Preoperative biliary drainage using a fully covered self-expandable metallic stent for pancreatic head cancer: A prospective feasibility study

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INTRODUCTION

Surgical resection is the only curative treatment option in patients with pancreatic cancer without evidence of major vascular invasion or distant metastasis. Obstructive jaundice is a common symptom in patients with pancreatic head cancer, and the performance and efficacy of preoperative biliary drainage (PBD) remains controversial. A meta-analysis revealed that...
preoperative adverse events related to the drainage procedure itself outweigh the benefits of PBD. A recent randomized controlled trial performed by van der Gaag et al. showed that PBD was associated with an increased incidence of perioperative adverse events. However, PBD is still performed in clinical practice because immediate surgery without PBD cannot be scheduled in many centers. Another flaw of the randomized study is the use of plastic stents (PSs) rather than self-expandable metallic stents (SEMSs). The major preoperative adverse events were cholangitis caused by PS occlusion, which might be resolved by the use of SEMSs. While the efficacy of SEMS placement has been increasingly reported in patients receiving neoadjuvant treatment, PS placement is still the standard treatment for PBD in patients with resectable pancreatic cancer without neoadjuvant treatment.

The aim of this prospective study was to evaluate the feasibility and safety of PBD using a fully-covered SEMS (FCSEMS) for the treatment of resectable pancreatic head cancer.

PATIENTS AND METHODS

Study design
A single-arm prospective feasibility study was conducted in three academic centers in Japan; Tokyo University Hospital, Hokkaido University Hospital, and Saitama Medical University International Medical Center. The protocol was approved by the institutional review board at each institution. This study was registered with the University Hospital Medical Information Network (UMIN) Clinical Trials Registry (UMIN000007183).

Patients
The eligibility criteria were (i) suspicion of pancreatic head cancer based on clinical and imaging findings, (ii) obstructive jaundice [total bilirubin (T-Bil) level of >5.0 mg/dL] or an elevated aspartate aminotransferase level (>3 times the upper limit of normal), irrespective of symptoms such as pruritis or cholangitis, and (iii) a candidate for definitive surgery. The exclusion criteria were (i) prior endoscopic, percutaneous, or surgical biliary drainage; (ii) suspicion of tumor involvement to the orifice of the cystic duct (OCD); (iii) not suitable for endoscopic procedures such as gastric outlet obstruction; (iv) severe heart disease, hepatic insufficiency, renal dysfunction, endocrine disease, or coagulopathy; and (v) pregnancy or possibility of pregnancy. Written informed consent was obtained from all patients before the endoscopic procedure.

Placement of FCSEMS and surgery
All FCSEMSs placed were 10-mm-diameter WallFlex™ Biliary RX Fully Covered Stents (Boston Scientific, Natick, MA) [Figure 1]. The proximal end of the stent was placed at least 2 cm below the hepatic hilum, and the distal end was placed in the duodenum. Sphincterotomy was performed before FCSEMS placement at the discretion of each endoscopist. Prophylactic antibiotics were administrated in all cases. Surgery was performed after improvement of jaundice or elevated liver enzyme levels.

Outcomes
The primary outcome was the incidence of preoperative and postoperative adverse events. Preoperative adverse events were diagnosed according to the TOKYO criteria 2014, a standard reporting system for biliary stenting based on the 1991 consensus guidelines. Insufficient resolution of jaundice was included as an adverse event of PBD. Postoperative adverse events up to 90 days after surgery were graded according to the International Study Group on Pancreatic Fistula (ISGPF) definition and Clavien–Dindo classification. Severe postoperative adverse events were defined as Clavien–Dindo grade III and IV. The cumulative occurrence of adverse events after FCSEMS placement both in patients undergoing surgical resection and in patients who were eventually diagnosed with unresectable cancer was evaluated by Kaplan–Meier analysis. Cases involving surgery without preoperative adverse events were censored at the time of surgery.

Sample size
Formal sample size calculation was not performed because this study was a pilot feasibility study. The sample size was determined to be 40 patients during the 2-year study enrollment based on the estimated annual number of patients with pancreatic head cancer amenable to surgical resection.

RESULTS
Twenty-six patients were enrolled in this study from April 2011 to March 2013. A flow chart of the study enrollment is shown in Figure 2. Two patients were excluded due to failed FCSEMS placement – one underwent percutaneous biliary drainage after failed endoscopic retrograde cholangiopancreatography (ERCP) and the other underwent PS instead of FCSEMS placement because of an unstable clinical condition during ERCP. FCSEMSs were successfully placed in the remaining 24 patients. Among these, seven patients were diagnosed with unresectable cancer after FCSEMS placement and did
not undergo surgery. Finally, 17 patients underwent surgery for pancreatic cancer after FCSEMS placement.

Patients’ characteristics
The patients’ characteristics are shown in Table 1. The patients comprised 11 males and 6 females with a median age of 65 years. The median T-Bil level before PBD was 12.4 mg/dL. Sphincterotomy was performed at the time of FCSEMS placement in seven patients. The surgery was performed at a median of 18 days after FCSEMS placement. The median T-Bil level just before the surgery was 2.2 mg/dL. The surgical procedures were pancreaticoduodenectomy (n = 3), pylorus-preserving pancreaticoduodenectomy (n = 6), subtotal stomach-preserving pancreaticoduodenectomy (n = 7), and explorative laparotomy (n = 1). Surgeons experienced no intraoperative difficulties attributable to preoperative FCSEMS placement. Pathological confirmation of pancreatic cancer was performed after the surgery in all cases.

Preoperative and postoperative adverse events in 17 patients who underwent surgery
The perioperative adverse events that occurred in this study are shown in Table 2. Two (12%) preoperative adverse events and eight (47%) postoperative adverse events were observed.

Neither pancreatitis nor stent migration occurred during the preoperative period. One patient developed acute cholecystitis 15 days after FCSEMS placement, which was resolved by percutaneous drainage. This patient underwent curative surgery 16 days after the gallbladder drainage. The other patient required repeated biliary drainage because of insufficient resolution of jaundice without stent occlusion. Although an endoscopic nasobiliary catheter was temporarily inserted through the indwelling FCSEMS, jaundice did not resolve and the endoscopic nasobiliary drainage tube was removed 14 days after its placement. The T-Bil level then gradually decreased, and the patient underwent surgery 45 days after FCSEMS placement.

Twelve postoperative adverse events occurred in eight patients within the follow-up period of 90 days. Severe adverse events occurred in five patients. Pancreaticojejunostomy leakage occurred in two patients, but improved without any further intervention (ISGPF grade A). All patients were alive 90 days after the surgery. Postoperative adverse events occurred in 7/15 (47%) patients among the group without preoperative adverse events and in 1/2 (50%) among the group with preoperative adverse events. Median hospital stay after the surgery was 19 days (interquartile range, 15–26 days).
Stent-related adverse events in 24 patients who underwent FCSEMS placement

Four stent-related adverse events occurred in all 24 patients (17 surgical cases and 7 unresectable cases) [Table 3]. The cumulative incidence of adverse events at 4 and 8 weeks after FCSEMS placement was 19% (95% confidence interval, 1.1–34.1) [Figure 3].

DISCUSSION

The role of PBD in the treatment of resectable pancreatic head cancer remains controversial. While early retrospective[20‑23] and randomized studies[3,5] showed decreases in postoperative mortality and morbidity, other randomized studies[1,2,4] and more recent retrospective studies[24,25] showed no significant benefit of PBD. The major disadvantage of PBD is its high rate of preoperative adverse events. The reported adverse event rate of PBD using PSs is 42% to 46%,[7,26] which outweighs the benefit of PBD.[27] Therefore, the advantage of PBD can be maximized if preoperative adverse events are reduced. In the present prospective study, the preoperative adverse event rate was low (12%), consistent with the short- and long-term adverse event rates of 8% and 4%, respectively, in a retrospective study of SEMS placement for PBD.[28] A larger-diameter SEMS was associated with a lower incidence of premature stent occlusion than was observed in PSs, as shown in patients with unresectable malignant biliary obstruction.[29,30]

The optimal duration of PBD is also controversial. An experimental study suggested that recovery of liver function depends on both the duration of obstructive jaundice and the duration of PBD, and at least 4 weeks of PBD was needed for liver function recovery.[31] A recent meta-analysis suggested that the optimal drainage duration to reduce the overall morbidity rate was more than 4 weeks.[32] However, it is sometimes difficult to schedule major surgery for patients with pancreatic head cancer within 4 weeks in clinical practice. Another study showed that, when PSs were used for PBD, the rate of preoperative adverse events was >40%[7] however, the present study demonstrated that FCSEMS placement can potentially reduce the cumulative incidence of preoperative adverse events (19% at 4- and 8-weeks). Thus, the superiority of FCSEMS over PS placement can be justified if the waiting time for surgery would be prolonged, such as in patients receiving neoadjuvant treatment.

The goal of PBD should be to reduce the morbidity and mortality associated with surgical resection. The use of a large-bore stent with self-expandable force can potentially cause inflammation and adhesion around the bile duct, which can hinder surgical resection.[33] However, SEMS placement reportedly does not affect surgical procedures compared with PS,[34] and the surgeons in the present study did not experience difficulties attributable to the FCSEMSs.

Cost is another issue associated with SEMS placement. Although a retrospective study of 366 patients undergoing pancreaticoduodenectomy concluded that SEMS should be used in selected cases because of its cost,[35] resectability is not readily confirmed at the time of initial biliary drainage. In another study, 20% and 26% of the patients with resectable pancreatic cancer exhibited liver metastasis.

Table 2: Preoperative and postoperative adverse events in 17 patients who underwent surgery

| Adverse events related to biliary drainage | (%) | 95% CI |
|------------------------------------------|-----|--------|
| Adverse events related to surgery        | 8 (47%) | [2.4, 72.2] |
| Delayed gastric emptying                 | 3 (18%) | [3.8, 43.4] |
| Pancreaticojejunostomy leakage           | 2 (12%) | [1.5, 36.4] |
| Intra-abdominal abscess                  | 2 (12%) | [1.5, 36.4] |
| Surgical site infection                  | 2 (12%) | [1.5, 36.4] |
| Hemorrhage                               | 1 (6%) | [0.1, 28.7] |
| Bile leakage                             | 1 (6%) | [0.1, 28.7] |
| Diarrhea                                 | 1 (6%) | [0.1, 28.7] |
| Need for repeated surgery                | 2 (12%) | [1.5, 36.4] |

CI: Confidence interval

Table 3: Biliary drainage-related adverse events in 24 patients who underwent FCSEMS placement

| Adverse events | (%) | 95% CI |
|----------------|-----|--------|
| Adverse events | 4 (17%) | [4.7, 37.4] |
| Cholecystitis  | 2 (8%) | [1.0, 27.0] |
| Stent occlusion| 1 (4%) | [0.1, 21.1] |
| Insufficient resolution of jaundice      | 1 (4%) | [0.1, 21.1] |

CI: Confidence interval
and peritoneal dissemination, respectively, on preoperative radiological imaging. In such cases, subsequent stent revision might be required since median patency of PS had been reported to be approximately 4 months or palliative surgery such as hepaticojejunostomy is sometimes performed during laparotomy. Therefore, initial SEMS placement regardless of resectability is reportedly more cost-effective.

Cholecystitis after SEMS placement is a well-known adverse event, and tumor involvement to the OCD is a reported risk factor of cholecystitis after SEMS placement. Although patients with tumor involvement to the OCD were excluded from this study, acute cholecystitis occurred in 2 of 24 patients who underwent FCSEMS placement, which is similar to the incidence of 10% in a previous report involving the use of partially covered WallFlex™ stents. Compression of the OCD caused by the flared ends or high axial force of the FCSEMS might result in the development of acute cholecystitis. Acute cholecystitis after SEMS placement remains an unsolved problem, and further improvement of SEMSs is necessary to reduce this stent-related adverse event.

There are some limitations of this study. This was a single-arm study with a small sample size. In addition to this study, we have completed another pilot study of covered SEMS in cases undergoing neoadjuvant chemotherapy for pancreatic cancer (UMIN000011855). Given the increasing evidence of covered SEMS as PBD for pancreatic cancer, we aim to start a large scale, multicenter, randomized control trial of a covered SEMS and PS in cases with pancreatic cancer who would undergo upfront surgery or neoadjuvant chemotherapy. In addition, we were unable to enroll the originally planned number of patients during the study period. Data regarding the effects of FCSEMS placement on the surgical procedure, such as blood loss and operative duration, were lacking. However, the surgeons did not experience any intraoperative difficulties attributable to FCSEMS placement, as previously reported in neoadjuvant settings.

CONCLUSIONS

FCSEMS placement is safe and feasible for PBD in patients with resectable pancreatic head cancer. FCSEMS placement can reduce the rate of preoperative adverse events such as stent occlusion, especially in patients undergoing elective surgery. A randomized controlled trial comparing FCSEMS with PS placement or no PBD is warranted to confirm our findings.

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Conflicts of interest
Hiroyuki Isayama has received honoraria for speaking at an event organized by the Boston Scientific Japan Corporation and has received research funds from the Boston Scientific Japan Corporation for another research project.

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