Title

Outcomes of endoscopic treatment for malignant biliary obstruction in patients with surgically altered anatomy: analysis of risk factors for clinical failure

Running title

Outcome of endoscopic treatment for MBO in patients with surgically altered anatomy

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Abstract

Background: To evaluate the outcomes of endoscopic retrograde cholangiopancreatography (ERCP) for malignant biliary obstruction (MBO) using short-type double-balloon enteroscope (sDBE) in patients with surgically altered anatomy.

Methods: A total of 45 patients with surgically altered anatomy underwent ERCP using sDBE for the treatment of MBO between April 2011 and March 2019. We retrospectively evaluated the clinical and technical success (insertion and biliary intervention success), adverse events, and risk factors for clinical failure.

Results: The scope was successfully inserted in the target site in 82.2% of patients (37/45), and among them, biliary intervention success was achieved in 86.4% (32/37). The overall technical success rate was 71.1% (32/45) and clinical success rate was 68.9% (31/45), with an adverse event rate of 11.1%. In multivariate analysis, the presence of peritoneal dissemination (odds ratio, 7.3; 95% confidence interval, 1.5–43.5, p=0.02) was as an independent risk factor for clinical failure. The clinical success rate was 38.5% in patients with peritoneal dissemination and 81.3% in those without peritoneal dissemination.

Conclusion: Endoscopic treatment using sDBE in patients without peritoneal

dissemination provided favorable outcomes, and it can be an initial treatment for MBO in patients with surgically altered anatomy.

Keywords

malignant biliary obstruction, double-balloon enteroscope, endoscopic retrograde cholangiopancreatography, surgically altered anatomy

Introduction

Endoscopic biliary stent placement with endoscopic retrograde cholangiography (ERCP) for the treatment of malignant biliary obstruction (MBO) has been widely accepted as an effective drainage method because it is less invasive and safe and has a high success rate (1–3). However, MBO is treated using percutaneous transhepatic biliary drainage (PTBD) or surgical bypass because of difficulties related to endoscopic access to the bile duct following gastrointestinal reconstruction. However, these methods are associated with marked adverse event (AE) rates (1–3).

Recently, balloon-assisted endoscopy (BAE) facilitates ERCP in patients with surgically altered anatomy. As for a double-balloon enteroscope (DBE), a short-type DBE (sDBE) is especially useful because it allows the use of many standard ERCP accessories.

The success rates of reaching the target site and ERCP-related interventions associated using these endoscopes range from 73–100% and 85–100%, respectively (4, 5). We previously reported that the success rate of reaching the target site and biliary intervention was 93.8% and 95.7%, respectively, in patients with benign

hepaticojejunostomy (HJ) anastomotic stricture (6).

However, inaccessibility of the target site may occur due to severe postoperative adhesions or a long insertion time (i.e., >60 minutes). Furthermore, previous reports have shown that the success rate of BAE in MBO cases was significantly lower than that in benign biliary diseases (7, 8). Few reports have investigated the outcome of BAE for MBO in patients with surgically altered anatomy. Additionally, the risk factors for clinical failure are not well-established.

Thus, we retrospectively evaluated the outcomes of endoscopic treatment for MBO using sDBE in patients with surgically altered anatomy and identified risk factors for clinical failure.

Methods

Patients

Between April 2011 and March 2019, 47 patients with MBO following gastrointestinal reconstruction underwent ERCP using sDBE for endoscopic biliary drainage at Okayama University Hospital. Indications for ERCP were clinical symptoms including

fever, jaundice, and abdominal pain; elevated hepatobiliary enzyme levels; and/or dilation of the intrahepatic bile duct detected on abdominal ultrasonography or using radiological studies, such as computed tomography and magnetic resonance cholangiopancreatography. MBO was diagnosed by biopsy or brush cytology from the biliary stricture, or clinical/imaging follow-up indicated the progression or metastasis of a lesion with malignant symptoms, such as weight loss or death. Two patients who underwent PTBD before ERCP were excluded from this analysis. Therefore, a total of 45 ERCP procedures using sDBE were considered eligible for inclusion. Informed consent was obtained from all subjects. The study protocol conformed to the ethical guidelines of the World Medical Association Declaration of Helsinki and was approved by The Okayama University Ethics Committee.

ERCP procedures

Patients were placed in a prone or semi-prone position. ERCP was performed under conscious sedation using intravenous diazepam (5–10 mg) and pethidine hydrochloride (35–140 mg) by an expert endoscopist who experienced at least 500 ERCP procedures using a side-view endoscope and 20 ERCP procedures using an sDBE or a non-expert supervised by an expert. An sDBE (EC-450BI5, EI-530B, or EI-580BT;

Fujifilm, Saitama, Japan) was used. It was inserted in the afferent loop until it reached the target site (i.e., the major papilla or HJ anastomosis). After the scope reached the target site, biliary cannulation was performed using a 4-Fr tapered catheter (PR-V234Q; Olympus) with a 0.025-inch guidewire (VisiGlide2; Olympus) in most cases. After cannulation, cholangiography was performed to confirm the presence of MBO, and the guidewire was manipulated again through the MBO. Then, we inserted 7-Fr plastic stents or self-expandable metal stents (SEMS) in the target biliary duct based on the endoscopist's discretion. Uncovered and fully covered SEMS were used for malignant hilar biliary obstruction and malignant distal biliary obstruction, respectively (Figure 1A–D).

Assessment of clinical outcome

Clinical outcome was evaluated based on the clinical and technical success (insertion and biliary intervention success), insertion and total procedure time, stent patency, and AE. Insertion success was defined as the success rate of reaching the target site. Biliary intervention success was evaluated depending on the completion of cholangiography and stent placement in the target biliary duct among patients who achieved insertion success. Technical success was defined as cases that achieved

insertion and biliary intervention success. Clinical success was defined as improvement in the pretreatment liver function test results and patient's clinical symptoms within 28 days of stent placement. Stent patency was defined as the time from stent placement to recurrent biliary obstruction (RBO). RBO was defined as elevated liver enzyme levels or cholangitis with images showing bile duct dilatation. Patient death before stent occlusion was treated as censored data. Stent patency was calculated using the Kaplan–Meier method. AEs were evaluated in accordance with the American Society for Gastrointestinal Endoscopy lexicon for endoscopic AEs (9).

Statistical analysis

Non-continuous variables were compared using the χ^2 test, while continuous variables were compared using the Wilcoxon rank-sum test. A p-value <0.05 was considered as statistically significant. To identify risk factors for clinical failure via endoscopic treatment of MBO in patients with surgically altered anatomy, factors with p-values <0.1 in a univariate analysis were analyzed using a multivariate logistic regression. The following variables were analyzed: sex; age (>67 years); etiology, cause, and location of MBO; presence of peritoneal dissemination; type of surgical anatomy; presence of major papilla; time from surgery to endoscopic treatment (>505 days); total

bilirubin (>2.5 mg/dL); aspartate aminotransaminase (>80 IU/L); alanine aminotransferase (>72 IU/L); g-glutamyl transpeptidase (>364 IU/L); alkaline phosphatase (>1205 IU/L); and type of scope. Cut-off values were set at the median of all patients in each variable. Peritoneal dissemination was defined as the presence of peritoneal lesions such as peritoneal nodules and mesenteric thickening based on the CT image preoperatively. All statistical analyses were performed using the JMP 12 software (SAS Institute Inc., Cary, NC, USA). Ranges of continuous variables were shown as interquartile ranges.

Result

Patient characteristics

A total of 45 patients [29 men and 16 women; median age: 67 years (range, 59–75 years)] with surgically altered anatomy who underwent ERCP using sDBE for MBO treatment were retrospectively evaluated in this study. Patients' characteristics are shown in Table 1. The most common etiology of MBO was malignant biliary disease. The type of MBO was mostly recurrent disease in 39 patients (86.7%), and peritoneal dissemination was seen in 13 cases (28.9%).

Clinical outcome

Endoscopic results are shown in Table 2. Among the 45 patients, insertion success was achieved in 82.2% of the patients (37/45). The median insertion time required to reach the target site was 17 minutes (range, 10–29 minutes). Among nine patients with unsuccessful insertion, three underwent Roux-en-Y (RY) HJ reconstruction, three underwent RY with gastrectomy, one underwent reconstruction via the modified Child's method, and one underwent Billroth II with gastrectomy, and the insertion success rates for RYHJ, RY with gastrectomy, modified Child's method, and Billroth II with gastrectomy were 66.7%, 76.9%, 94.4%, and 80.0%, respectively. In cases where the modified Child's method was used, the insertion success rate tended to be high, but the change was not statistically significant ($p=0.08$); however, this may be due to the small sample size. Insertion failure was observed in four patients with malignant digestive tract obstruction, in three with severe adhesion of the afferent loop, in one with failure to identify the HJ anastomosis, and in one with small intestinal perforation. We did not reattempt scope insertion with another type of scope if we encountered any difficulties. Of the unsuccessful cases, five patients were treated using PTBD, one was treated using endoscopic ultrasound-guided biliary drainage (EUS-BD), one was managed conservatively, and the other one patient with perforation

was surgically treated. Biliary intervention success was achieved in 32 of 37 patients (86.4%). The total procedure time was 66 minutes (range, 40–92 minutes). In five patients with unsuccessful biliary intervention, cannulation failure in the native papilla (n=3) and severe biliary stricture which hindered guidewire advancement to the target biliary duct (n=2) contributed to biliary intervention failure. Two patients were managed conservatively because of refusing to undergo PTBD and choosing palliative care for terminal cancer, while the remaining three required PTBD. Moreover, technical success was achieved in 71.1% of patients (32/45). Among them, one patient had unimproved jaundice and was managed conservatively. Finally, clinical success was achieved in 68.9% of patients (31/45). Risk factors for clinical failure via endoscopic treatment of MBO in patients with surgically altered anatomy were analyzed using logistic regression analyses (Table 3). In multivariate analysis, the presence of peritoneal dissemination (odds ratio, 7.3; 95% confidence interval, 1.5–43.5) (p=0.02) was as an independent risk factor for clinical failure.

Endoscopic treatment details

Among the 31 patients with clinical success, 14 patients received plastic stent (PS) deployment (PS group) and 17 received SEMS deployment (MS group) as an endoscopic

treatment. Characteristics of each group are shown in Table 4.

Among them, RBO occurred in seven patients in each group, and the median stent patency was 120 (range, 105–280 days) and 141 (104–271 days) days (p=0.43), in the PS and MS groups, respectively (Figure 2). The median survival time from endoscopic treatment was 144 days.

Adverse events

Adverse events were observed in five patients (11.1%), including mild pancreatitis in three, moderate in one, and severe small intestinal perforation in one. Intestinal perforation by the tip of scope—during stretching of the scope—occurred at the transverse part of duodenum in a case with a Billroth II reconstruction. This case underwent emergent pancreaticoduodenectomy for a pancreatic head tumor and an intestinal perforation, and the postoperative course was uneventful, whereas the other patients were successfully managed conservatively. The AE rate was 0% (0/19) for the Modified Child's method, 23.1% (3/13) for RY with gastrectomy, 0% (0/9) for RYHJ, and 40% (2/5) for Billroth II with gastrectomy. For Billroth II with gastrectomy, the rate of AEs was significantly higher than rates for the other methods (p=0.03). Peritoneal dissemination was observed in 20% of cases with AEs

and was not related to the frequency of AE (p=0.64).

Discussion

In this study, we assessed the outcomes of endoscopic treatment for MBO using sDBE in patients with surgically altered anatomy. The technical success rate of endoscopic treatment was 71.1% and clinical success rate was 68.9%, with an AE rate of 11.1%. This result was comparable to the previous report that showed a technical success rate of 78.3% (8).

In this study, insertion failure occurred in 61.5% (8/13) of technical failure cases, and malignant digestive tract obstruction or severe adhesion caused difficulty in sDBE insertion to the target site. Among 8 patients with failed scope insertion, peritoneal dissemination was noted in 5 patients based on the CT image before endoscopy (62.5%). Furthermore, the presence of peritoneal dissemination in CT image prior to endoscopy was as an independent risk factor for clinical failure. The clinical success rate was 38.5% in patients with peritoneal dissemination and 81.3% in those without peritoneal dissemination. Failure in these patients was managed using PTBD or EUS-BD as an alternative treatment. Thus, pre-procedural CT image is important

to determine treatment decisions, such as the appropriate use of EUS-BD or PTBD.

The results of this study revealed no difference in stent patency between the PS and MS groups. In general, it is believed that the MS group had a longer patency period than the PS group. However, the median survival time was 144 days, and many patients died before RBO. This may have caused no significant difference in the patency period between both groups. Therefore, stent selection should be based on the prognosis of each case.

EUS-BD has been reported as an effective alternative biliary drainage technique after a failed standard ERCP (10). Recent systematic analyses have shown that the high technical success rate of this procedure (90–94.7%) is associated with a high AE rate (16.5–23.3%) (11–14). Moreover, in the report of Iwashita et al. that evaluated the outcome of EUS-BD for MBO in patients with surgically altered anatomy whose subjects were similar to this study, the technical success and AE rates were 95% and 20%, respectively. As such, AEs associated with EUS-BD procedures remain important problems to be resolved. Our result showed that endoscopic treatment using sDBE in patients without peritoneal dissemination on CT image before the procedure provided

favorable outcomes with regard to the procedural success and AE rates. Therefore, we proposed the use of ERCP with sDBE as an initial treatment of MBO in patients with surgically altered anatomy, if peritoneal dissemination was not seen on CT image prior to the procedure. If peritoneal dissemination was indicated before the procedure, it may be better to attempt PTBD or EUS-BD as the initial treatment.

This study had some limitations. First, it was retrospective in nature and was performed in a single center. Second, the sample size was small. Third, this study had no control group. Therefore, a prospective study involving sufficient number of patients is required to confirm our results.

In conclusion, this study evaluated the outcomes of endoscopic treatment of MBO using sDBE in patients with surgically altered anatomy. Peritoneal dissemination on a CT image is an independent risk factor for clinical failure of an endoscopic procedure. Without peritoneal dissemination, ERCP using sDBE can be an initial treatment for MBO in patients with surgically altered anatomy.

Disclosures

Takeshi Tomoda, Hironari Kato, Kazuya Miyamoto, Akihiro Matsumi, Eijiro Ueta, Yuuki Fujii, Yousuke Saragai, Tatsuhiro Yamazaki, Daisuke Uchida, Kazuyuki Matsumoto, Shigeru Horiguchi, Koichiro Tsutsumi, and Hiroyuki Okada have no conflicts of interest or financial ties to disclosure.

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Figure legends

Figure 1: A patient underwent endoscopic retrograde cholangiopancreatography using short-type double-balloon endoscope for obstructive jaundice following pancreaticoduodenectomy with reconstruction via the modified Child's method for pancreatic ductal adenocarcinoma (PDAC).

A: Computed tomography image revealed intrahepatic bile duct dilation caused by malignant biliary obstruction (MBO) of hepaticojejunostomy (HJ) anastomosis for local recurrence of PDAC (arrowhead).

B: Endoscopic image revealed local recurrence of PDAC in HJ anastomosis.

C: Cholangiogram showed approximately 10-mm long MBO.

D: Two uncovered self-expandable metallic stents were deployed in the right and left hepatic duct using the stent in stent method.

Figure 2: Comparison of the cumulative stent patency after the treatment between the plastic stent (PS) (dotted line) and MS (solid line) groups. No significant difference was noted in stent patency between the groups ($p=0.43$).