A long (7 cm) prophylactic pancreatic stent decreases incidence of post-endoscopic papillectomy pancreatitis: a retrospective study

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Background and study aims
Endoscopic papillectomy (EP) is a minimally invasive treatment for ampullary neoplasms and is recognized as an alternative treatment to surgical resection; however, there are few reports on a suitable pancreatic stent (PS) after EP for preventing pancreatitis. The aim of this study was to evaluate the efficacy of a long PS after EP.

Patients and methods
In this retrospective single-center study, 39 patients with pathologically proven ampullary neoplasms who underwent EP between March 2012 and August 2018 were enrolled. The study participants were divided into two subgroups according to the PS length: those with a PS shorter than 5 cm (short PS group, n = 17) and those with a PS of 7 cm (long PS group, n = 22). The incidence of adverse events and risk factors for pancreatitis were evaluated.

Results
The diameter of all PSs was 5 Fr. Post-EP pancreatitis occurred in nine patients (23.1 %), with two cases of severe pancreatitis (5.1 %). Pancreatitis occurred more frequently in the short PS group (7/17, 41.2 %) than in the long PS group (2/22, 9.1 %) (P = 0.026). There were no significant differences between the two groups in terms of other adverse events. Univariate and multivariate analyses showed that a long PS was the only factor associated with a decreased incidence of post-EP pancreatitis (P = 0.042; odds ratio, 0.16; 95 % confidence interval, 0.027–0.94).

Conclusion
A long (7 cm) PS significantly decreased incidence of pancreatitis after EP. Prospective randomized studies with a larger number of patients and wider range of PS lengths are required.

Introduction
Endoscopic papillectomy (EP) was first reported in Japan in 1983 [1]. Since then, it has been reported that EP has a higher success rate and fewer adverse events compared to open surgery [2–4]. Although resection is typically recommended for ampullary neoplasms even if the tumor is benign, because of the adenoma-carcinoma sequence [5,6], EP is currently recognized as an alternative to surgical resection for ampullary neoplasms. However, EP has a potential risk of severe adverse events (AEs), with a procedure-related mortality rate of 0 % to 7 % [7]. Previous studies have reported that the rate of AEs varies from 8 % to 35 %, with a bleeding rate of 2 % to 16 % and a pancreatitis incidence rate of 5 % to 15 % [8].
pancreatitisis frequently occurs because of pancreatic duct stricture after resection or a direct burn effect in the pancreatic parenchyma.

To date, various methods for EP have been developed for better prevention of AEs, including placement of a pancreatic stent (PS) [9,10], endoscopic closure using hemoclips for distal-side mucosal defects [11], wire-guided papillactomy [12], and submucosal injection [13]. Despite these efforts, EP remains challenging, and a standard method for EP has not yet been established.

It is well known that PS placement is effective for preventing post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis [14,15]. Furthermore, several studies have shown the efficacy of PS placement after EP [16,17]. Although the number of patients was low, one randomized controlled trial showed that PS placement after EP significantly reduced frequency of pancreatitis (33% vs 0%, *P* = 0.02) [17]. Thus, PS may play a role in improving intra-pancreatic duct pressure and preventing pancreatic duct stenosis due to papillary edema and scarring. However, it remains unclear which PS features (in terms of length, thickness, and form) are optimal in EP. For post-ERCP pancreatitis prevention, a longer and larger PS is recommended, based on previous studies [18,19]; however, controversy exists, and selecting the type of PS currently depends on the endoscopist’s preference. Moreover, the optimal PS length after EP has not yet been considered. Therefore, the aim of the current study was to evaluate outcomes of EP for different PS lengths, focusing on a suitable PS for prevention of pancreatitis.

**Patients and methods**

**Study design and patients**

A retrospective observational study was conducted. Patients who underwent EP in our institution between March 2012 and August 2018 were enrolled. The indication for EP was detection of a pathological neoplasm, without pancreatic or biliary invasion, with a tumor diameter <40 mm. Patients with an intraductal papillary mucinous neoplasm (IPMN) were excluded, as it is well-known that an IPMN without a dilated pancreatic head duct is a possible risk factor for pancreatitis after prophylactic pancreatic duct stenting [20]. We classified patients into two groups according to PS length; those with a PS ≤5 cm were classified into the short PS group and those with a PS >7 cm were classified into the long PS group. This study was approved by our institutional review board (20150245).

**EP procedure**

EP was performed using a therapeutic duodenoscope with a large working channel (TJF260V; Olympus, Tokyo, Japan) (Fig. 1). After detection of the target lesion, mucosal resection was performed using a standard loop snare (spiral snare forceps; Olympus). The tumor was strangulated, and mucosal resection was performed electro-surgically. Tumor resection was performed in Endocut or Autocut mode (120 W, Effect3, ICC200; ERBE Elektromedizin GmbH, Tubingen, Germany). Next, the resected specimen was grasped using a net snare and removed along with the endoscope. After reintroducing the scope, a 0.025-inch guidewire (VisiGlide2; Olympus) was inserted into the biliary and pancreatic tracts via a catheter. Endoscopic biliary sphincterotomy (EST) was then performed and a PS was placed to prevent papillary stenosis. According to American Society of Gastrointestinal Endoscopy guidelines, difficult cannulation was defined as repetitive attempts or prolonged duration before cannulation (>5–10 minutes) [21]. In all cases, the PS was a 5-Fr diameter straight stent with double flanges (Advantis; Boston Scientific Japan, Tokyo, Japan). We used a double-flanged stent to prevent it from spontaneously falling off. Choice of PS length was dependent on operator preference because the most suitable stent length has not been established. If necessary, endoscopic closure was performed on the caudal side using an endoscopic hemoclip (Resolution; Boston Scientific Japan, Tokyo, Japan), as delayed bleeding frequently occurs from the vessels at the base or cut edge on the caudal side of the ulcer [22]. Immediate bleeding was controlled with local injection of hypertonic saline-epinephrine (HSE), hemoclips, argon plasma coagulation (APC), hemostats, and cold water or epinephrine spray.

In all cases, a suppository containing nonsteroidal anti-inflammatory drugs was used after EP to help prevent pancreatitis. Five to 7 days after EP, a second-look endoscopy was performed, and the PS was removed.

**Study outcome and definition of adverse events**

We defined post-EP pancreatitis in accordance with the consensus definition and classification for procedure-related pancreatitis as reported in the study by Cotton et al. [23]. Delayed bleeding was defined as clinical evidence of bleeding that required endoscopic haemostasis occurring from hours to weeks after the procedure. Perforation was defined based on symptoms and abdominal computed tomography findings. Cholangitis was defined based on findings of a high fever (>38°C) and elevated liver enzymes. Serum amylase level on the day after EP was also obtained.

**Statistical analysis**

Categorical data were compared using the Fisher’s exact or chi-square test. Continuous data were compared using the Student’s *t*-test or Mann-Whitney *U* test. PS length, treatment regimen after EP, and several factors recognized as independent risk factors for post-ERCP pancreatitis were evaluated in univariate analyses [21]. In addition, we performed a multivariate logistic regression analysis to identify risk factors for post-EP pancreatitis. *P* <0.05 was considered statistically significant. Statistical analysis was performed using SPSS software version 23.0 (IBM Corp., Armonk, New York, United States).

**Results**

**Patient characteristics**

Thirty-nine patients with papillary neoplasm who underwent EP at our institution were included. A PS ≤5 cm was placed in 17 patients (short PS group), and a PS ≥7 cm was placed in the remaining 22 patients (long PS group).
Patient characteristics are described in Table 1. For all 39 patients, mean age was 61.5 years, 79.5% were men, and mean tumor size was 13.9 mm. After EP, 33 lesions (84.6%) were diagnosed as adenomas and two lesions were diagnosed pathologically as adenocarcinom as. There were no significant differences between the groups in terms of collected background characteristics. Although not described in the table, there were no patients with prior post-ERCP pancreatitis, suspected sphincter of Oddi dysfunction, or pancreatic sphincterotomy. In addition, there were no patients with chronic pancreatitis, and all patients had a normal serum bilirubin level and underwent a pancreatic injection to cannulate into the duct. These items are known risk factors for post-ERCP pancreatitis [23]. Furthermore, serum amylase levels before EP were normal in all patients.

Outcomes
Table 2 lists proportions of AEs according to PS length. Post-EP pancreatitis occurred in nine patients (23.1%), with two cases of severe pancreatitis (5.1%). One patient with severe pancreatitis required invasive treatment, and subsequently recovered. The other patient recovered with conservative treatment alone. The proportion of post-EP pancreatitis was significantly higher in the short PS group (41.2%) than in the long PS group (9.1%) (P = 0.026). There were no significant differences between the groups in terms of other AEs and serum amylase levels.

Analysis of risk factors for post-EP pancreatitis
Table 3 and Table 4 show results of the univariate and multivariate analyses, respectively. In univariate analyses, PS length was the only factor significantly related to post-EP pancreatitis (P = 0.026). Given the small number of cases, only two factors – PS length and difficulty of pancreatic duct cannulation – were included in the multivariate analysis. A long (7 cm) PS was the only decreasing factor for post-EP pancreatitis (P = 0.042; odds ratio, 0.16; 95% confidence interval, 0.027–0.94) in the multivariate analysis.

Discussion
In this retrospective study, the proportion of post-EP pancreatitis cases was significantly lower in patients who received a long PS than in patients who received a short PS (9.1% vs 41.2%, P = 0.026). Furthermore, in the univariate and multivariate analyses, a long PS was the only factor significantly associated with a decreased risk of post-EP pancreatitis. The current study is the first to evaluate AEs after EP according to PS length, and
the results reveal the efficacy of a long PS (7 cm) for prevention of post-EP pancreatitis.

As mentioned in the introduction, it is well known that PS placement is effective for preventing post-ERCP pancreatitis. However, several reports have shown that dislocation of a prophylactic PS can occur, which might result in delayed-onset pancreatitis due to secondary obstruction of flow [24]. However, actual rates of PS dislocation and migration after ERCP in previous reports are not very high (4.9%–5.2%) [25, 26]. Furthermore, most studies reporting AEs following PS placement comprise only case reports [27–30]. Therefore, in conventional ERCP, many doctors consider the possibility of PS dislocation as a relatively unimportant problem compared to the efficacy of PS placement.

In contrast, rates of PS dislocation and migration after EP remain unclear. Thus far, our study is the first to show the relationship between PS length and post-EP pancreatitis. We presume that the stability of a short PS may be lost after EP because the sphincter of Oddi was resected together with the ampullary neoplasm (Fig. 2). Therefore, a short PS might easily

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Total (n = 39)</th>
<th>Short PS (n = 17)</th>
<th>Long PS (n = 22)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), mean (SD)</td>
<td>61.5 (10.0)</td>
<td>61.3 (11.9)</td>
<td>61.7 (8.6)</td>
<td>0.91</td>
</tr>
<tr>
<td>Sex (men), n (%)</td>
<td>31 (79.5)</td>
<td>12 (70.6)</td>
<td>19 (86.4)</td>
<td>0.26</td>
</tr>
<tr>
<td>Tumor size (mm), mean (SD)</td>
<td>13.9 (5.4)</td>
<td>14.5 (4.5)</td>
<td>13.4 (6.1)</td>
<td>0.55</td>
</tr>
<tr>
<td>Previous pancreatitis, n (%)</td>
<td>1 (2.6)</td>
<td>0</td>
<td>1 (4.5)</td>
<td>1.00</td>
</tr>
<tr>
<td>Difficult pancreatic duct cannulation, n (%)</td>
<td>4 (10.3)</td>
<td>3 (17.6)</td>
<td>1 (4.5)</td>
<td>0.30</td>
</tr>
</tbody>
</table>

**Biliary treatment, n (%)**
- EST | 30 (76.9) | 12 (70.6) | 18 (81.8) | 0.47 |
- Stent placement | 6 (15.4) | 3 (17.6) | 3 (13.6) | 1.00 |
- ENBD | 4 (10.3) | 2 (11.8) | 2 (9.1) | 1.00 |

**Haemostatic treatment, n (%)**
- Clipping | 35 (89.7) | 15 (88.2) | 20 (90.9) | 1.00 |
- APC | 19 (48.7) | 11 (64.7) | 8 (36.4) | 0.08 |
- HSE | 8 (20.5) | 2 (11.8) | 6 (27.3) | 0.43 |

**Pathological diagnosis after EP, n (%)**
- Adenoma | 33 (84.6) | 14 (82.4) | 19 (86.4) | 1.00 |
- Carcinoma in adenoma | 2 (5.1) | 0 | 2 (9.1) | 0.50 |
- Adenocarcinoma | 2 (5.1) | 2 (11.8) | 0 | 0.18 |
- Hyperplasia | 2 (5.1) | 1 (5.9) | 1 (4.5) | 1.00 |

APC, argon plasma coagulation; ENBD, endoscopic nasobiliary drainage; EST, endoscopic sphincterotomy; EP, endoscopic papillectomy; HSE, hypertonic saline-epinephrine; PS, pancreatic stent; SD, standard deviation

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Total (n = 39)</th>
<th>Short PS (n = 17)</th>
<th>Long PS (n = 22)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post-EP pancreatitis, n (%)</td>
<td>9 (23.1)</td>
<td>7 (41.2)</td>
<td>2 (9.1)</td>
<td>0.026</td>
</tr>
</tbody>
</table>
- Severe pancreatitis, n (%) | 2 (5.1) | 1 (5.9) | 1 (4.5) | 1.00 |
| Delayed bleeding, n (%) | 8 (20.5) | 4 (23.5) | 4 (18.2) | 0.71 |
| Cholangitis, n (%) | 1 (2.6) | 1 (5.9) | 0 | 0.44 |
| Perforation, n (%) | 2 (5.1) | 0 | 2 (9.1) | 0.50 |
| Papillary stenosis, n (%) | 2 (5.1) | 0 | 2 (9.1) | 0.50 |
| Post-EP amylase (U/L), median (range) | 171 (61–3140) | 257 (61–3140) | 147 (73–1168) | 0.23 |

EP, endoscopic papillectomy; PS, pancreatic stent
### Table 3 Risk factors for post-EP pancreatitis (univariate analysis).

<table>
<thead>
<tr>
<th>Factors</th>
<th>No pancreatitis (n= 30)</th>
<th>Pancreatitis (n=9)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), mean (SD)</td>
<td>62.0 (10.0)</td>
<td>59.8 (10.4)</td>
<td>0.56</td>
</tr>
<tr>
<td>Sex (men), n (%)</td>
<td>23 (76.7)</td>
<td>8 (88.9)</td>
<td>0.65</td>
</tr>
<tr>
<td>Tumor size (mm), mean (SD)</td>
<td>14.0 (5.8)</td>
<td>13.5 (3.8)</td>
<td>0.83</td>
</tr>
<tr>
<td>Difficult pancreatic duct cannulation, n (%)</td>
<td>2 (6.7)</td>
<td>2 (22.2)</td>
<td>0.22</td>
</tr>
<tr>
<td>Previous pancreatitis, n (%)</td>
<td>1 (3.3)</td>
<td>0</td>
<td>1.00</td>
</tr>
</tbody>
</table>

Haemostatic treatment, n (%)
- Clipping                                    | 28 (93.3)               | 7 (77.8)           | 0.22    |
- APC                                        | 13 (43.3)               | 6 (66.7)           | 0.27    |
- HSE                                        | 6 (20.0)                | 2 (22.2)           | 1.00    |
- Long PS, n (%)                             | 20 (66.7)               | 2 (22.2)           | 0.026   |

APC, argon plasma coagulation; CI, confidence interval; EP, endoscopic papillectomy; HSE, hypertonic saline-epinephrine; PS, pancreatic stent; SD, standard deviation

### Table 4 Risk factors for post-EP pancreatitis (multivariate analysis).

<table>
<thead>
<tr>
<th>Post-EP pancreatitis (n =9)</th>
<th>Odds ratio (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Difficult pancreatic duct cannulation</td>
<td>2.56 (0.26–25.3)</td>
<td>0.42</td>
</tr>
<tr>
<td>Long PS</td>
<td>0.16 (0.027–0.94)</td>
<td>0.042</td>
</tr>
</tbody>
</table>

CI, confidence interval; EP, endoscopic papillectomy; PS, pancreatic stent

### Fig. 2 Images of pancreatic stent placement. 
(a) Conventional endoscopic retrograde cholangiopancreatography. Stent position is stable. 
(b) Endoscopic papillectomy. Stent position is unstable because of the loss of the ampulla of Vater.
dislocate, possibly causing a pancreatic fluid flow disorder, resulting in pancreatitis (Fig. 3). Indeed, the rate of post-EP pancreatitis has been reported to be higher than that for post-ERCP pancreatitis [3, 13, 21, 31]. However, we could not determine the accurate number of cases with PS dislocation, because computed tomography or early endoscopic examination was not performed in patients without AEs. Concerning such patients, when we removed PS 5 to 7 days after EP, slight PS dislocation was found in five patients (2 in the short PS group and 3 in the long PS group), although we could not determine when it happened (early post-EP period or effect of endoscopic insertion). Therefore, in this retrospective report, we could not statistically analyse the relationship between PS dislocation and post-EP pancreatitis. It is one of our hypotheses, and another detailed examination is required in the future. Furthermore, in EP, the burn effect associated with tumor resection is another...
factor contributing to incidence of pancreatitis. Thus, this should also be verified.

Although there are no studies reporting the rate of stent dislocation after EP, we consider that a short stent tends to cause kinking in the duct at a curve between the pancreatic head and body when PS dislocation occurs. In contrast, a long stent can adequately and deeply reach the pancreatic body; thus, even if it gets dislocated to some extent, this dislocation may not cause a problem. When we performed PS placement in this study, no cases had a unique form of the pancreatic duct, such as a loop or Z shape. Although the curve of the pancreatic duct was slightly different in every case, the long PS was placed over the curve of the pancreatic body. Table 5 shows details of the cases with post-EP pancreatitis. Regrettably, we could not definitively confirm our hypothesis that incidence of stent dislocation is higher with a shorter PS than with a longer PS. At this point, further examination is required. Because pancreatitis is caused by various factors, not just a pancreatic fluid flow disorder, it is impossible to prevent it completely by using a long PS. However, use of a long PS might contribute to decreasing the rate of post-EP pancreatitis.

The current study has several limitations. First, it was single-center and retrospective, therefore, the number of patients was small. Furthermore, as mentioned above, pancreatitis is caused by various factors and few items were examined in this study. Second, we did not use a PS longer than 7 cm. Therefore, it remains unclear whether a longer PS can better prevent pancreatitis. There is a possibility that a 7-cm PS is more suitable than a shorter or longer PS. Given these limitations, the results of our study should be interpreted carefully. Third, the strategy of PS placement after EP was not common in all cases. The operator selected the length of the PS considered to be effective based on several factors. The shape of the pancreatic duct might be one factor; however, we could not determine the true reason for selecting the length of PS. Fourth, we tended to use more 7-cm PS in the late study period. Therefore, the learning curve might have affected incidence of pancreatitis. In the future, randomized controlled trials are required to confirm this result.

Conclusion
Our study revealed that a long PS significantly decreased incidence of pancreatitis after EP. In the future, prospective randomized studies with a large number of patients are required to establish the optimal method for EP.

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Competing interests

None

References

[18] Afghani E, Akshintala VS, Khashab MA et al. 5-Fr vs. 3-Fr pancreatic stents for the prevention of post-ERCP pancreatitis in high-risk patients: A systematic review and network meta-analysis. Endoscopy 2014; 46: 573–580


