into account by

performing competing risk analysis. Secondly, the definitions of WON were not as well formulated before the Atlanta guidelines and potential patients could be missed due to misclassification [2]. To obtain our total cohort, all endoscopically treated PFC were retrospectively analyzed with the most recent guidelines. Thirdly, the recurrence rate is likely an underestimation as not all patients underwent routine follow-up imaging to assess this, as shown by the large rate of recurrences who did not undergo a re-ETD. However, this is likely not to be clinically relevant as these patients would have presented themselves with symptoms. Also, it is difficult to assess whether a PFC is an actual recurrence, or a PFC/WON at another location. Fourth, the rate of spontaneous migration of indwelling DPS may have been an underestimation as follow-up imaging was not routinely performed. Finally, choice of removal or leaving the DPS indwelling changed over time and differed between treatment centers.

In conclusion, in this largest study up to date on the effect of removal of DPS after ETD on recurrence rates of PFC, our results suggest that DPS can be left indwelling indefinitely in order to lower the risk of (symptomatic) recurrence. The effect of removing or leaving the DPS indwelling, should be included in future randomized controlled trials with long term follow-up and larger patient cohorts to enable vast multivariable regression analyses.

Conflicts of interest

M.J. Bruno received research support from Boston Scientific, Cook Medical, Pentax Medical, Mylan, ChiRoStim and acts as a consultant/lecturer for Boston Scientific, Cook Medical, Pentax Medical and AMBU. R.P. Voermans received research funding for investigator initiated studies from Boston Scientific and Prion Medical. He is a consultant with speakers fee for Boston Scientific. D.M. de Jong, P.M.C. Stassen, I.G. Schoots, R.C. Verdonk and P.J.F. de Jonge declare that they have no conflicts of interest.

REFERENCES

1. Singh VK, Bollen TL, Wu BU, et al. An assessment of the severity of interstitial pancreatitis. Clin Gastroenterol Hepatol. 2011;9(12):1098-1103.
2. Arvanitakis M, Dumonceau JM, Albert J, et al. Endoscopic management of acute necrotizing pancreatitis: European Society of Gastrointestinal Endoscopy (ESGE) evidence-based multidisciplinary guidelines. Endoscopy. 2018;50(5):524-546.
3. Bugiantella W, Rondelli F, Boni M, et al. Necrotizing pancreatitis: A review of the interventions. Int J Surg. 2016;28 Suppl 1:S163-171.
4. van Santvoort HC, Bakker OJ, Bollen TL, et al. A conservative and minimally invasive approach to necrotizing pancreatitis improves outcome. Gastroenterology. 2011;141(4):1254-1263.
5. Jang JW, Kim MH, Oh D, et al. Factors and outcomes associated with pancreatic duct disruption in patients with acute necrotizing pancreatitis. Pancreatology. 2016;16(6):958-965.
6. Onnekink AM, Boxhoorn L, Timmerhuis HC, et al. Endoscopic Versus Surgical Step-Up Approach for Infected Necrotizing Pancreatitis (ExTENSION): Long-term Follow-up of a Randomized Trial. Gastroenterology. 2022;163(3):712-722 e714.
7. van Brunschot S, van Grinsven J, van Santvoort HC, et al. Endoscopic or surgical step-up approach for infected necrotising pancreatitis: a multicentre randomised trial. Lancet. 2018;391(10115):51-58.
8. Boxhoorn L, Verdonk RC, Besselink MG, et al. Comparison of lumen-apposing metal stents versus double-pigtail plastic stents for infected necrotising pancreatitis. Gut. 2023;72(1):66-72.
9. Chandrasekhara V, Barthet M, Deviere J, et al. Safety and efficacy of lumen-apposing metal stents versus plastic stents to treat walled-off pancreatic necrosis: systematic review and meta-analysis. Endosc Int Open. 2020;8(11):E1639-E1653.
10. Bang JY, Navaneethan U, Hasan MK, et al. Non-superiority of lumen-apposing metal stents over plastic stents for drainage of walled-off necrosis in a randomised trial. Gut. 2018;gutjnl-2017-315335 [pii]

10.1136/gutjnl-2017-315335.
11. Bang JY, Wilcox CM, Navaneethan U, et al. Impact of Disconnected Pancreatic Duct Syndrome on the Endoscopic Management of Pancreatic Fluid Collections. Ann Surg. 2018;267(3):561-568.
12. Shekhar C, Maher B, Forde C, et al. Endoscopic ultrasound-guided pancreatic fluid collections' transmural drainage outcomes in 100 consecutive cases of pseudocysts and walled off necrosis: a single-centre experience from the United Kingdom. Scand J Gastroenterol. 2018;53(5):611-615.
13. Bang JY, Mel Wilcox C, Arnoletti JP, et al. Importance of Disconnected Pancreatic Duct Syndrome in Recurrence of Pancreatic Fluid Collections Initially Drained Using Lumen-Apposing Metal Stents. Clin Gastroenterol Hepatol. 2021;19(6):1275-1281 e1272.
14. Chavan R, Nabi Z, Lakhtakia S, et al. Impact of transmural plastic stent on recurrence of pancreatic fluid collection after metal stent removal in disconnected pancreatic duct: a randomized controlled trial. Endoscopy. 2022;54(9):861-868.
15. Jagielski M, Smoczynski M, Jablonska A, et al. The role of endoscopic ultrasonography in endoscopic debridement of walled-off pancreatic necrosis--A single center experience. Pancreatology. 2015;15(5):503-507.
16. Arvanitakis M, Delhaye M, Bali MA, et al. Pancreatic-fluid collections: a randomized controlled trial regarding stent removal after endoscopic transmural drainage. Gastrointest Endosc. 2007;65(4):609-619.

17. Rana SS, Bhasin DK, Rao C, et al. Consequences of long term indwelling transmural stents in patients with walled off pancreatic necrosis & disconnected pancreatic duct syndrome. Pancreatology. 2013;13(5):486-490.
18. Siddiqui AA, Kowalski TE, Loren DE, et al. Fully covered self-expanding metal stents versus lumen-apposing fully covered self-expanding metal stent versus plastic stents for endoscopic drainage of pancreatic walled-off necrosis: clinical outcomes and success. Gastrointest Endosc. 2017;85(4):758-765.
19. Rana SS, Shah J, Sharma RK, et al. Clinical and morphological consequences of permanent indwelling transmural plastic stents in disconnected pancreatic duct syndrome. Endosc Ultrasound. 2020;9(2):130-137.
20. Schmidt PN, Novovic S, Roug S, et al. Endoscopic, transmural drainage and necrosectomy for walled-off pancreatic and peripancreatic necrosis is associated with low mortality--a single-center experience. Scand J Gastroenterol. 2015;50(5):611-618.
21. Jagielski M, Smoczynski M, Adrych K, et al. Endoscopic necrosectomy under fluoroscopic guidance during transmural drainage of walled-off pancreatic necrosis (WOPN). Pol Przegl Chir. 2019;92(1):12-17.
22. Varadarajulu S, Wilcox CM. Endoscopic placement of permanent indwelling transmural stents in disconnected pancreatic duct syndrome: does benefit outweigh the risks? Gastrointest Endosc. 2011;74(6):1408-1412.
23. Tellez-Avina FI, Casasola-Sanchez LE, Ramirez-Luna MA, et al. Permanent Indwelling Transmural Stents for Endoscopic Treatment of Patients With Disconnected Pancreatic Duct Syndrome: Long-term Results. J Clin Gastroenterol. 2018;52(1):85-90.
24. Watanabe Y, Mikata R, Yasui S, et al. Short- and long-term results of endoscopic ultrasound-guided transmural drainage for pancreatic pseudocysts and walled-off necrosis. World J Gastroenterol. 2017;23(39):7110-7118.
25. Chen YI, Yang J, Friedland S, et al. Lumen apposing metal stents are superior to plastic stents in pancreatic walled-off necrosis: a large international multicenter study. Endosc Int Open. 2019;7(3):E347-E354.
26. Basha J, Lakhtakia S, Nabi Z, et al. Impact of disconnected pancreatic duct on recurrence of fluid collections and new-onset diabetes: do we finally have an answer? Gut. 2021;70(3):447.
27. Pawa R, Dorrell R, Russell G, et al. Long-term transmural drainage of pancreatic fluid collections with double pigtail stents following lumen-apposing metal stent placement improves recurrence-free survival in disconnected pancreatic duct syndrome. Dig Endosc. 2022;34(6):1234-1241.
28. Rana SS, Gupta R. Long-term transmural plastic stenting after metal stent removal in disconnected pancreatic duct: is the debate over? Endoscopy. 2022;54(09):920-920.
29. Vanbiervliet G. Prevention of pancreatic fluid collection recurrence after metal stent removal: plastic is not so fantastic! Referring to Chavan R et al p 861–868. 2022;54(09):869-870.
30. Dhar J, Sachan A, Samanta J. To stent or not to stent: do we have an answer yet? Endoscopy. 2022;54(07):728-728.
31. Rana SS, Bhasin DK, Sharma R, et al. Factors determining recurrence of fluid collections following migration of intended long term transmural stents in patients with walled off pancreatic necrosis and disconnected pancreatic duct syndrome. Endosc Ultrasound. 2015;4(3):208-212.
32. Gkolfakis P, Bourguignon A, Arvanitakis M, et al. Indwelling double-pigtail plastic stents for treating disconnected pancreatic duct syndrome-associated peripancreatic fluid collections: long-term safety and efficacy. Endoscopy. 2021;53(11):1141-1149.
33. Anderloni A, Fabbri C, Nieto J, et al. The safety and efficacy of a new 20-mm lumen apposing metal stent (lams) for the endoscopic treatment of pancreatic and peripancreatic fluid collections: a large international, multicenter study. Surg Endosc. 2020;10.1007/s00464-020-07567-8

10.1007/s00464-020-07567-8 [pii].
34. Khan S, Chandran S, Chin J, et al. Drainage of pancreatic fluid collections using a lumen-apposing metal stent with an electrocautery-enhanced delivery system. J Gastroenterol Hepatol. 2021;10.1111/jgh.15658.
35. Mohan BP, Jayaraj M, Asokkumar R, et al. Lumen apposing metal stents in drainage of pancreatic walled-off necrosis, are they any better than plastic stents? A systematic review and meta-analysis of studies published since the revised Atlanta classification of pancreatic fluid collections. Endosc Ultrasound. 2019;8(2):82-90.

Figure legend

Figure 1. Flowchart of included patients
WON = Walled Off pancreatic Necrosis, ETD = Endoscopic Transmural Drainage, IQR = Inter Quartile Range, PFC = Pancreatic Fluid Collection
* = In one patient stents migrated 22.7 months after a recurrence was diagnosed and in one patient stents were removed 11.5 months after recurrence was diagnosed

	Multivariate		
Characteristic	**HR**	**95% CI**	**p-value**
Age (in years)	0.98	0.96 – 1.00	0.025
Infected (Yes)*	0.47	0.24 – 0.93	0.030
DPDS diagnosis (Yes)	7.06	1.82 – 27.4	0.005
Stent removal or migration**	3.91	1.07 – 14.3	0.039
Stent removal or migration (Yes)** x DPDS diagnosis (Yes)	0.79	0.16 – 3.76	0.764

Table S1. Results from multivariate competing risk regression analysis using cause-specific hazard regression for chance of recurrence of symptomatic PFC

HR = Hazard Ratio, CI = Confidence Interval, ANP = Acute Necrotizing Pancreatitis, DPDS = Disconnected Pancreatic Duct Syndrome, ETD = Endoscopic Transmural Drainage, PFC = Pancreatic Fluid Collection

* = At baseline or after ETD
** = Analyzed as time-varying covariate

Characteristic	Total population (n = 320)	Missing - n (%)
Sex = Female (%)	114 (35.6)	0
Age in years (median [IQR])	58.00 [48.00, 68.00]	0
WON characteristics		
Type of Pancreatitis = ANP (%)	306 (95.6)	0
Aetiology of Pancreatitis (%)		0
- Alcohol	57 (17.8)	
- Biliary	126 (39.4)	
- Idiopathic	78 (24.4)	
- Post-ERCP	21 (6.6)	
- Other**	38 (11.9)	
WON location (%)		39 (12.2)
- Total	94 (33.5)	
- Head	38 (13.5)	
- Head + Body	32 (11.4)	
- Body + tail	39 (13.9)	
- Body	35 (12.5)	
- Tail	43 (15.3)	
Length in cm (median [IQR])	11.71 [8.60, 15.20]	31 (10)
Volume (median [IQR])	725.20 [402.60, 1483.02]	163 (51)
DPDS diagnosis = Yes (%)	55 (17.2)	0
Signs of infection on imaging, fine-needle aspiration, clinical presentation or initial endoscopic findings, prior to ETD = Yes (%)	182 (74.0)	74 (23.1)
Interventions prior to first ETD		
Percutaneous drainage prior to ETD = Yes (%)	32 (10.0)	0

Surgical procedure prior to ETD = Yes (%)	5 (1.6)	0

Table 1. Baseline characteristics of all included patients

IQR = Inter Quartile Range, ANP = Acute Necrotizing Pancreatitis, Post-ERCP = Post Endoscopic Retrograde Cholangiopancreatography, WON = Walled Off Pancreatic Necrosis, DPDS = Disconnected Pancreatic Duct Syndrome, ETD = Endoscopic Transmural Drainage

* = versus acute on chronic pancreatitis

** = Other presumed causes of WON: L-asparaginase (n = 2), Endo-barrier (n = 1), Hypertriglyceridemia (n = 5), ischemia (n = 3), pancreas divisum (n = 2), pancreatic cancer (n = 2), Peutz-Jeghers polyp (n = 1), pharmacological (n = 12), surgery (n = 5), post-partum hypercalcemia (n = 1), post-single balloon enteroscopy (n = 1), systemic lupus erythematosus (n = 1) and traumatic injury (n = 1)

Characteristic	Total population (n = 320)	Missing - n
ETD location (%)		0
- Duodenum/Bulbus	28 (8.8)	
- Stomach	291 (90.9)	
- Oesophagus	1 (0.3)	
Number of stents at placement (%)		0
- 1	13 (4.1)	
- 2	224 (70.0)	
- ≥3	83 (25.9)	
Total number of endoscopic interventions (median [IQR])	2 [1, 4]	0
Nasocystic catheter placed = Yes (%)	249 (77.8)	0
Necrosectomy performed = Yes (%)	169 (52.8)	0
Infection WON = Yes (%)	66 (20.6)	0
LAMS placement (%)		0
- Other WON	3 (0.9)	
- Before DPS placement	29 (9.1)	
Interventions after first ETD		
Percutaneous drainage after to ETD = Yes (%)	33 (10.3)	0
Surgical procedure prior to ETD = Yes (%)	13 (4.1)	0

Table 2. Characteristics of the performed drainage procedures

ETD = Endoscopic Transmural Drainage, IQR = Inter Quartile Range, WON = Walled Off Pancreatic Necrosis, DPS = Double pigtail stent, LAMS = lumen apposing metal stent

Characteristic	Total population (n = 320)	Missing - n (%)
Recurrence = Yes (%) - After removal (n = 153) - After migration (n = 27) - Indwelling (n = 140)	57 (17.8) 39 (68.4) 4 (8.8) 14 (24.6)	0
Time to recurrence in days (median [IQR])	370 [198, 767]	0
Symptomatic recurrence = Yes (%) - Mechanic obstruction* - Inflammation/Infection	36 (63.2) 5 (13.9) 26 (72.2)	5 (8.8)
Same location as initial WON = Yes (%)	40 (70.2)	7 (12.3)
Intervention performed = Yes (%) - Re-ETD - Percutaneous drainage - Surgery - ERCP with biliary stent placement	25 (43.9) 12 (48.0)*** 9 (36.0) 1 (4.0) 2 (8.0)	1 (1.8)**
Total follow-up period in days (median [IQR])	690.50 [166.8, 2004.8]	0
Death during follow-up = Yes (%)	54 (16.9)	0

Table 3. Long-term follow up data

IQR = Inter Quartile Range

* = gastric outlet obstruction in three patients, biliary duct compression in two patients
** = Intervention performed elsewhere, unclear whether this was percutaneous or re-ETD
*** = In 1 patient with asymptomatic recurrence

	Univariate			Multivariate		
Characteristic	**HR**	**95% CI**	**p-value**	**HR**	**95% CI**	**p-value**
Age (in years)	0.98	0.97 - 1.00	0.033	0.99	0.97 – 1.00	0.135
Sex (Female)	1.26	0.74 - 2.16	0.389			
ANP (vs acute on chronic)	0.40	0.16 – 1.01	0.052			
Infected (Yes)*	0.52	0.31 - 0.90	0.018	0.61	0.35 - 1.05	0.076
ETD Location						
- Duodenum/bulbus	Ref	Ref	Ref			
- Stomach	1.40	0.51 – 3.88	0.513			
- Oesophagus	0.00	0.00 - Inf	0.996			
Nasocystic catheter (Yes)	1.04	0.54 – 2.02	0.902			
Necrosectomy (Yes)	1.28	0.75 – 2.17	0.367			
Percutaneous intervention (Yes)	0.98	0.49 - 1.94	0.951			
Surgery intervention (Yes)	1.82	0.83 - 4.02	0.138			
DPDS diagnosis (Yes)	3.82	2.26 - 6.45	<0.001	5.08	1.84 – 14.0	0.002
Stent removal or migration**	2.66	1.43 – 4.93	0.002	3.45	1.37 – 8.70	0.009
ETD number (per procedure)	0.98	0.87 - 1.11	0.803			
Stent removal or migration (Yes)** x DPDS diagnosis (Yes)				0.87	0.26 – 2.88	0.819

Table 4. Results from univariate and multivariate competing risk regression analysis using cause-specific hazard regression for chance of recurrence of PFC

HR = Hazard Ratio, CI = Confidence Interval, ANP = Acute Necrotizing Pancreatitis, DPDS = Disconnected Pancreatic Duct Syndrome, ETD = Endoscopic Transmural Drainage, PFC = Pancreatic Fluid Collection

* = At baseline or after ETD
** = Analyzed as time-varying covariate