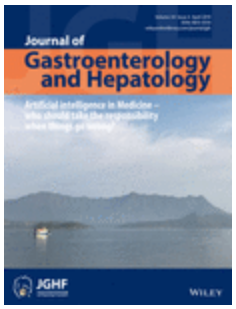

Evaluation of complications after ERCP using a short type double balloon endoscope in patients with altered gastrointestinal anatomy: a single-center retrospective study of 1,576 procedures

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Evaluation of complications after ERCP using a short type double balloon endoscope in patients with altered gastrointestinal anatomy: a single-center retrospective study of 1,576 procedures

Running title: Complications after short type double-balloon endoscopic ERCP

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Abstract

Background and Aims : Endoscopic retrograde cholangiopancreatography (ERCP) using balloon assisted endoscope (BAE) such as double balloon endoscope (DBE) is even effective for patients with surgically altered anatomy. Yet comprehensive studies on complications of ERCP using BAE (BAE-ERCP) have not been made. We analyzed the characteristics and the causes of complications of ERCP using DBE (DB-ERCP) procedures and aimed to suggest effective managements.

Methods : 1,576 procedures of DB-ERCP in 716 patients with surgically altered gastrointestinal anatomy in our hospital were evaluated retrospectively using a statistic analysis.

Results : The overall complication occurrence rate was 5.8%. By type of complications are; perforation 3.2%, mucosal laceration 0.5%, hemorrhage 1.0%, pancreatitis: 0.6%, respiratory disorder 0.4%, and others 0.2%. By type of surgical reconstruction methods were ; Roux-en-Y (R-Y) reconstruction with choledocho-jejunal anastomosis (CJA) 4.2%, R-Y without CJA 6.7%, pancreaticoduodenectomy (PD) 4.5%, pylorus preserving pancreaticoduodenectomy (PpPD) 4.2%, Billroth-II gastrectomy (B-II) 11.6%, and other reconstruction method (others) 7.4%. The contributing factors calculated by a multivariate analysis were B-II (odds ratio [OR]: 1.864, 95% confidence

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interval [CI]: 1.001-3.471, p = 0.050), and the presence of naïve papilla (OR: 3.268, 95% CI: 1.426-7.490, p = 0.005).

Conclusions : DB-ERCP is a safe method with a total complication rate of 5.8% which could be considered within an acceptable range. The most common complication was the injury of the digestive tract such as perforation. Affecting risk factors for complications were B-II, and the presence of naïve papilla. DB-ERCP procedures should be performed carefully of these factors.

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Introduction

Endoscopic retrograde cholangiopancreatography (ERCP) is widely applied as an endoscopic diagnostic and therapeutic modality for pancreatobiliary disease[1,2]. Many papers have reported its efficacy for patients with normal anatomy[3,4]. Though as to in patients with surgically altered gastrointestinal anatomy, it has been considered technically challenging to thoroughly complete the ERCP-related interventions for pancreatobiliary diseases[5-7]. In 2001, the innovative double-balloon assisted endoscopy (DBE) was introduced as a new technique to allow visualization and intervention in the entire small intestine[8]. The concept of balloon assisted endoscope (BAE) such as single balloon endoscopy (SBE) has become widespread[9,10] allowing ERCP in postoperative

patients. Many studies report the efficacy of BAE-ERCP[11-25] and the endoscopic treatment has come to be established as a standard therapeutic procedure for pancreatobiliary disease in postoperative patients. Also many studies on complications and risk factors have been reported focusing on conventional ERCP[26-35] in patients with normal anatomy, while only a few comprehensive studies on complications of BAE-ERCP in patients with surgically altered gastrointestinal anatomy are reported.

In this present study, our aim was to retrospectively evaluate the characteristics of complications by type of reconstruction methods analyzing 1,576 procedures of DB-ERCP performed in our hospital from February 2006 to December 2018, and also to suggest effective methods of management.

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PATIENTS AND METHODS

Patients

From February 2006 to December 2018, 1,576 DB-ERCP procedures were performed for pancreatobiliary diseases in 716 patients with altered gastrointestinal anatomy in our hospital. Patient's conditions were evaluated with American society of anesthesiologists physical status (ASA-PS)[36]. All the procedures performed during the last 154 months were analyzed retrospectively in this study. The types of reconstruction

methods were; Roux-en-Y (R-Y) with choledocho-jejunal anastomosis (CJA) 429 procedures in 134 patients, R-Y without CJA 404 procedures in 276 patients, pancreaticoduodenectomy (PD) 287 procedures in 103 patients, pylorus preserving pancreaticoduodenectomy (PpPD) 216 procedures in 78 patients, Billroth-II gastrectomy (B-II) 172 procedures in 103 patients, and other reconstruction method (others) 68 procedures in 38 patients.

Endoscopes and instruments

The DBE system is characterized by two balloons. The first is attached to the tip of the endoscope, and the second is attached to the tip of the overtube. The balloons can be inflated or deflated with a specially designed air pump controller with one-touch controls with concurrent monitoring of the air pressure. Both are used to hold the intestinal tract and are manipulated simultaneously to advance the scope into deep regions by shortening the intestinal tract[8]. The balloon at the tip of the endoscope was always kept fixed to the scope with string so that the DBE can be pulled out through the overtube with the balloon attached.

There are two types of short type DBEs. One is the conventional short type DBE (C-short DBE) (EI-530 B; FUJIFILM Co, Tokyo, Japan) with a 1,520 mm working length and a 2.8 mm working channel. The other is the N-short DBE (EI-580 BT;

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FUJIFILM Co, Tokyo, Japan) with a 1,550 mm working length and a 3.2 mm working channel. A soft transparent hood (DH-17EN; FUJIFILM, Tokyo, Japan) was used when necessary. C-short DBE or N-short DBE was used for DB-ERCP in this study.

Methods

Patients were laid in the prone position and premedicated with midazolam (0.15–0.3 mg/kg), pentazocine (15 mg), and scopolamine butylbromide (10-20mg) on an as-needed basis. CO_2 insufflation was used in all procedures. $PtcCO_2$ was measured by non-invasive sensor (KOHKEN, Tokyo, Japan) throughout DB-ERC. Patients were simultaneously monitored for SpO_2 and pulse rate, as well as intermittent measurement of blood pressure[37]. DB-ERCP involved the following two major steps. The first step was to insert an endoscope deeply to the blind end. The second step was to perform ERCP-related interventions. Any adverse events that occurred during DB-ERCP or post DB-ERCP procedures were recorded as complications.

DB-ERCP was performed by three endoscopists with more than 500 experiences with conventional ERCP. One is an experienced endoscopist with more than 100 cases of DB-ERCP, the other is with 50-99 cases of DB-ERCP, and the other is with less than 49 cases of DB-ERCP. Neither the effects of different level of experience of those endoscopists on the complication nor the effects of different skills of the endoscopic

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technicians on the complication was recognized.

Definitions and outcome measurement

The primary outcome was the complication occurrence rate. The secondary outcome was the contributing factors for complication, and its control after occurrence.

Procedure time was defined as from DBE insertion to withdrawal. Management time against complication was not included in the procedure time. Perforations were defined by the presence of gas or luminal contents outside the gastrointestinal tract by any radiographic technique. Basically, the presence of free air was checked by the X-ray during the procedure (especially the free air around the kidney and iliopsoas). As free air caused by microperforation is difficult to be detected, abdominal computed tomography (CT) scan was applied in all cases where lacerations were visually found by endoscopy or patients had symptoms such as abdominal pain after procedures. Perforations were defined according to the classification by Stapfer et al.: type I, perforations of the lateral or medial wall of the intestine; type II, perforations with perivaterian injuries; type III, perforations with distal bile duct injuries related to guidewire-basket instrumentation; type IV, retroperitoneal air alone[34]. Intestinal lacerations without the presence of gas or luminal contents outside the gastrointestinal tract were defined as mucosal laceration. Post DB-ERCP pancreatitis (PEP) was

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defined by new or worsened abdominal pain requiring prolonged admission with increased serum levels of pancreatic enzymes (amylase or lipase) higher than twice of the normal upper limit after procedure[38]. Bleeding that required endoscopic hemostasis during procedures or presences of clinical evidence of bleeding such as melena or hematemesis, with an associated decrease of at least 2 g per deciliter in the hemoglobin concentration, or the need for a blood transfusion were defined as hemorrhage[38]. The condition of hypoxemia, hypercapnia, and respiratory arrest need for emergence from deep sedation or tracheal intubation was defined as respiratory disorder. Other complications were defined as others.

Management of type II, III, and IV perforations and mucosal lacerations (Endoscopic treatments)

If the mucosal injury site is visible, clipping disclosure was performed. In addition, endoscopic nasal biliary drainage tube (ENBD) was inserted into the bile duct and the guide wire (GW) was placed at the blind end (Figure 1A). Then, with the overtube remaining near the blind end, the scope was withdrawn while ENBD and GW were placed (Figure 1B). Finally, a nasal intestinal drainage tube was placed near the blind end under GW guidance through the remaining overtube (Figure 1C).

This study was conducted accordingly to the Declaration of Helsinki, approved

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by Institutional Review Board (IRB). The method, its effectiveness, and the possibility of complications were explained to the patients and the written informed consent was obtained before the procedure.

Statistical analysis

In order to make comparison in proportion between patients with each surgical gastrointestinal reconstruction and patients without each surgical gastrointestinal reconstruction, the chi-square test was used. For assessment of difference in mean values between patients with complication and those without complication, the unpaired t-test was used. For comparison in proportion of complications in patients with potential confounding factors and without those factors, the chi-square test was used. Variables with p values of <0.1 in these analyses were considered as confounding factors between a predictor and an outcome. Multivariate analysis was performed using logistic regression analysis after adjusting those confounding factors. P-values of <0.05 were considered to indicate statistical significance. For comparison in proportion of complications between the initial procedure and recurrent procedures, the chi-square test was used. All analyses were performed using SPSS Statistics Desktop for Japan, Version 22 (IBM Japan, Ltd., Tokyo, Japan).

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Result

Table 1 shows the patients' medical background. As the reason for reconstructive surgery, gastroduodenal disease (malignant) was the most common. By type of surgical reconstruction method, R-Y with CJA 429 procedures was the most common closely followed by R-Y without CJA 404 procedures, and others 68 procedures included double tract 19 procedures, gastrojejunal bypass 17 procedures, Imanaga method 13 procedure, choledoco-duodenostomy 17 procedures, B-II gastrectomy with R-Y reconstruction 1 procedure and double R-Y 1 procedure. Regarding indications for DB-ERCP, CJA stenosis with stones was the most common followed by common bile duct stones.

Complication occurrence rate

Table 2 shows the characteristics of complications. The overall complication occurrence rate was 5.8%. By type of reconstruction method, R-Y with CJA 4.2%, R-Y without CJA 6.7%, PD 4.5%, PpPD 4.2%, B-II 11.6% and others 7.4%. In B-II cases, the occurrence rate was significantly higher than those in others ($P<0.001$). By characteristics of complications, perforation was the highest at 3.2%, and all other complications were less than 1%. About half the complications were perforation, most of which were type II, III, and IV perforation (48.9%) (Figure 2).

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Contributing factors of complication occurrence

Table 3 shows the contributing factors of complications. The age, sex, procedure time, poor patient's status (ASA-PS >=3), using old type endoscope (EI-530B), type of reconstruction method, state of papilla Vater, and indication for DB-ERCP were analyzed. By the multivariate analysis performed by adjusting the confounding factors, B-II (odds ratio [OR]: 1.864, 95% confidence interval [CI]: 1.001-3.471, p = 0.050), and the presence of naïve papilla (OR: 3.268, 95% CI: 1.426-7.490, p = 0.005) were proved to be statistically significant risk factors. The complication occurrence rate in the initial procedural cases was 9.2% (66/716 procedures), while in the recurrent procedural cases was 3.0% (26/860 procedures), suggesting the former was significantly higher (p <0.001).

Management and prognosis of complications

Table 4 shows the management and prognosis of complications. As the management of complications, endoscopic treatment was the most common at 56.5%. Emergency surgery was necessary in 5.4%. As management for perforation cases in our hospital, surgery was basically selected for type I perforation, and endoscopic treatment was basically selected for type II, III, and IV perforation. Hemorrhages occurred in total of 15 cases, hemorrhage of papilla Vater portion due to endoscopic sphincterotomy (EST) 10 cases, hemorrhage of choledocho-jejunal anastomosis portion due to balloon dilatation

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of choledocho-jejunal anastomosis 4 cases, intestinal mucosal hemorrhage due to mucosal suction during scope insertion 1 case. For hemorrhages, either endoscopic hemostasis or conservative treatment was principally selected as follows; clipping 1 case, hypertonic saline-epinephrine (HSE) injection 7 cases, balloon oppression 3 cases. Only in 1 case where endoscopic hemostasis was not possible, transcatheter arterial embolization (TAE) was applied. Regarding the PEP, most cases were mild and severe pancreatitis occurred only in 1 case where intensive care was required. Respiratory disorder occurred as follows; CO_2 narcosis in 4 cases, requiring endotracheal intubation in 3 cases. Others were caused by deep sedation. In 2 cases, CO_2 supply was changed to room air supply, and the other 2 cases were awoken from deep sedation. As other minor complications, drainage of the thoracic cavity was required in a case of subcutaneous emphysema and right pneumothorax, and for the iatrogenic choledocho-duodenal fistula generated during endoscopic papillary large balloon dilation (EPLBD), plastic stent placement was performed. Among all the complications cases, 7 patients (7.6%) died, the overall mortality rate was 1.0% (7 of 716 patients). However, the major cause of death was due to exacerbation of primary disease or aspiration pneumonia after the treatment for complications. DB-ERCP was regarded as directly related to the cause of death in 2 patients (0.3%; 2 of 716 patients).

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The mean period of extended hospitalization of complications cases was 12.9 ± 15.0 days. PEP cases resulted in the longest (27.6 ± 28.9 days), followed by type II, III, and IV perforation cases (15.4 ± 12.3 days).

Discussion

ERCP in patients with surgically altered anatomy is considered technically more challenging than in patients with normal anatomy posing a higher risk of complications. Complications of ERCP-related interventions for normal anatomy (conventional ERCP; C-ERCP) have been reported in many studies[26-35,38], although, there have been few systematic reports for surgically altered anatomy[6,18,21,39-44].

Furthermore the complication rates of BAE-ERCP reported from existing studies ranged widely between (4.8-12.4%)[6,12,18,21,39-44]. All have been reported in a small or medium case series.

The first multicenter prospective study for 311 procedures from Japan reported[45] the complication rate was 10.6%, including injury of digestive tract 3.9% (perforation 2.3% inclusive) as most common complication. The complication rate was 5.8% in our study, showing a lower rate compared to that in the existing studies.

According to the latest retrospective cohort study from 2014 using a large data

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base of 2,715 patients who underwent C-ERCP[29], the complication rate was 12 % suggesting that DB-ERCP should not bring about any higher when compared with C-ERCP. However, since more of recurrent procedural cases were performed with DB-ERCP, in comparison of the complication rates limited to the DB-ERCP initial cases and C-ERCP initial cases in order to eliminate the possible biases, the former was 9.2% (66/716 procedures), which was almost equivalent to that of C-ERCP. Therefore DB-ERCP was no more complication-risk-posing than C-ERCP, suggesting it is a safe therapeutic modality (Table 3).

In addition, by characteristic of complications of C-ERCP were; pancreatitis 4.9%, bleeding 4.5%, and perforation 0.11%, showing their most common complication was pancreatitis, while in our study was perforation, which clearly showed the difference in characteristic of complications. The presence of postoperative adhesion is reported to increase the risk of perforation significantly[46], and the risk of perforation in DB-ERCP is higher than that in C-ERCP. Thus, it was suggested DB-ERCP should be performed carefully for the risk of perforation.

As the reference of management to control perforation, European Society of Gastrointestinal Endoscopy (ESGE) Position Statement is applied in our hospital[33]. For type I perforation, endoscopic closure is recommended when the lesion of perforation

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can be identified immediately, endoscopic closure is recommended, however, should an endoscopic closure fail, surgery must be immediately applied. There is a report suggesting that endoscopic closure for obvious perforation should be considered carefully because the laceration needs to be closed tightly including the submucosa[31], therefore, in our hospital, surgical treatment is basically selected. For type II, III, and IV perforation, it is recommended to place an intestinal drainage tube and bile duct drainage tube to reduce the leak of intestinal fluid and bile juice into the abdominal cavity and retroperitoneal space, and to administer antibiotics[33,34]. In this study, endoscopic intestinal and biliary drainage and antibiotics were applied for type II, III, and IV perforation as described above.

Regarding the respiratory disorder was observed in 7 cases (0.4%), including CO_2 narcosis in 4 cases. There is a study reporting appropriate monitoring and management of hemodynamics by capnography monitor and non-invasive continuous transcutaneous carbon dioxide monitor ($PtcCO_2$ measurement) are necessary for early detection of respiratory disorders including CO_2 narcosis[37], and monitoring with the $PtcCO_2$ monitor as well as a pulse oximeter should be necessary during DB-ERCP procedure.

In this study, B-II and the presence of naïve papilla were the factors affecting

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complications in DB-ERCP. Itoi et al[47]. also reported that naïve papilla cases were difficult to accomplish the procedure from bile duct cannulation to ERCP-related interventions. Thus, DB-ERCP for naïve papilla cases is technically challenging and must be performed carefully for possible occurrence of the complication.

In B-II cases, the complication occurrence rate and the perforation rate were significantly the highest among all reconstruction methods. There are short afferent loop (SAL) type and long afferent loop (LAL) type for B-II. The distance from the gastro-jejunal anastomosis to the Treitz ligament in the afferent loop and the strength of the fixation point of the anastomosis are different. The distance between the gastro-jejunal anastomosis and Treitz ligament in SAL type is extremely short because the afferent loop is lifted and sutured above the superior margin of the resected stomach to prevent reflux of meal content into the afferent loop. Therefore, it is suggested that the perforation risk is increased by a strong pushing force when inserting a scope into the afferent loop (Figure 3A). On the other hand, LAL type has a Braun anastomosis that expands like a hole near the pelvic cavity, and the distance between the gastro-jejunal anastomosis and the Treitz ligament is long, which allow the afferent loop to be not much tensioned by pushing force to advance scope (Figure 3B). In our study, all the perforation cases in B-II were SAL type.

For Peer Review

In addition, the afferent loop is rarely over-tensioned by a pushing force in R-Y reconstruction cases when the scope is inserted. The distance between the Y-anastomosis fixed loosely in the abdominal cavity and Treitz ligament is basically long (Figure 3C). Therefore, it is considered that the risk of perforation caused by scope advancement is low.

Regarding 2 cases of complications directly related death, in one case, perforation could not be detected during the procedure and no intestinal or bile duct drainage tube was placed. On the next day, a perforation was found and the patient died of peritonitis. This case suggested that placing at least intestinal and bile duct drainage tubes could be useful for possible perforation cases. In the other case, the patient had poor cardiac function and had undergone antithrombotic therapy. Hemorrhagic shock suddenly occurred at night, and the patient was transferred to our hospital for endoscopic treatment, but died because hemostasis was too late. This suggested that it was necessary to pay attention especially to patients on antithrombotic therapy and in cases after performing EST during DB-ERCP, patients should be hospitalized in a facility where BAE can be used and the endoscopic hemostasis is possible.

The limitation of this study is being a retrospective single center study, however, the study evaluating 1,500 procedures is the first large case report up to date. Yet,

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further studies of a larger-scale prospective multiple center are necessary.

Conclusion

In this study, complications of DB-ERCP in large cases exceeding 1,500 procedures were evaluated. The overall complication occurrence rate was 5.8%, which was no significant different compared to the frequency of complications in C-ERCP in patients with normal anatomy. The most common complication was gastrointestinal damages such as perforation, however even if complications occurred, most cases could be recovered if appropriately handled. The affecting factors for complications were B-II, and the presence of naïve papilla. Thus, complication of DB-ERCP was within an acceptable range and the procedures should be performed carefully of risk-posing factors.

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For Peer Review

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Figure legends

Figure 1: Management of type II, III, and IV perforations and mucosal lacerations (Endoscopic treatments)

A; Nasal biliary drainage tube (ENBD) was inserted into the bile duct and the guide wire (GW) was placed at the blind end.

B; ENBD and GW were placed with the overtube remaining near the blind end.

C; Nasal intestinal drainage tube was placed near the blind end under GW guidance through the remaining overtube.

Figure 2: Complication occurrence by characteristics

Figure 3: Scheme of Billroth II gastrectomy and Roux-en-Y reconstruction

○; Firm fixed point (Gastro-jejunal anastomosis, Lifting of the afferent loop, and Treitz ligament).

□; Loose fixed point (Braun anastomosis, Y-anastomosis).

→; Direction of the scope.

A; Scheme of short afferent loop (SAL) type Billroth II gastrectomy

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The distance between the gastro-jejunal anastomosis and Treitz ligament in B-II SAL type is extremely short and tight.

B; Scheme of long afferent loop (LAL) type Billroth II gastrectomy

The distance between the gastro-jejunal anastomosis and the Treitz ligament in B-II LAL type is long and loose.

C; Scheme of Roux-en-Y reconstruction

The distance between the gastro-jejunal anastomosis and the Treitz ligament in Roux-en-Y reconstruction is long and loose.

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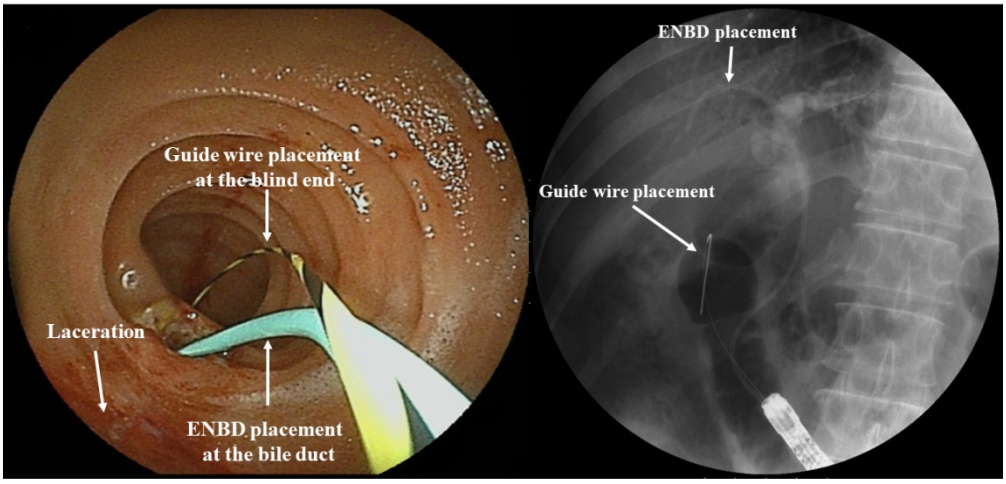
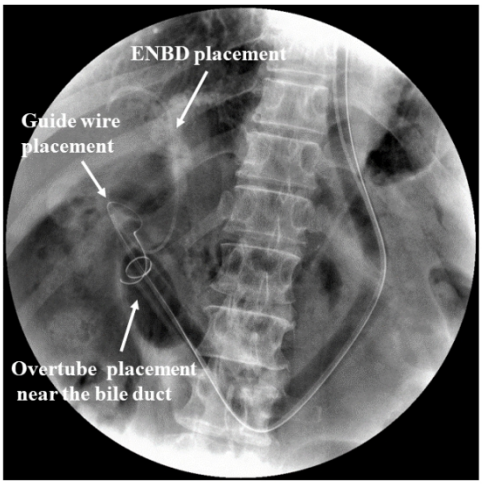
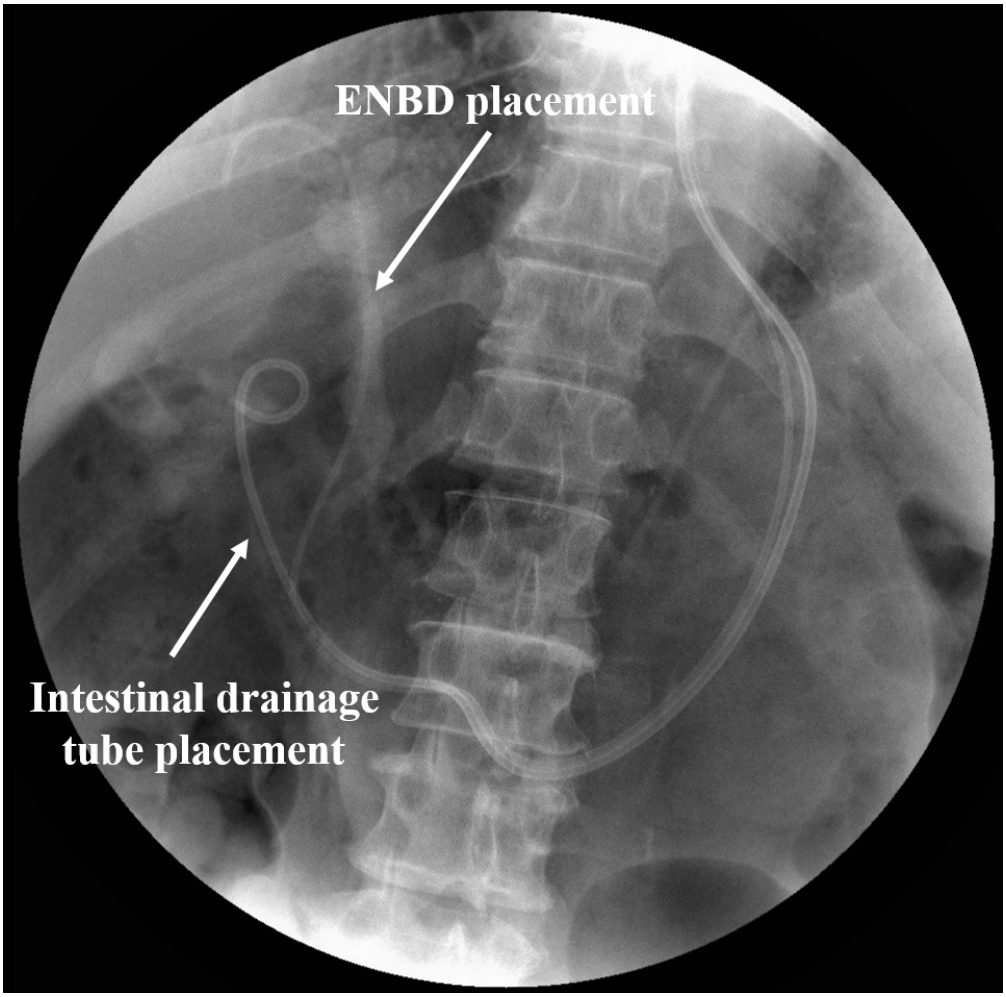


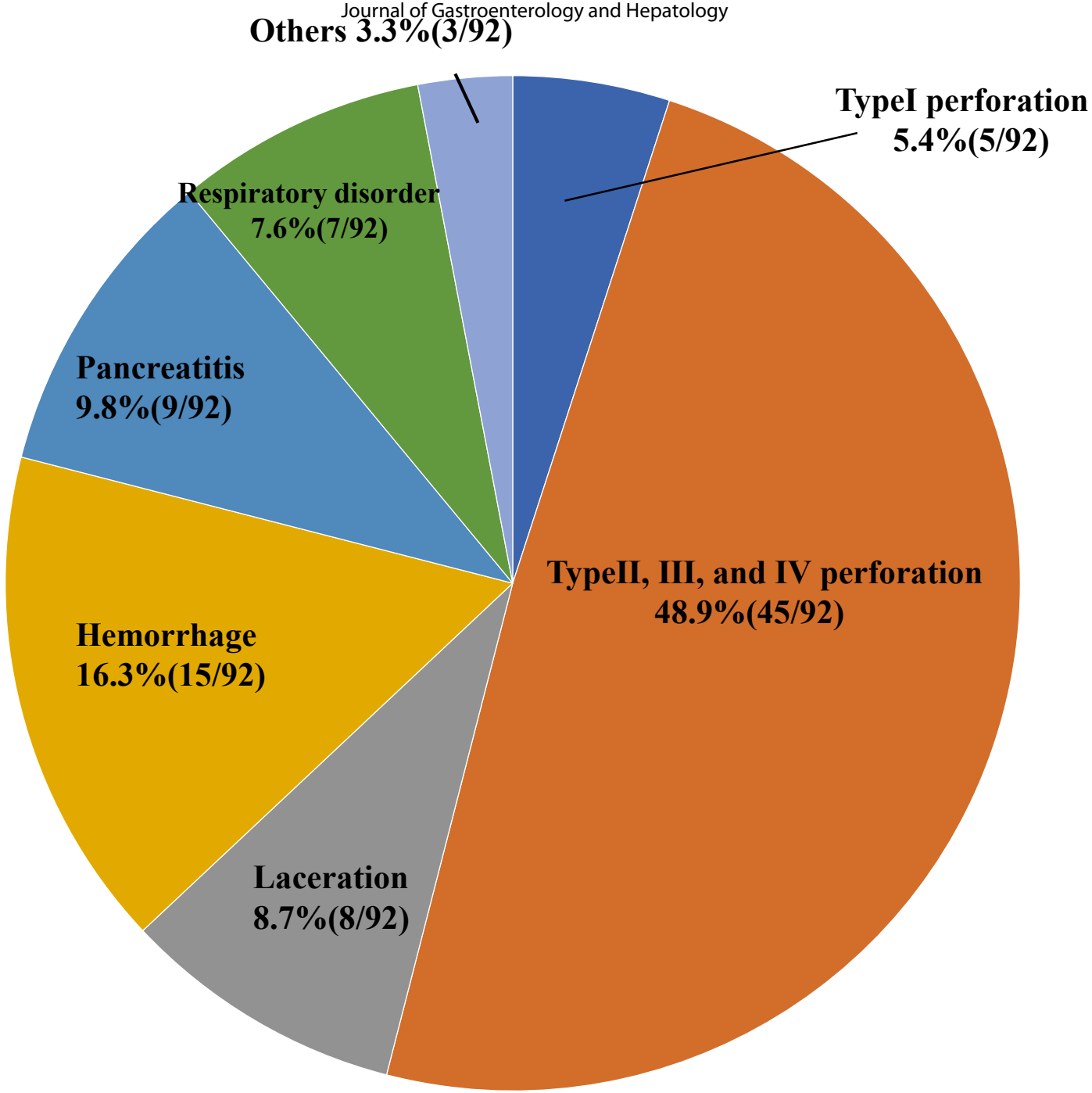
Figure 1: Management of type II, III, and IV perforations and mucosal lacerations (Endoscopic treatments) A; Nasal biliary drainage tube (ENBD) was inserted into the bile duct and the guide wire (GW) was placed at the blind end.

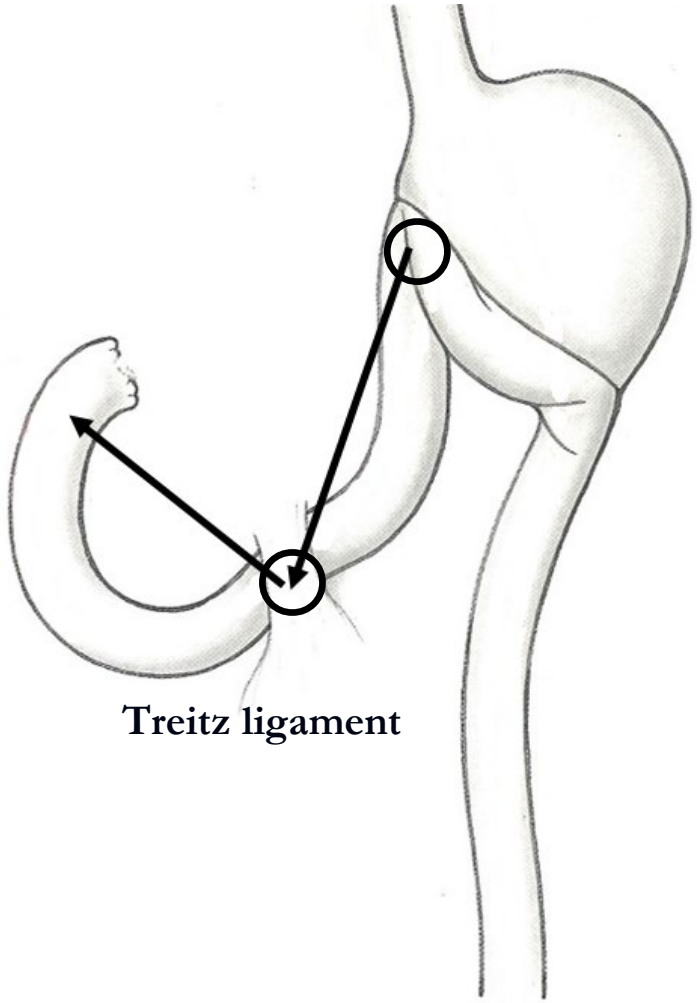


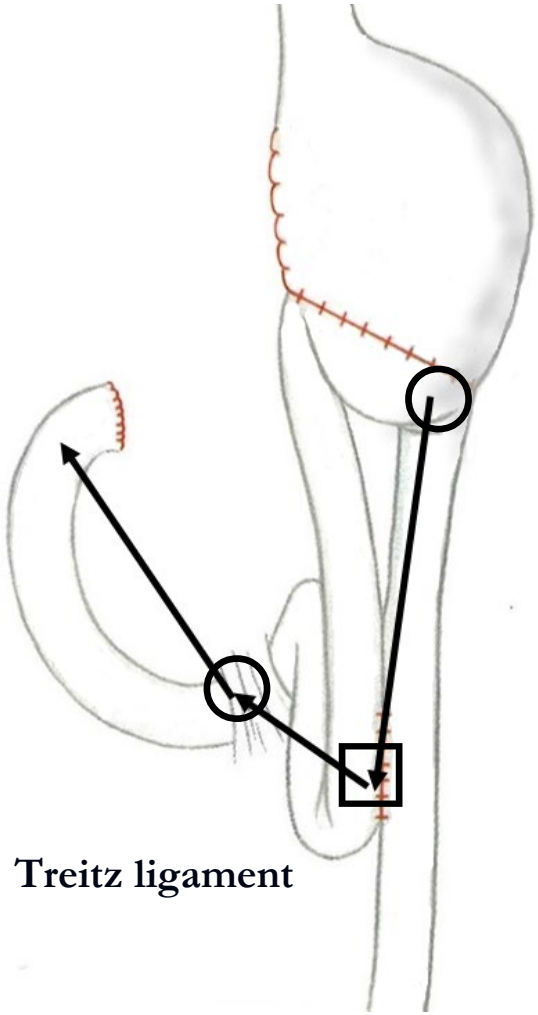
B; ENBD and GW were placed with the overtube remaining near the blind end.



C; Nasal intestinal drainage tube was placed near the blind end under GW guidance through the remaining overtube.


Others 3.3%(3/92)
TypeI perforation
5.4%(5/92)
Respiratory disorder
7.6%(7/92)
Pancreatitis
9.8%(9/92)
TypeII, III, and IV perforation
48.9%(45/92)
Hemorrhage
16.3%(15/92)
Laceration
8.7%(8/92)


Treitz ligament


Treitz ligament

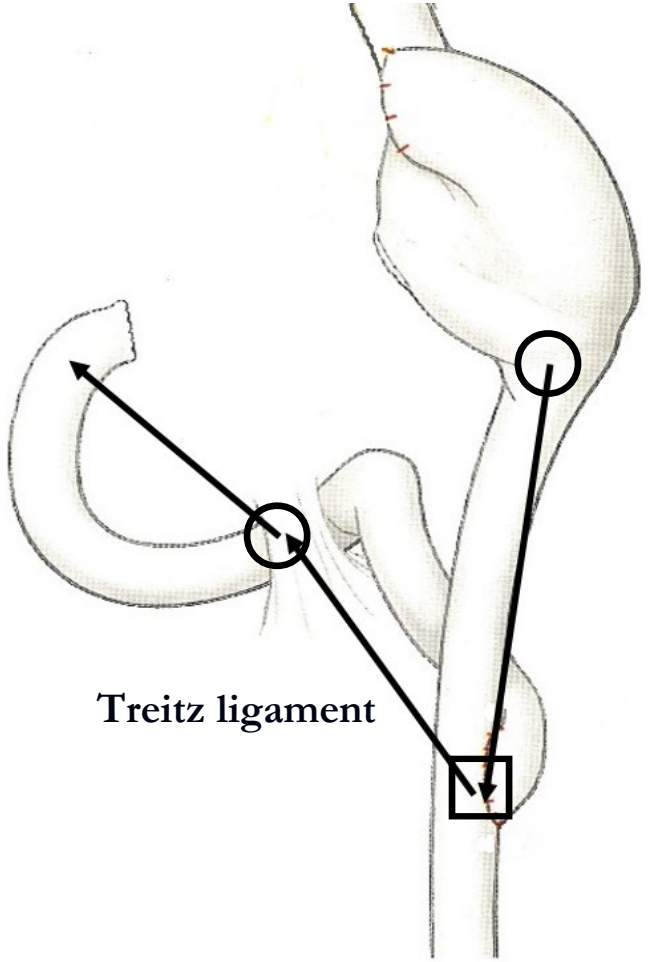

Treitz ligament

Table 1 Patients' medical background

	R-Y with CJA n=429	R-Y without CJA n=404	PD n = 287	PpPD n = 216	B-II n = 172	others n = 68	Total n = 1576
Sex, male, n (%)	200 (46.6)	345 (85.4)	203 (70.7)	123 (56.9)	146 (84.9)	36 (52.9)	1053 (66.8)
Age, mean ± SD, years	57.3 ± 16.7	73.1 ± 9.2	70.3 ± 9.5	66.9 ± 13.1	74.2 ± 9.1	60.7 ± 20.3	67.0 ± 14.4
Reason for surgical gastrointestinal reconstruction							
Gastric cancer	19	388	1	2	49	31	490
Congenital biliary dilatation	171	1	0	0	0	1	173
Intraductal papillary mucinous neoplasm	8	0	79	75	0	0	162
Bile duct cancer	83	2	19	44	1	5	154
Pancreatic cancer	5	1	90	51	0	5	152
Gastro-duodenal ulcer	2	5	2	0	120	5	134
Trauma and injury due to surgical operation	57	1	3	8	2	0	71
Papilla of Vater cancer	0	0	35	14	0	0	49
Pancreaticobiliary maljunction	39	0	0	0	0	3	42
Duodenal cancer	0	1	28	7	0	1	37
Pancreatic benign tumor	0	0	10	4	0	12	26
Common bile duct stones	23	2	0	0	0	0	25
Chronic pancreatitis	0	0	11	0	0	0	11
Neuroendocrine tumor	0	0	4	5	0	0	9
Hepatic stones	8	0	0	0	0	0	8
Metastatic liver tumor	6	0	0	0	0	0	6
Insulinoma	0	0	0	5	0	0	5
Gastrointestinal stromal tumor	0	0	4	0	0	0	4
Hepatic blastoma	0	0	0	0	0	4	4
Liver transplantation	2	0	0	0	0	0	2
Mirizzi syndrome	2	0	0	0	0	0	2
Others	4	3	1	1	0	1	10
Indication for DB-ERCP							
CJA stenosis with stones	226	1	105	83	1	5	421
Common bile duct stones	0	251	0	0	118	16	385
CJA stenosis without stones	136	3	101	92	6	4	342
Malignant biliary stricture	24	112	18	10	28	18	210
Pancreatic disease	0	5	31	15	3	14	68
Others	43	32	32	16	16	11	150

DB-ERCP, duble balloon assisted endoscopic retrograde cholangiopancreatography; R-Y, Roux-en-Y reconstruction; CJA, choledocho-jejunal anastomosis; PD, pancreaticoduodenectomy; PpPD, pylorus preserving pancreaticoduodenectomy, B-II; Billroth-II gastrectomy.

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Table 2 Characteristics of complications

Complication, n (%)	R-Y with CJA, n=429 n (%)	R-Y without CJA, n=404 n (%)	PD, n=287 n (%)	PpPD, n=216 n (%)	B-II, n=172 n (%)	others, n=68 n (%)
Perforation, 50 (3.2)	**11 (2.6)**	**16 (4.0)**	**3 (1.0)**	**6 (2.8)**	**13 (7.6)**	**1 (1.5)**
Type Ⅰ, 5 (0.3)	0 (0)	2 (0.5)	0 (0)	1 (0.5)	2 (1.2)	0 (0)
Type Ⅱ, Ⅲ and Ⅳ, 45 (2.9)	11 (2.6)	14 (3.5)	3 (1.0)	5 (2.3)	11 (6.4)	1 (1.5)
Mucosal laceration, 8 (0.5)	**2 (0.5)**	**0 (0)**	**5 (1.7)**	**0 (0)**	**1 (0.6)**	**0 (0)**
Hemorrhage, 15 (1.0)	**2 (0.5)**	**6 (1.5)**	**1 (0.3)**	**2 (0.9)**	**2 (1.2)**	**2 (2.9)**
Pancreatits, 9 (0.6)	**1 (0.2)**	**4 (1.0)**	**1 (0.3)**	**0 (0)**	**3 (1.7)**	**0 (0)**
Respiratory disorder, 7 (0.4)	**0 (0)**	**1 (0.2)**	**3 (1.0)**	**1 (0.5)**	**0 (0)**	**2 (2.9)**
Others, 3 (0.2)	**2 (0.5)**	**0 (0)**	**0 (0)**	**0 (0)**	**1 (0.6)**	**0 (0)**
Total, 92 (5.8)	**18 (4.2)** **P^a = 0.089**	**27 (6.7)** **P^a = 0.401**	**13 (4.5)** **P^a = 0.296**	**9 (4.2)** **P^a = 0.26**	**20 (11.6)** **P^a < 0.001**	**5 (7.4)** **P^a = 0.586**

Type I, Stapfer's classification type I (perforations of the lateral or medial wall of the intestine); type II, Stapfer's classification type II (perforations with perivaterian injuries); type III, Stapfer's classification type III (perforations with distal bile duct injuries related to guidewire-basket instrumentation); type IV, Stapfer's classification type IV (retroperitoneal air alone).

[a]To compare proportion between patients with each surgical gastrointestinal reconstruction and patients without each surgical gastrointestinal reconstruction, the chi-square test was used.

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Table 3 Contributing factors of complications

	Clinical success - rate, n (%) Total; 1502 (95.3)	Non complication n = 1484	Complication n = 92	Complication - rate 5.8%	Univariate analysis p-value	Multivariate analysis p-value	Odds ratio (95% CI)
Age, mean ± SD, years	—	66.8 ± 14.5	70.6 ± 13.7	—	0.015[a]	0.169[c]	
Sex, male, n=1053	1004 (95.3)	988	65	6.2%	0.421[b]		
Procedure time (excluded treatment time for complication)	—	75.8 ± 49.6	86.1 ± 51.2	—	0.054[a]	0.118[c]	
Poor patient's status (ASA-PS >=3), n = 240	218 (90.8)	225	15	6.3%	0.767[b]		
Using old type endoscope (EI-530B) , n = 966	916 (94.8)	900	66	6.8%	0.034[b]	0.144[c]	
Reconstruction method							
R-Y with CJA, n=429	419 (97.7)	411	18	4.2%	0.089[b]	0.792[c]	
R-Y without CJA, n=404	379 (93.8)	377	27	6.7%	0.401[b]		
PD , n=287	273 (95.1)	274	13	4.5%	0.296[b]		
PpPD, n=216	205 (94.9)	207	9	4.2%	0.260[b]		
B-II, n=172	163 (94.8)	152	20	11.6%	<0.001[b]	0.050[c]	1.864 (1.001 - 3.471)
Others, n=68	63 (92.6)	63	5	7.4%	0.586[b]		
State of papilla Vater							
Nonexistent, n=961	925 (96.3)	921	40	4.2%	<0.001[b]	0.085[c]	
Naïve, n= 420	385 (91.7)	375	45	10.7%	<0.001[b]	0.005[c]	3.268 (1.426 - 7.490)
Post EST or/and EPBD, n =195	192 (98.5)	188	7	3.6%	0.153[b]		
Indication for DB-ERCP							
CJA stenosis with stones, n=421	416 (98.8)	405	16	3.8%	0.037[b]	0.349[c]	
Common bile duct stones, n=385	372 (96.6)	347	38	9.9%	<0.001[b]	0.203[c]	
CJA stenosis without stones, n=342	333 (97.4)	323	19	5.6%	0.802[b]		
Malignant biliary stricture, n=210	196 (93.3)	200	10	4.7%	0.475[b]		
Pancreatic disease, n=68	57 (83.8)	67	1	1.5%	0.116[b]		
Others, n=150	128 (85.3)	142	8	5.4%	0.782[b]		
At the initial procedure, n = 716	654 (91.3)	650	66	9.2%	<0.001[d]		
At recurrent procedures, n = 860	848 (98.6)	834	26	3.0%			

ASA-PS, American society of anesthesiologists physical status; ASA-PS 3, A patient with a severe systemic disease that is not life-threatening; EST,endoscopic sphincterotomy; EPBD, endoscopic papillary balloon dilation.

[a]Uusing the unpaired t-test to asses difference in mean values between patients with complication and those without complication.

[b]Using the chi-square test to compare proportion of complications in patients with potential confounding factors and without those factors.

[c]Multivariate analysis was performed using logistic regression model after adjusting for confounding factors with p values of <0.1 on univariate analysis.

[d]Using the chi-square test to compare proportion of complications between the initial procedure and recurrent procedures.

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Table 4 Management and prognosis of complications

	Treatment, n (%)	Recovery, n (%)	Death, n (%)	The cases of complications directly related death, n (%)	Period of extended hospitalization mean ± SD, days
Perforation, n=50		**46 (92.0)**	**4 (8)**	**1 (2)**	**15.1 ± 12.6**
Type I, n = 5	Surgery, 4 (80) Endoscopy, 1 (20)	3 (60)	2 (40)	0 (0)	12.0 ± 16.8
Type Ⅱ, Ⅲ and Ⅳ, n = 45	Endoscopy, 35 (77.8) Conservative management, 9 (20.0) Surgery, 1 (2.2)	43 (95.6)	2 (4.4)	1 (2.2)	15.4 ± 12.3
Mucosal laceration, n=8	Conservative management, 5 (62.5) Endoscopy, 3 (37.5)	**8 (100)**	**0 (0)**	**0 (0)**	**3.1 ± 3.9**
Hemorrhage, n=15	Endoscopy, 11 (73.3) Conservative management, 3 (20.0) Transcatheter arterial embolization (TAE), 1 (6.7)	**13 (86.7)**	**2 (13.3)**	**1 (6.7)**	**4.1 ± 5.9**
Pancreatitis, n=9	Conservative management, 8 (88.9) Intensive care, 1 (11.1)	**8 (88.9)**	**1 (11.1)**	**0 (0)**	**27.6 ± 28.9**
Respiratory disorder, n=7	Endo-tracheal intubation, 3 (42.9) Insufflation change CO_2 to room air, 2 (28.6) Emergence from deep sadation, 2 (28.6)	**7 (100)**	**0 (0)**	**0 (0)**	**10.0 ± 12.9**
Others, n=3		**3 (100)**	**0 (0)**	**0 (0)**	**8.3 ±12.7**
Subcutaneous emphysema and right pneumothorax, n=1	Drainage of the thoracic cavity, 1 (100)	1 (100)	0 (0)	0 (0)	23 ± 0
Migration of the gidewire, n=1	Endoscopy, 1 (100)	1 (100)	0 (0)	0 (0)	0 ± 0
Choledocho-duodeno fistula, n=1	Endoscopy, 1 (100)	1 (100)	0 (0)	0 (0)	2 ± 0
Total, n=92	**Endoscopy, 52 (56.5)** **Conservative management, 25 (27.2)** **Surgery, 5 (5.4)** **Endo-tracheal intubation, 3 (3.3)** **Insufflation change CO_2 to room air, 2 (2.2)** **Emergence from deep sadation, 2 (2.2)** **TAE, 1 (1.1)** **Intensive care, 1 (1.1)** **Drainage of the thoracic cavity, 1 (1.1)**	**85 (92.4)**	**7 (7.6)**	**2 (2.2)**	**12.9 ± 15.0**

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