Comparison of early and delayed EUS-guided drainage of pancreatic fluid collection

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ABSTRACT

Background and study aims While endoscopic ultrasound (EUS)-guided drainage of pancreatic fluid collection (PFC) is recommended to be performed ≥4 weeks after onset of acute pancreatitis (AP), early (<4 weeks) interventions are needed in some symptomatic cases. Despite feasibility of early percutaneous drainage, there have been few studies about early EUS-guided drainage of PFC.

Patients and methods Consecutive patients who received EUS-guided drainage (EUS-PCD) of infected or symptomatic PFC at the University of Tokyo were retrospectively studied. Contraindications for EUS-PCD are lack of encapsulation or adhesion to the gastrointestinal tract. Safety and effectiveness of early vs delayed (≥4 weeks) EUS-PCD were compared.

Results A total of 35 patients underwent EUS-PCD (12 early and 23 delayed) using 19 large-bore fully-covered metallic stent and 16 plastic stents. The median diameter of PFC was 110 mm (40–180) and 122 mm (17–250) in the early and delayed drainage groups, respectively. Median time from onset of AP to drainage was 23 and 85 days for early and delayed drainage, respectively. The technical success rate of EUS-guided drainage was 100 %. Endoscopic necrosectomy was performed in six early and 16 cases of delayed drainage. The adverse event rate was 25 % (3 bleeding) and 13 % (2 perforations and 1 CO2 retention) in the early and delayed drainage groups, respectively. Two patients died (1 early and 1 delayed) due to multiorgan failure.

Conclusion Endoscopic drainage and subsequent necrosectomy of symptomatic PFC within 4 weeks after onset of acute pancreatitis was feasible, given that the collection was encapsulated and attached to the gastrointestinal tract.

Introduction
Pancreatic fluid collections (PFC) are local complications of acute pancreatitis in which secondary infection leads to significant morbidity and mortality [1]. According to the revised Atlanta classification, PFC that is seen 4 weeks after onset of acute pancreatitis is classified as either pancreatic pseudocyst (PP) or walled-off necrosis (WON) depending on absence or presence of pancreatic necrosis [2]. In most cases, the 4-week interval allows these collections to become well encapsulated. In severe acute pancreatitis, multiorgan failure (MOF), which is related to the extent of pancreatic necrosis with concomitant
infection, is not uncommon and can be fatal [3]. In symptomatic cases or when infection is suspected, therapeutic intervention is indicated when the condition is refractory to conservative treatment, such as endoscopic drainage, percutaneous drainage, and surgical debridement [4–7]. The trend for drainage approach has moved from a surgical procedure to endoscopic and percutaneous procedures with a step-up approach [1, 8, 9], as the latter was found to be associated with lower morbidity and mortality [1].

The IAP/APA guideline suggested that endoscopic treatment for WON should be delayed at least 4 weeks after onset of pancreatitis whenever possible to allow encapsulation of necrotic tissue. Also, there has been supporting data demonstrated that mortality was decreased if endoscopic necrosectomy (EN) was delayed until 30 days after hospitalization [10, 11]. Studies based on open surgical intervention of necrotizing pancreatitis showed higher mortality when surgery was performed earlier than 4 weeks [5, 11], which leads to the recommendation that endoscopic drainage should be performed 4 weeks after its onset. However, in some cases, indications for drainage such as infection or pressure effects to the surrounding organ may occur earlier, warranting early intervention. Feasibility of percutaneous drainage within 4 weeks has been reported [12–14] but study regarding the feasible timing of endoscopic drainage for pancreatic fluid collection (PFC) has been limited. The aim of this study was to evaluate feasibility and safety of early (<4 weeks) endoscopic drainage for PFC.

Patients and methods

Patients

This was a retrospective analysis based on a prospectively collected database in our center. Consecutive patients receiving endoscopic ultrasound (EUS)-guided drainage for PFC at the University of Tokyo hospital from September 2007 to February 2017 were retrospectively studied. Indications for EUS-guided drainage included symptomatic lesions (local infection, pain, biliary, pancreatic or enteric obstruction and compartment syndrome) or symptoms refractory to conservative treatment. EUS-guided drainage was performed only when the lesion appeared well encapsulated and accessible from the stomach or duodenum as confirmed by pre-procedure computed tomography (CT) scan (Fig. 1). Presence of air inside the PFC or of ascites prior to endoscopic drainage was noted. Contraindications were severe coagulopathy and general conditions unsuitable for endoscopic interventions. Data on patient characteristics, timing of endoscopic drainage after onset of acute pancreatitis and its outcomes, endoscopic procedures as well as other additional treatment after endoscopic drainage were collected from our EUS database and medical records.

Response to endoscopic drainage was evaluated based on clinical symptoms such as fever and pain, blood tests such as changes in white blood cell counts and serum C-reactive protein level (CRP) and image findings such as CT. CT scan was routinely performed 1 day after the drainage procedure to evaluate immediate procedure-related complications, and evidence of free perforation (pneumoperitoneum) and newly developed ascites were evaluated (Fig. 2). CT scan was repeated to evaluate response to drainage and necrosectomy every 1 to 4 weeks as clinically needed.

The primary outcome was technical success rate. Secondary outcomes were complications, mortality, length of hospital stay, need for second intervention, number of endoscopic necrosectomy or other endoscopic, percutaneous and surgical interventions [15].
Procedures

Endoscopic procedures were performed by six experienced endoscopists. Written informed consent regarding the procedure and its complications was obtained from all patients. Initial EUS-guided drainage was performed using either curvilinear echoendoscope EG-UCT240 (Olympus Medical Systems, Tokyo, Japan) or EG-580UT (Fujifilm Corp., Tokyo, Japan) and subsequent endoscopic necrosectomy was performed using an upper gastrointestinal endoscope with water jet (GIF-Q260J, Olympus Medical Systems). All endoscopic procedures were performed under conscious sedation using intravenous diazepam, pethidine hydrochloride, or pentazocine.

Initial EUS-guided PFC drainage was performed as follows. After identification of PFC on EUS image, the optimal location for endoscopic access was evaluated under endoscopic, EUS, and fluoroscopic guidance. For EUS-guided interventions, after confirmation of absence of intervening vessels using Doppler EUS, the collection was punctured through the stomach or the duodenum using a 19-gauge EUS fine-needle aspiration (EUS-FNA) needle (Fig. 3a). A guidewire was inserted through the needle and coiled inside the cavity. The tract was dilated using a bougie dilator, a balloon dilator, a 6-Fr cautery dilator (Cystogastro set, Endo-flex, Voerde, Germany, Fig. 3b) or its combination (Fig. 3c). Size and type of fistula dilation and stent selection were decided at the discretion of the attending physician. In cases of PFC without debris, multiple plastic stents

![Fig. 3a](image-url) Under EUS guidance, the collection was punctured using the 19 G EUS fine-needle aspiration (EUS-FNA) needle. b The guidewire was inserted through the EUS-FNA needle and the tract was initially dilated using a 6 Fr coaxial dilator. c Additional balloon dilation was performed. d Subsequently, the fully-cover self-expandable metal stent (Nagi stent, Taewoong Medical Co, Ltd, Gyeonggi-do, Korea) was inserted, e followed by the pigtail nasocystic tube.
were selected. In case of PFC with debris, a fully-covered self-expanding metal stent (FCSEMS) was preferred. However, during the study period, FCSEMS dedicated for EUS-PCD was not commercially available in Japan but was used in a clinical trial [10]. When insertion of multiple stents was planned, a second guidewire was inserted prior to stent insertion using a double lumen catheter (Uneven Double Lumen Cannula, Piolax Medical Devices). Subsequently, a large-bore, FCSEMS (Nagi stent, Taewoong Medical Co, Ltd, Gyeonggi-do, Korea) [10] or a double pigtail plastic stent was placed between the cavity and the gastrointestinal lumen (Fig. 3d). Finally, a 7-Fr pigtail nasocystic drainage tube was placed for external drainage and/or irrigation by continuous infusion of 500 mL of normal saline solution per day (Fig. 3e).

Decision to perform further interventions in each patient was made depending on the patient’s clinical condition based on step-up approaches. Transpapillary pancreatic duct stenting was performed in cases with pancreatic duct disruption. According to the Asian consensus, when clinical response (pain, fever, improvement of inflammatory markers) was not observed within a few days after the initial drainage with and without irrigation through a nasocystic drainage tube or incomplete PFC resolution was not demonstrated in follow-up imaging, EN was performed. In some patients, direct endoscopic necrosectomy was performed after initial EUS-PCD, at the discretion of the attending physician. In cases with Nagi stent placement, the upper endoscope was inserted into the cavity through the Nagi stent. In cases with double pigtail stent placement, after fistula dilation up to 15 mm using a balloon catheter, the endoscope was inserted into the cavity. EN was repeated until the necrotic tissue was removed from the WON cavity and clinical signs of infection improved. Irrigation using nasocystic drainage was performed between each EN session. After resolution of PFC, the Nagi stent was replaced by double pigtail stents 3 to 4 months after stent insertion.

Definition
Early drainage was defined as endoscopic drainage within 4 weeks (≤28 days) after onset of acute pancreatitis. Delayed drainage was defined as endoscopic drainage more than 4 weeks (>28 days) after onset of acute pancreatitis. Technical success was defined as successful stent placement at initial EUS-guided drainage. Clinical success was defined as improvement in clinical symptoms such as fever and pain and inflammatory markers such as serum C-reactive protein and white blood cell count. Adverse events were diagnosed and graded according to the American Society of Gastrointestinal Endoscopy lexicon [16].

Statistics
Demographic data such as age, timing of intervention, size, American Society of Anesthesia (ASA) score, success rates and complication rates between early and delayed drainage groups were compared using Mann-Whitney U test and Chi-Square test as appropriate. The difference between types of stents was calculated by Fisher’s exact test. A P value <0.05 was considered statistically significant. All analyses were performed using JMP software (version 12.2, SAS International Inc., Cary, North Carolina, United States).

Results
Patient characteristics and EUS-guided PFC drainage
A total of 35 EUS-guided PFC drainage procedures were performed in 34 patients. One patient underwent EUS-guided drainage twice after two episodes of alcoholic pancreatitis 26 months apart with an intervening full-recovery period. Patient characteristics are shown in Table 1. PFCs were located in the body in 23, tail in nine, head in two and there was diffuse involvement of the pancreas in one patient. The largest diameter of PFC ranged from 17 to 250 mm. Endoscopic drainage was performed under EUS guidance in 34 cases and using a gastroscope through a spontaneous cysto-gastric fistula in one case. The puncture site was through the stomach in 32 and through the duodenum in three cases. For fistula dilation, a coaxial cautery dilator, a balloon catheter and a bougie dilators were used as an initial dilator in 45.7%, 31.4% and 22.8%, respectively. A Nagi stent was inserted in 19 cases (9 in early drainage and 10 in delayed drainage) and multiple double pigtail stents were inserted in 16 cases (3 in early drainage and 13 in delayed drainage). A nasocystic drainage tube was concurrently inserted in 24 cases.

The median interval between onset of pancreatitis and endoscopic drainage was 64 days (range, 15 to 264), while the median interval between first detection of PFC and drainage was 36 days (range, 1 to 243). As a result, 12 cases received endoscopic drainage within 4 weeks after onset of acute pancreatitis (the early drainage group) while 23 cases received endoscopic treatment after 4 weeks (the delayed drainage group). Interval differences between those receiving early and delayed drainage groups are demonstrated in Table 1. Indications for drainage included infection in 24, pain in six, compartment syndrome in two, and failed conservative treatment in three patients.

Comparisons of early and delayed drainage
Clinical outcomes, need for further interventions, hospital stay, mortality, and complications between early and delayed drainage groups are shown in Table 2. Technical success with EUS-guided PFC drainage was achieved in all patients in both the early and delayed drainage groups. Immediately after EUS-guided PFC drainage, direct endoscopic necrosectomy was performed in one case in early drainage and five cases in the delayed drainage group. Subsequently, five patients in the early drainage group and 11 cases in the delayed drainage group received endoscopic necrosectomy as a step-up approach. As EN was performed both for non-responsive cases and for non-resolving lesion, the interval between first EUS-PCD and first EN ranged from 0 in direct endoscopic necrosectomy to 28 days after first EUS-PCD (Table 2). Direct endoscopic necrosectomy was performed in one and five patients in the early and delayed drainage groups, respectively, as shown in Fig. 4. The number of EN sessions varied from three to seven in the early drainage group, and one to nine sessions in the delayed drainage.
Other than EN, four additional EUS-guided drainage and four percutaneous drainage of the ascites, percutaneous transhepatic biliary drainage (PTBD) and percutaneous transhepatic gallbladder drainage (PTGBD) were performed, respectively. No PCD was performed in the same lesion as EUS-PCD.

Early complications related to EUS-guided drainage were observed in 25.0% (3 /12) and 21.7 % (5 /23) in the early and delayed groups. Two cases of perforation after the procedure were seen during the first drainage procedure in the delayed group, with the interval between EUS-PCD of 144 and 264 days after the onset of acute pancreatitis. Free perforation after subsequent EN was experienced in two cases in the delayed drainage group. Intra-procedure bleeding was observed in three cases in the early drainage group and one case in the delayed drainage group. In one case of bleeding from the cavity wall occurred during subsequent endoscopic necrosectomy, while in another two patients, bleeding from the puncture site was seen during the first EUS intervention. In the former case, bleeding was controlled by vascular embolization and in the latter cases, it was controlled by endoscopic hemostasis.

There were two cases of mortality (one case in the early and one case in the delayed group) due to persistent MOF as a result of severe acute pancreatitis. The death in the early drainage group was complicated by bleeding after necrosectomy. Bleeding and local infection were well managed by additional percutaneous drainage but the patient died due to persistent MOF. In both cases, the cause of death was due to severe acute pancreatitis rather than the procedure itself.

### Table 1  Comparison of baseline characteristics and inflammatory markers between early and delayed drainage groups prior to endoscopic drainage.

<table>
<thead>
<tr>
<th></th>
<th>All (N = 35)</th>
<th>Early drainage (N = 12)</th>
<th>Delayed drainage (N = 23)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (range), years</td>
<td>59 (33 – 84)</td>
<td>55 (33 – 77)</td>
<td>64 (33 – 84)</td>
<td>0.29</td>
</tr>
<tr>
<td>Male gender</td>
<td>82.8%</td>
<td>83.3%</td>
<td>82.6 %</td>
<td>0.96</td>
</tr>
<tr>
<td>ASA-PS, 1/2/3/4</td>
<td>2/14/23/6</td>
<td>0/4/7/1</td>
<td>2/12/16/5</td>
<td>0.54</td>
</tr>
<tr>
<td>Etiology</td>
<td></td>
<td></td>
<td></td>
<td>0.12</td>
</tr>
<tr>
<td>• Alcohol</td>
<td>6</td>
<td>2</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>• Gallstone</td>
<td>15</td>
<td>8</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>• PEP</td>
<td>2</td>
<td>0</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>• Pancreatic cancer</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>• Idiopathic</td>
<td>6</td>
<td>0</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Indication for drainage</td>
<td></td>
<td></td>
<td></td>
<td>0.864</td>
</tr>
<tr>
<td>• infection</td>
<td>24</td>
<td>8</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>• pain</td>
<td>6</td>
<td>3</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>• compartment syndrome</td>
<td>2</td>
<td>0</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>• Not response to conservative treatment</td>
<td>3</td>
<td>1</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Type of PFC</td>
<td></td>
<td></td>
<td></td>
<td>0.72</td>
</tr>
<tr>
<td>• APFC/PP</td>
<td>7</td>
<td>2</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>• ANC/WON</td>
<td>28</td>
<td>10</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>Median diameter (range), mm</td>
<td>121 (17 – 250)</td>
<td>94 (40 – 180)</td>
<td>123 (17 – 250)</td>
<td>0.17</td>
</tr>
<tr>
<td>Median interval after AP (range), days</td>
<td>39 (15 – 264)</td>
<td>23 (15 – 28)</td>
<td>85 (29 – 264)</td>
<td>0.09</td>
</tr>
<tr>
<td>Median interval after PFC detection (range), days</td>
<td>19 (1 – 243)</td>
<td>14 (1 – 27)</td>
<td>46 (5 – 243)</td>
<td>0.44</td>
</tr>
<tr>
<td>Mean pre-drainage CRP (SD), mg/dL</td>
<td>10.19 (8.86)</td>
<td>16.37 (9.25)</td>
<td>6.96 (6.84)</td>
<td>0.42</td>
</tr>
<tr>
<td>Mean pre-drainage WBC (SD), x10³/µl</td>
<td>10.05 (5.92)</td>
<td>12.33 (6.17)</td>
<td>8.85 (5.54)</td>
<td>0.48</td>
</tr>
<tr>
<td>Stent type</td>
<td></td>
<td></td>
<td></td>
<td>0.076</td>
</tr>
<tr>
<td>• Metallic stent</td>
<td>19</td>
<td>9</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>• Plastic stent</td>
<td>16</td>
<td>3</td>
<td>13</td>
<td></td>
</tr>
</tbody>
</table>

ANC, acute necrotic collection; AP, acute pancreatitis; APFC, acute peripancreatic fluid collection; ASA-PS, American Society of Anesthesiologists-Physical Status; CRP, C-reactive protein; PEP, post-ERCP pancreatitis; PFC, pancreatic fluid collection; PP, pancreatic pseudocyst; SD, standard deviation; WBC, white blood cell.
Discussion

In management of PFC, the step-up approach is standard of care and it is recommended that endoscopic intervention be delayed more than 4 weeks after onset of acute pancreatitis. However, early interventions are required earlier than 4 weeks in some symptomatic patients whose condition does not respond to conservative treatment. Our retrospective study suggested that early (<4 weeks) endoscopic drainage of PFC could be performed safely as long as it is encapsulated, in line with...
the feasible results of early percutaneous drainage of PFC [14]. However, because we did not intervene until PFC was encapsulated on CT scan, the earliest intervention was 15 days after onset of acute pancreatitis and most patients underwent drainage procedure more than 3 weeks after acute pancreatitis.

Perforation is one of the concerns when early interventions are performed, especially in cases with immature encapsulation but perforation was not seen in the early drainage group, even after subsequent EN was performed in our study. Rather, perforation was seen during the first attempt at drainage and after subsequent EN in the delayed drainage group, which was treated conservatively. This finding suggests that perforation cannot be prevented by a delayed drainage procedure during EUS-guided intervention. The overall complication rate was also comparable between the early and delayed drainage groups. Interestingly, more bleeding complications were observed in the early drainage group, one of which occurred during subsequent EN.

While the step-up approach is the current standard for necrotizing pancreatitis, there are some concerns that late intervention might cause necrotic tissue too solid to be readily drained or removed by EN [17]. In our study, the rate of EN was higher in the delayed group but the number of EN sessions was similar once EN was performed. Recently, the lumen-opposing metal stent (LAMS) has become popular as the drainage method for pancreatic fluid collection. With a larger-drainage lumen provided, the rate of EN might be lower when a (LAMS) was used as a EUS-PCD. Unfortunately, during the study period, LAMS was not widely available in many institutions, including ours. Because our study confirmed the feasibility of early EUS-PCD, appropriate timing of EUS-PCD using a LAMS should be further investigated a large-scale study, in terms of the need for EN and the number of EN sessions.

In most recommendations, PCD is the treatment of choice in patients who need PFC drainage within 4 weeks after onset of pancreatitis. A retrospective study recently was performed in 23 patients to evaluate the role of combined percutaneous and endoscopic drainage in the early phase of acute pancreatitis and showed safety and efficacy for the procedure even when performed within 4 weeks after onset [18]. In this study, mean interval of EUS-PCD after the onset of acute pancreatitis was 26 days (range 25–52). On the other hand, our study mainly focused on the endoscopic intervention and it is the first study to evaluate the impact of timing after onset of acute pancreatitis on outcomes of EUS-PCD. However, there are still some limitations. First, our study was a single-center, retrospective and non-randomized although no significant differences were seen in baseline characteristics between the early and delayed drainage groups. Second, our study cohort was small and patients were enrolled during a relatively long period, causing some changes in devices, i.e use of a metal stent during the study period. With these limited data, it is difficult to draw a solid conclusion and more studies in a larger number of patients are needed. Fewer patients were in the early drainage group than in the delayed drainage group as we only performed endoscopic drainage of PFC after encapsulation had been confirmed. With these limited data, it is still unclear whether an endoscopic approach is feasible for PFC with immature encapsulation. Therefore, a percutaneous approach should be selected in those cases, if interventions are necessary.

Conclusion
In conclusion, endoscopic treatment of PFC within 4 weeks after onset of acute pancreatitis appeared to be feasible, given that the collection was encapsulated and attached to the upper gastrointestinal tract. However, due to limited data, early intervention should be undertaken only when absolutely necessary and further studies are needed.

Competing interests
None

References
ence and observations in patients with sterile and infected necrosis. AJR Am J Roentgenol 2009; 192: 110–116


