Acute Cholangitis and Pancreatitis After Duodenal Stent Placement in the Descending Duodenum: A Retrospective Study

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Abstract

Background

Metallic stents placed in the descending duodenum can cause compression of the major duodenal papilla, resulting in acute cholangitis and pancreatitis. These are notable early adverse events of duodenal stent placement; however, they have been rarely examined. This study aimed to assess the incidence of and risk factors for acute cholangitis and/or pancreatitis after duodenal stent placement in the descending duodenum.

Methods

We retrospectively reviewed data of consecutive patients who underwent metallic stent placement in the descending duodenum for malignant gastric outlet obstruction at a tertiary referral cancer center between April 2014 and December 2019. Risk factors for acute cholangitis and/or pancreatitis were analyzed using a logistic regression model.

Results

Sixty-five patients were included. Acute cholangitis and/or pancreatitis occurred in 11 patients (17%): seven with cholangitis, two with pancreatitis, and two with both cholangitis and pancreatitis. Multivariate analysis indicated that female sex (odds ratio: 9.2, 95% confidence interval: 1.4–58.6, \(P = 0.02\)), absence of biliary stents (odds ratio: 12.9, 95% confidence interval: 1.8–90.2, \(P = 0.01\)), and tumor invasion to the major duodenal papilla (odds ratio: 25.8, 95% confidence interval: 2.0–340.0, \(P = 0.01\)) were significant independent risk factors for acute cholangitis and/or pancreatitis.

Conclusions

The incidence of cholangitis and/or pancreatitis after duodenal stent placement in the descending duodenum was non-negligible. Female sex, absence of biliary stents, and tumor invasion to the major duodenal papilla were the primary risk factors. Risk stratification can allow endoscopists to better identify patients at significant risk and permit detailed informed consent.

Background

Malignant gastric outlet obstruction (mGOO) caused by several advanced cancers leads to nausea, vomiting, and food intake intolerance, resulting in deterioration of quality of life. Surgical gastrojejunostomy and endoscopic duodenal stent placement (DSP) using self-expandable metallic stents (SEMSs) are widely utilized to relieve symptoms of mGOO. Several previous studies have demonstrated that DSP allows for earlier resumption of food intake, a shorter hospitalization period, and
earlier administration of chemotherapy after interventions relative to surgical gastrojejunostomy [1–5]. Thus, DSP has recently become more common than surgical gastrojejunostomy. However, several early adverse events (AEs) of DSP have been reported, including bleeding, perforation, obstruction, stent migration, cholangitis, and pancreatitis [1–16].

Of these, acute cholangitis and pancreatitis can be caused by compression of the major duodenal papilla (MDP) due to SEMSs [11, 17, 18]. Thus, acute cholangitis and pancreatitis can develop only after DSP in the descending duodenum. A previous retrospective study reported that 11% of patients (9/94) developed pancreatitis after DSP in the descending duodenum and that SEMS bridging the MDP can cause pancreatitis [11]. In contrast, few studies have investigated cholangitis after DSP in the descending duodenum. Acute cholangitis and/or pancreatitis after DSP in the descending duodenum (CPAD) is a notable early AE because it may require additional treatment, delay chemotherapy, and prolong the duration of hospitalization; however, few studies have focused on CPAD. Accordingly, this study aimed to assess the incidence of and risk factors for CPAD.

**Methods**

**Study design and patients**

In this retrospective study, we reviewed data of consecutive patients who underwent their first SEMS placement in the duodenum, including the descending duodenum, at the Shizuoka Cancer Center between April 2014 and December 2019. The exclusion criteria were absence of computed tomography (CT) imaging within 1 month before DSP and the presence of percutaneous or transmural biliary drainage. All patients provided written informed consent for DSP, and the study was approved by the institutional review board (IRB) of Shizuoka Cancer Center (IRB number: J2019-174-2019-1). All investigations were performed in accordance with the ethical standards of the Declaration of Helsinki.

**Duodenal stent placement**

DSP was performed with the patient under conscious sedation. An endoscope (GIF 1T-240, PCF 240 or JF 260V; Olympus, Tokyo, Japan) and an endoscopic retrograde cholangiopancreatography (ERCP) catheter with a biliary guidewire were used. Uncovered or covered SEMSs were used, and the type of SEMS was selected at the discretion of the attending endoscopists. SEMS lengths were 60 mm, 80 mm, 100 mm, and 120 mm. Uncovered and covered SEMSs were 22 mm and 20 mm in diameter, respectively.

The endoscope was first used to approach the stenosis site, after which a guidewire and a catheter were passed through the site (Fig. 1a). A water-soluble radiographic contrast medium was injected through the catheter to determine the location and length of the stenosis site under fluoroscopic guidance (Fig. 1b). Multiple SEMSs were used if the stenosis was long. All patients were monitored in the hospital for at least 3 days after DSP. Patients without immediate AEs were allowed liquid diet intake 1–2 days after DSP. The patient’s diet was gradually changed according to their symptoms. If the patient developed any AEs, prompt treatment was provided at the discretion of the attending physicians. For example, in patients
who developed cholangitis, antibiotics were administered and biliary drainage was considered. In patients
who developed pancreatitis, intravenous therapy was initiated immediately after diagnosis.

**Data collection and definitions**

Data were collected from the patient medical records. The oral intake status was evaluated using the
Gastric Outlet Obstruction Scoring System (GOOSS): 0, no oral intake; 1, liquids only; 2, soft solid diet; and
3, full solid diet [19]. The maximum diameters of the extrahepatic bile duct and main pancreatic duct
were measured, with extrahepatic bile duct and pancreatic duct dilations being defined as >10 mm and >3
mm, respectively. Biliary stents were defined as those deployed across the MDP prior to DSP. The
presence of tumor invasion to the MDP was evaluated by an experienced radiologist (K.A.) using a CT
image obtained within 1 month before DSP (Fig. 2a, b). All identifying information was removed from the
CT images, and the radiologist reviewing the images was also blinded to the information.

Technical success was defined as adequate DSP across the stenosis site as confirmed by endoscopy and
fluoroscopy. Clinical success was defined as a GOOSS score of ≥2 and improvement in the GOOSS score
after DSP.

CPAD was defined as acute cholangitis and/or pancreatitis that developed within 1 week after DSP in the
descending duodenum. Diagnoses of cholangitis/pancreatitis and assessments of severity were made in
accordance with the lexicon for endoscopic AEs advocated by the American Society of Gastrointestinal
Endoscopy [20]. According to the lexicon, cholangitis was diagnosed based on fever lasting >24 hours
with cholestasis and pancreatitis was diagnosed based on the presence of typical pain with an
amylase/lipase level >3 times the normal value.

**Statistical analysis**

Continuous variables are presented as the median and range and were compared using the Mann–
Whitney U-test. Categorical variables are presented as n values (%) and were compared using Fisher’s
exact test. The risk factors for CPAD were analyzed using a logistic regression model for the following
nine variables: age (≤69 vs. >69 years), sex (male vs. female), tumor diagnosis (pancreatic cancer vs.
others), absence of extrahepatic bile duct dilation (yes vs. no), absence of pancreatic duct dilation (yes
vs. no), biliary stents (yes vs. no), tumor invasion to the MDP (yes vs. no), location of duodenal stents (1st
to 3rd vs. others), and type of duodenal stent (covered vs. uncovered). The factors with substantial
impact (P<0.2) in the univariate analysis were subsequently evaluated in a multivariate analysis. A P-
value of <0.05 was considered statistically significant for all tests. All statistical analyses were performed
using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user
interface for R (The R Foundation for Statistical Computing, Vienna, Austria). More precisely, it is a
modified version of R Commander designed to add statistical functions frequently used in biostatistics
[21].

**Results**
Patient characteristics

Ninety consecutive patients who underwent SEMS placement in the descending duodenum were enrolled. Among these, 11 and 14 patients were excluded because of absence of CT images obtained within 1 month prior to DSP and the presence of percutaneous or transmural biliary drainage, respectively. Finally, the data of 65 patients were included in the analysis.

Patient characteristics are shown in Table 1. Technical success and clinical success were achieved in 65 (100%) and 53 patients (82%), respectively. Of the patients in whom clinical success was not achieved, five exhibited no improvement in their GOOSS scores and seven did not achieve a GOOSS score ≥2, although their GOOSS scores had improved.

Acute cholangitis and/or pancreatitis after duodenal stent placement in the descending duodenum

CPAD developed in 11 patients (17%); cholangitis in seven patients, pancreatitis in two patients, and both cholangitis and pancreatitis in two patients. The clinical course of CPAD is summarized in Table 2. The median time from DSP to the onset of pancreatitis was significantly shorter than that from DSP to the onset of cholangitis (0 days vs. 2 days, \( P<0.01 \)). Among the patients with cholangitis, three were treated with antibiotic therapy alone, and six underwent biliary drainage along with antibiotic administration. Biliary drainage was considered in one patient with cholangitis after DSP, but it could not be performed because of poor general health due to advanced cancer. The patient later died of exacerbations of primary cancer while in the hospital. Meanwhile, all patients with pancreatitis improved with intravenous therapy and did not require intensive care or interventional therapy.

Multivariate analysis revealed that female sex (odds ratio: 9.2, 95% confidence interval: 1.4–58.6, \( P=0.02 \)), absence of biliary stents (odds ratio: 12.9, 95% confidence interval: 1.8–90.2, \( P=0.01 \)), and tumor invasion to the MDP (odds ratio: 25.8, 95% confidence interval 2.0–340.0, \( P=0.01 \)) were independent risk factors for CPAD (Table 3).

Early adverse events other than cholangitis and pancreatitis

There was stent migration in one patient. The migrated SEMS was removed, and a new one was deployed, after which the patient’s symptoms improved without any further stent migration.

Discussion

In this retrospective study, CPAD occurred in 17% (11/65) of patients with DSP in the descending duodenum. In addition, female sex, tumor invasion to the MDP, and absence of biliary stents were identified as risk factors for CPAD.

Several studies have reported the development of CPAD [11, 17, 18]. SEMSs placed over the MDP can obstruct the flow of the bile and pancreatic ducts, resulting in CPAD. Thus, ideally, SEMS placement over the MDP should be avoided. However, this is often difficult for the following reasons. First, in cases with
duodenal stenosis on the oral side of the MDP, the endoscope cannot approach the MDP, resulting in failure to confirm the location of the MDP. Second, in cases with duodenal stenosis on or near the MDP, SEMSs must be placed over the MDP for the treatment of mGOO symptoms, even though the MDP can be confirmed endoscopically. As SEMS placement over the MDP often cannot be avoided, endoscopists should be aware of the risk of CPAD when they place SEMSs in the descending duodenum. Therefore, knowledge regarding the incidence of and risk factors for CPAD is useful in clinical practice.

In this study, three main risk factors for CPAD were observed: female sex, tumor invasion to the MDP, and absence of biliary stents. The following points may explain our findings. First, female sex is a known risk factor for post-ERCP pancreatitis, although the reasons underlying this association remain unclear [22, 23]. Female patients may be more responsive to MDP-related irritation than male patients. Second, in patients with tumor invasion to the MDP, the biliary or pancreatic duct may exhibit a pre-obstructive state, and compression from the SEMS may easily trigger symptoms. This mechanism may be similar to that of acute cholecystitis after SEMS placement in the bile duct. Several previous studies have indicated that tumor involvement in the orifice of the cystic duct is a risk factor for cholecystitis after SEMS placement in the bile duct [24–26]. Third, biliary stents deployed across the MDP may create space between the MDP and duodenal stents, thus relieving MDP compression. Although our study revealed the three main risk factors associated with CPAD, the evidence that supports our results remains insufficient. Thus, further research will be required to validate our results.

According to our results, biliary stents prior to DSP may reduce the incidence of CPAD in patients with stenosis of the descending duodenum; however, previous studies have reported that DSP is a risk factor for the dysfunction of biliary stents deployed over the MDP; thus, transmural biliary drainage may be preferred over transpapillary biliary drainage for patients with mGOO accompanied by biliary obstruction [27, 28]. The common alternative treatment for DSP is surgical gastrojejunostomy, but patients with mGOO are often in poor general condition and unsuitable for surgical gastrojejunostomy. Recent studies have demonstrated the efficacy of endoscopic ultrasonography-guided gastroenterostomy (EUS-GE) in the management of mGOO [29]. In one retrospective study, EUS-GE had a higher rate of initial clinical success and lower rate of stent failure requiring repeat intervention than DSP [30]. In addition, in EUS-GE, there is no risk for cholangitis or pancreatitis because the SEMS is not placed over the MDP. Thus, EUS-GE may be suitable for patients with mGOO with a high risk of CPAD. However, EUS-GE poses many challenges, including the lack of dedicated devices and non-availability at many hospitals in Japan. Currently, DSP is the standard for mGOO treatment, even for patients at high risk of CPAD. Therefore, risk stratification for CPAD is required to inform patients in detail prior to DSP.

The present study had several limitations. First, there may have been unintentional bias because of its retrospective study design. Second, the sample size was too small given the single-center nature of the study. Third, although we assessed the risk for cholangitis and/or pancreatitis, the individual risk for cholangitis and pancreatitis could not be evaluated because of the small sample size. Thus, larger clinical trials are required to assess risk factors for cholangitis and pancreatitis separately.
In conclusion, our findings indicated that the incidence of acute cholangitis and/or pancreatitis was non-negligible among patients who underwent DSP in the descending duodenum. Female sex, absence of biliary stents, and tumor invasion to the MDP were identified as potential risk factors for CPAD. Risk stratification can allow endoscopists to better identify patients who are at significant risk and permit detailed informed consent and high-risk groups may be offered non-DSP treatment in the future.

**List Of Abbreviations**

AE  
adverse event  
CPAD  
acute cholangitis and/or pancreatitis after DSP in the descending duodenum  
CT  
computed tomography  
DSP  
duodenal stent placement  
ECOG  
Eastern Cooperative Oncology Group  
ERCP  
endoscopic retrograde cholangiopancreatography  
EUS-BD  
endoscopic ultrasound-guided biliary drainage  
EUS-GE  
endoscopic ultrasonography-guided gastroenterostomy  
GOOSS  
gastric Outlet Obstruction Scoring System  
IRB  
institutional review board  
MDP  
major duodenal papilla  
mGOO  
malignant gastric outlet obstruction  
PTBD  
percutaneous transhepatic biliary drainage  
SEMS  
self-expandable metallic stents  

**Declarations**
Ethics approval and consent to participate: All patients provided written informed consent for DSP, and the study was approved by the institutional review board (IRB) of Shizuoka Cancer Center (IRB number: J2019-174-2019-1); all investigations were performed in accordance with the ethical standards of the Declaration of Helsinki.

Consent for publication: Not applicable.

Availability of data and materials: All data generated or analysed during this study are included in this published article and its supplementary information files.

Competing interests: Drs. Junichi Kaneko, Hirotoshi Ishiwatari, Koiku Asakura, Tatsunori Satoh, Junya Sato, Kazuma Ishikawa, Hiroyuki Matsubayashi, Yohei Yabuuchi, Yoshihiro Kishida, Masao Yoshida, Sayo Ito, Noboru Kawata, Kenichiro Imai, Kohei Takizawa, Kinichi Hotta, and Hiroyuki Ono have no conflicts of interest or financial ties to disclose.

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Authors' contributions: Junichi Kaneko, Hirotoshi Ishiwatari, Koiku Asakura, Tatsunori Satoh, Junya Sato, Kazuma Ishikawa, and Hiroyuki Matsubayashi: Substantial contributions to the conception or design of the work, or acquisition, analysis, or interpretation of data for the work. Yohei Yabuuchi, Yoshihiro Kishida, Masao Yoshida, Sayo Ito, Noboru Kawata, Kenichiro Imai, Kohei Takizawa, Kinichi Hotta, and Hiroyuki Ono: Final approval of the version to be published.

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References


Tables

Table 1. Patient characteristics (n=65).
<table>
<thead>
<tr>
<th>Clinical Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (median, year) [range]</td>
<td>68 [40-91]</td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>38/27</td>
</tr>
<tr>
<td>ECOG performance status score (0/1/2/3/4)</td>
<td>4/23/23/13/2</td>
</tr>
<tr>
<td>Previous history (cholangitis/chronic pancreatitis/post-ERCP pancreatitis)</td>
<td>34/1/3</td>
</tr>
<tr>
<td>Gastric outlet obstruction scoring system score (0/1/2)</td>
<td>22/35/8</td>
</tr>
<tr>
<td>Extrahepatic bile duct diameter (median, mm) [range]</td>
<td>10 [2-24]</td>
</tr>
<tr>
<td>Pancreatic duct diameter (median, mm) [range]</td>
<td>4 [1-10]</td>
</tr>
<tr>
<td>Serum bilirubin (median, mg/dl) [range]</td>
<td>0.7 [0.1-8.4]</td>
</tr>
<tr>
<td>Biliary stents (yes/no)</td>
<td>34/31</td>
</tr>
<tr>
<td>Type of stent (metallic stent/plastic stent)</td>
<td>32/2</td>
</tr>
<tr>
<td>Tumor invasion to the major duodenal papilla (yes/no)</td>
<td>42/23</td>
</tr>
<tr>
<td>Duodenal stent</td>
<td></td>
</tr>
<tr>
<td>Location of duodenum stents</td>
<td>2/28/19/16</td>
</tr>
<tr>
<td>(only 2nd part/1st part-2nd part/2nd part-3rd part/1st part-3rd part)</td>
<td></td>
</tr>
<tr>
<td>Length (6-9 cm/10 cm/12 cm/multiple stents)</td>
<td>16/21/26/2</td>
</tr>
<tr>
<td>Type (covered/uncovered)</td>
<td>6/59</td>
</tr>
<tr>
<td>ECOG, Eastern Cooperative Oncology Group; ERCP, endoscopic retrograde cholangiopancreatography</td>
<td></td>
</tr>
<tr>
<td>Data are presented as n unless otherwise noted.</td>
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</table>

Table 2. Clinical course of acute cholangitis and pancreatitis after DSP in the descending duodenum
<table>
<thead>
<tr>
<th></th>
<th>Cholangitis (n=9)</th>
<th>Pancreatitis (n=4)</th>
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</thead>
<tbody>
<tr>
<td>Time to onset from DSP (median, days) [range]</td>
<td>2 [1-7]</td>
<td>0 [0-1]</td>
</tr>
<tr>
<td>Severity (mild/moderate/severe/fatal)</td>
<td>1/7/1/0</td>
<td>2/2/0/0</td>
</tr>
<tr>
<td>Interventional therapy (%)</td>
<td>6 (67)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>EUS-BD (%)</td>
<td>3 (33)</td>
<td></td>
</tr>
<tr>
<td>PTBD (%)</td>
<td>3 (33)</td>
<td></td>
</tr>
</tbody>
</table>

DSP, duodenal stent placement; EUS-BD, endoscopic ultrasound-guided biliary drainage; PTBD, percutaneous transhepatic biliary drainage.

Data are presented as n unless otherwise noted.

Table 3. Results of the univariate and multivariate analyses of risk factors for acute cholangitis and/or pancreatitis after DSP in the descending duodenum
<table>
<thead>
<tr>
<th></th>
<th>Univariate analysis</th>
<th>Multivariate analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤69</td>
<td>38</td>
<td>2.48 (0.60-10.20)</td>
</tr>
<tr>
<td>&gt;69</td>
<td>27</td>
<td>1</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>27</td>
<td>3.58 (0.95-13.50)</td>
</tr>
<tr>
<td>Male</td>
<td>38</td>
<td>1</td>
</tr>
<tr>
<td>Tumor diagnosis</td>
<td></td>
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<tr>
<td>Pancreatic cancer</td>
<td>37</td>
<td>0.71 (0.20-2.49)</td>
</tr>
<tr>
<td>Other</td>
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<td>1</td>
</tr>
<tr>
<td>Extrahepatic bile duct dilatation</td>
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<td></td>
</tr>
<tr>
<td>Yes</td>
<td>21</td>
<td>1.65 (0.46-5.99)</td>
</tr>
<tr>
<td>No</td>
<td>44</td>
<td>1</td>
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<tr>
<td>Pancreatic duct dilation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>27</td>
<td>2.31 (0.65-8.27)</td>
</tr>
<tr>
<td>Yes</td>
<td>38</td>
<td>1</td>
</tr>
<tr>
<td>Biliary stents</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>31</td>
<td>7.62 (1.52-38.30)</td>
</tr>
<tr>
<td>Yes</td>
<td>34</td>
<td>1</td>
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<tr>
<td>Tumor invasion to the major duodenal papilla</td>
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<tr>
<td>Yes</td>
<td>42</td>
<td>7.81 (0.94-64.90)</td>
</tr>
<tr>
<td>No</td>
<td>23</td>
<td>1</td>
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<tr>
<td>Position of duodenum covered by duodenal stents</td>
<td></td>
<td></td>
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<tr>
<td>1st-3rd</td>
<td>16</td>
<td>4.30 (1.14-16.20)</td>
</tr>
<tr>
<td>Others</td>
<td>49</td>
<td>1</td>
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<tr>
<td>Types of duodenal stent</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Covered</td>
<td>6</td>
<td>0.87 (0.09-8.24)</td>
</tr>
<tr>
<td>Uncovered</td>
<td>59</td>
<td>1</td>
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</tbody>
</table>
Figures

Figure 1

DSP, duodenal stent placement; OR, odds ratio; CI, confidence interval; \( P<0.05^* \)
The process of duodenal stent placement. (a) A catheter with a guidewire is passed through the stenosis site, and a water-soluble radiographic contrast medium is injected to determine the location and length of the stenosis site under fluoroscopic guidance. (b) A duodenal stent is deployed under endoscopic and fluoroscopic guidance.

Figure 2
Computed tomography images showing tumor invasion to the main duodenal papilla (a) Pancreatic cancer is shown invading the main duodenal papilla directly (arrowhead). (b) Duodenal infiltration of the uterine cancer is shown invading the main duodenal papilla (arrow).

**Supplementary Files**

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