



# BMJ Open Trial protocol: a randomised controlled trial to verify the non-inferiority of a partially covered self-expandable metal stent to an uncovered self-expandable metal stent for biliary drainage during neoadjuvant therapy in patients with pancreatic cancer with obstructive jaundice (PUN-NAC trial)

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## ABSTRACT

**Introduction** Neoadjuvant chemotherapy or neoadjuvant chemoradiotherapy (NAC/NACRT) for resectable/borderline resectable pancreatic cancers was recently performed to improve clinical outcomes and led to good results, although it remains controversial whether NAC/NACRT is beneficial for resectable pancreatic cancer. A few recent studies revealed longer patency and lower cost related to the stent occlusion of a metal stent than those of a plastic stent during NAC/NACRT. It also remains controversial which type of self-expandable metal stent (SEMS) is the most suitable for patients with resectable/borderline resectable pancreatic cancer during NAC/NACRT: an uncovered SEMS (USEMS), a fully covered SEMS (FCSEMS) or a partially covered SEMS (PCSEMS). So far, two randomised controlled trials indicated that a USEMS and an FCSEMS were similar in preoperative stent dysfunction and adverse event rate. Thus, we aimed to verify the non-inferiority of a PCSEMS to a USEMS in this multicentre randomised controlled trial.

**Methods and analysis** We designed a multicentre randomised controlled trial, for which we will recruit 100 patients with resectable/borderline resectable pancreatic cancer and distal biliary obstruction scheduled for NAC/NACRT from 13 high-volume institutions. Patients will be randomly allocated to the PCSEMS group or USEMS group. The primary outcome measure is the preoperative biliary event rate. Data will be analysed after completion of the study. We will calculate the 95% CIs of the incidence of preoperative biliary events in each group and analyse whether the difference between them is within the non-inferiority margin (10%).

**Ethics and dissemination** This study has been approved by the institutional review board of Hokkaido University

## Strengths and limitations of this study

- This would be the first prospective study to potentially confirm the non-inferiority of a partially covered self-expandable metal stent (SEMS) in patients with resectable/borderline resectable pancreatic cancer and distal biliary obstruction scheduled for neoadjuvant chemotherapy or neoadjuvant chemoradiotherapy (NAC/NACRT).
- Prospective designed, multicentre, large sample size protocol.
- Not including cases drained by an fully covered SEMS.
- The judgement of resectable/borderline resectable pancreatic cancer will be performed by each institution.
- NAC/NACRT regimens are not standardised in all institutions.

Hospital. The results will be submitted for presentation at an international medical conference and published in a peer-reviewed journal.

**Trial registration number** UMIN000041737; jRCT1012200002.

## INTRODUCTION

The early detection and treatment of pancreatic cancer are extremely difficult, and the 5-year survival rate of patients with pancreatic cancer (3.3%–5%) is worse than that of patients with other cancers.<sup>1 2</sup> Considering tumour staging, the current 5-year

survival rates for all types of pancreatic cancer by stage are reported by the Surveillance, Epidemiology and End Results Programme of the USA as follows: localised, 39%; regional, 13%; distant, 3%; and all stages combined, 10% (2010–2016). Neoadjuvant chemotherapy/neoadjuvant chemoradiotherapy (NAC/NACRT) for resectable or borderline resectable pancreatic cancers was recently performed to improve clinical outcomes and led to good results in some institutions, although it remains controversial whether NAC/NACRT is beneficial for resectable pancreatic cancer.<sup>3–5</sup> Since NAC/NACRT requires approximately 2–5 months, appropriate and sustainable biliary drainage in patients with obstructive jaundice is necessary to accomplish neoadjuvant therapy.<sup>6,7</sup> Furthermore, the prevention of preoperative cholangitis using appropriate biliary drainage can reduce the incidence of severe postoperative complications.<sup>8</sup>

Many previous studies on biliary drainage for patients with unresectable pancreatic cancer indicated that a metal stent is superior to a plastic stent in terms of patency<sup>9</sup>; however, a few recent studies also revealed longer patency and lower cost related to the stent occlusion of a metal stent than those of a plastic stent during NAC/NACRT.<sup>10–14</sup> It remains controversial which type of self-expandable metal stent (SEMS) is the most suitable for patients with resectable or borderline resectable pancreatic cancer during NAC/NACRT: an uncovered SEMS (USEMS), fully covered SEMS (FCSEMS) or partially covered SEMS (PCSEMS). During NAC/NACRT in patients with pancreatic cancer, the USEMS has been the standard SEMS for biliary decompression as well as during chemotherapy in patients with unresectable pancreatic cancer, but there have been few comparative studies on the patency and safety of SEMSs in curative surgery after neoadjuvant therapy. We can currently refer to the results of two randomised controlled trials (RCTs) (ClinicalTrials.gov identifiers: NCT01038713 and NCT02238847) in which an FCSEMS and a USEMS were compared during neoadjuvant therapy for pancreatic cancer: preoperative stent dysfunction (25% vs 35%; 27.8% vs 27.1%) and adverse event rate (25% vs 18%; 23.7% vs 20%) were not significantly different between them.<sup>12,15</sup> However, in the latter trial, tumour ingrowth occurred more frequently in patients with a USEMS (16.7% vs 0%), while stent migration occurred more frequently in patients with an FCSEMS (6.8% vs 0%).<sup>15</sup>

Meanwhile, the PCSEMS has a bare site at each end to prevent migration due to the anchoring effect and a covered site in the centre for the prevention of tumour ingrowth. Thus, it has a combination of good and bad features of the USEMS and FCSEMS. One retrospective study with a small cohort of patients with unresectable malignant distal biliary obstruction indicated that a PCSEMS (n=28) had longer patency than a USEMS (n=44) or an FCSEMS (n=29) (444, 199 and 194 days, respectively, vs uncovered, p=0.013, vs fully covered, p=0.010).<sup>16</sup> Another recent study with a large cohort indicated that a PCSEMS (n=141) and an FCSEMS (n=151)

yielded similar recurrent biliary obstruction (RBO) rates (29% vs 33%, p=0.451) including stent migration and stent patency (318 vs 373 days, p=0.382).<sup>17</sup> However, no study has clarified the efficacy of a PCSEMS during neoadjuvant therapy for pancreatic cancer with biliary drainage, in which the drainage period is limited until radical resection and the subsequent perioperative administration could be affected.

Taken together, a PCSEMS used during NAC/NACRT could also achieve similar stent performance to a USEMS and an FCSEMS in preoperative biliary events including stent occlusion and migration. In addition, if the non-inferiority of a PCSEMS to a USEMS as a standard metal stent in such a situation is proven, the three types of SEMS (USEMS, FCSEMS and PCSEMS) would be scientifically equivalent in NAC/NACRT for pancreatic cancer, which can result in a wide range of SEMS options and subsequent benefits for the patients. Thus, we aimed to verify the non-inferiority of a PCSEMS to a USEMS in this multicentre RCT.

## MATERIALS AND METHODS

### Design

To verify our clinical hypothesis, the non-inferiority of a PCSEMS to a USEMS, we designed this multicentre, open-label RCT. The research protocol of this study was registered with the University Hospital Medical Information Network (UMIN) Clinical Trial Registry and Japan Registry of Clinical Trials (jRCT). The study stage is 'preresults'. This is not an industry-sponsored study.

### Setting

This study is conducted at the department of Gastroenterology and Hepatology, Hokkaido University Hospital, Japan, and 12 other high-volume pancreaticobiliary intervention institutions in Japan (box 1).

### Participants and recruitment

Patients with resectable/borderline resectable pancreatic cancer and distal biliary obstruction who are scheduled for NAC/NACRT will be enrolled. Patients will be

#### Box 1 Thirteen participating institutions

Hokkaido University Hospital.  
Yokohama City University Medical Center.  
Mie University.  
Kagawa University.  
Shizuoka Cancer Center.  
Sapporo City General Hospital.  
Gifu University.  
Sapporo Medical University.  
Kagoshima University.  
Wakayama Medical University.  
Asahikawa Medical University.  
IMS Sapporo Digestive Disease Center General Hospital.  
Teine Keijinkai Hospital.

recruited from among those referred to the 13 participating institutions for endoscopic biliary drainage.

### Inclusion criteria

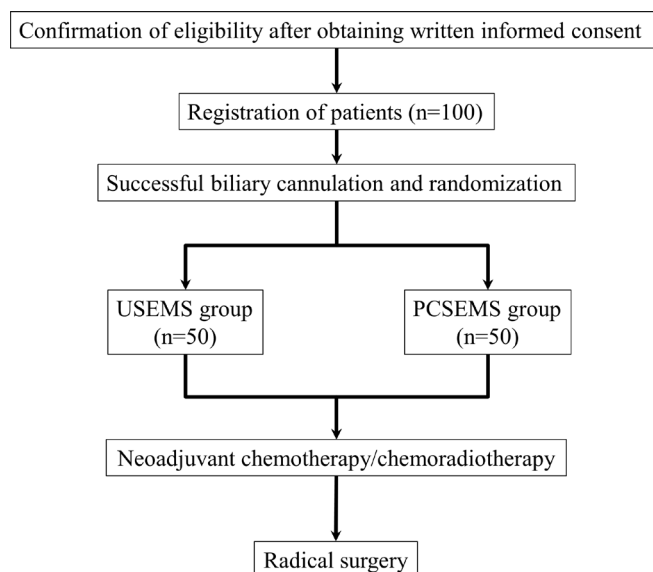
The inclusion criteria for the study are as follows: (1) pathological diagnosis of pancreatic ductal adenocarcinoma/adenosquamous carcinoma; (2) clinical diagnosis of resectable/borderline resectable pancreatic cancer according to the seventh edition of the General Rules for the Study of Pancreatic Cancer by the Japan Pancreas Society, which is almost the same as National Comprehensive Cancer Network Guideline version 1.2020; (3) scheduled for NAC/NACRT; (4) confirmed distal biliary obstruction (defined as stricture at the common bile duct located downstream of the confluence of the cystic duct according to the Classification of Biliary Tract Cancers established by the Japanese Society of Hepato-Biliary-Pancreatic Surgery: third English edition) requiring endoscopic biliary drainage (or a history of endoscopic/percutaneous transhepatic biliary drainage using a plastic stent/tube), which leads to abnormal serum total bilirubin or liver function test results (aspartate aminotransferase, alanine aminotransferase, gamma-glutamyl transferase or alkaline phosphatase values not within normal reference ranges at each institution) with or without bile duct dilatation; (5) 20 years of age or older; and (6) willingness to provide informed consent.

### Exclusion criteria

The exclusion criteria for the study are as follows: (1) history of biliary drainage with a metal stent, (2) history of chemotherapy/chemoradiotherapy for pancreatic cancer, (3) biliary obstruction that has progressed to the hepatic hilum, (4) Eastern Cooperative Oncology Group Performance Status (ECOG-PS) 4, (5) history of gastrointestinal tract reconstruction except for Billroth I reconstruction, (6) the major duodenal papilla unreachable by a duodenal endoscope, (7) current pregnancy or suspected pregnancy and (8) unsuitable for inclusion at the discretion of the physician.

### Study outline and intervention

Figure 1 illustrates the planned study flow. First, all potential participants will be asked to provide written informed consent by the physicians in charge of this study at each institution. The registration is performed after identifying whether the patient fulfils the inclusion criteria and whether any exclusion criteria are applicable. When successful biliary cannulations are accomplished on endoscopic retrograde cholangiopancreatography, the participants will be randomly assigned to the USEMS group or the PCSEMS group using dynamic allocation (allocation factors comprise institution, history of biliary drainage [nasobiliary or percutaneous tube/tube stent placement] and resectability [resectable/borderline resectable]) with a web-based randomised allocation system. Patients assigned to the USEMS group will undergo the insertion of a USEMS (Evolution, Biliary



**Figure 1** Flow diagram of the study participants. USEMS, uncovered self-expandable metal stent; PCSEMS, partially covered self-expandable metal stent.

Controlled-Release Stent—Uncovered, Cook Medical, Bloomington, Indiana, USA) for biliary decompression, while those assigned to the PCSEMS group will undergo insertion of a PCSEMS (Evolution, Biliary Controlled-Release Stent—Partially Covered, Cook Medical). Details of the stenting procedure are summarised in box 2. Patient background factors (including sex, age, medical history and ECOG-PS), medical information (results of a pathological examination, if possible), lesion site, clinical cancer stage and procedure characteristics (the category of the operator (trainee/fellow/expert), SEMS type, diameter and length, history of biliary drainage, past/present procedure for the papilla, stricture length and total procedure time) will be recorded in the electronic data capture system operated by Hokkaido University (NorthNet, V.1.4.5). Patients will be followed up for approximately 6 months after SEMS stenting to obtain laboratory, clinical symptom and CT imaging data within the preoperative and perioperative periods. These data will be collected at the following scheduled times: prior to the procedure, on the procedure day, 1 day after the procedure, during NAC/NACRT and just before and after radical surgery (table 1).

Adverse events occurring during the therapeutic intervention and observation period will be covered by the usual insurance coverage.

### Neoadjuvant chemotherapy/neoadjuvant chemoradiotherapy

Each participating institute has an institutional cancer board, which decides the necessity and protocols of NAC/NACRT. There is no definite NAC/NACRT protocol for this study. However, NAC/NACRT will be scheduled according to each institution's protocol based on the recently published clinical studies as follows: oral S-1 alone, irradiation and oral S-1 (on the radiation day alone) with/without subsequent chemotherapy with

## Box 2 Details of the stenting procedure with a self-expandable metal stent

Intravenous injection of an antispasmodic agent and sedative and analgesic agent.  
 Insertion of a duodenal endoscope and biliary cannulation.  
 Allocation to the uncovered self-expandable metal stent (USEMS) or partially covered self-expandable metal stent (PCSEMS) group to place a metal stent.  
 Placement of a USEMS or a PCSEMS.  
 Removal of a duodenal endoscope.

gemcitabine, gemcitabine and oral S-1 and gemcitabine and nab-paclitaxel.

After NAC/NACRT, the patients will be scheduled to undergo radical surgery within 6–8 weeks after the last administration of an anticancer agent when contrast-enhanced CT does not reveal metastasis or local progression that prohibits curative resection.

### Definitions

Biliary events in this study are defined as follows: (1) RBO after stenting with a SEMS is defined as a composite endpoint of stent occlusion, dislocation or migration on the basis of the Tokyo criteria<sup>18</sup>; (2) complete dislocation of the SEMS without biliary obstruction/cholangitis detected by an imaging test; (3) acute cholangitis as defined by the Tokyo Guidelines 2018<sup>19</sup> without biliary obstruction due to the reflux of gastrointestinal content, ischaemia and bleeding; (4) acute cholecystitis defined by Tokyo Guidelines 2018<sup>20</sup>; and (5) liver abscess with symptoms such as fever, pain and discomfort.

Adverse events related to the stenting procedure with a USEMS or a PCSEMS such as pancreatitis, cholangitis, bleeding, perforation and fever are defined based on the lexicon of the American Society for Gastrointestinal Endoscopy.<sup>21</sup> Complications after radical surgery will be evaluated and graded based on the extended Clavien-Dindo classification.<sup>22</sup> Postoperative pancreatic fistula is defined

as an abnormal communication between the pancreatic ductal system and another epithelial surface containing a pancreas-derived, enzyme-rich fluid according to the International Study Group definition and grading of postoperative pancreatic fistula.<sup>23</sup> The final tumour size is defined as the size measured on contrast-enhanced CT within 2 weeks before the pancreatoduodenectomy.

### Study outcome

The primary outcome measure is the preoperative biliary event rate. The secondary outcome measures are (1) rate of achievement of radical resection; (2) time to RBO; (3) NAC/NACRT accomplishment, delay and discontinuation rates; (4) SEMS-related adverse events; and (5) postoperative adverse events.

### Sample size

A sample size of 100, including 50 patients in the USEMS group and 50 patients in the PCSEMS group, is required in this study. The calculation of the sample size was performed using SAS V.9.4 software and PASS V.14.0.9 as follows: by reference to only two RCTs by Gardner *et al*<sup>12</sup> and Seo *et al*<sup>15</sup> (preoperative stent dysfunction rate: FCSEMS 25% vs USEMS 35% and FCSEMS 27.8% vs USEMS 27.1%, respectively), we assumed that the rates of preoperative biliary events would be 25% in the USEMS group as a standard (the best result) and 20% in the PCSEMS group, and we set the non-inferiority margin of the PCSEMS to the USEMS as 10% (35%: the worst result). To investigate the non-inferiority with a power of 0.8 and an alpha error of 0.025 (one sided) using the HR of the USEMS of 0.048 and the HR of 1.93 as the null hypothesis in the log-rank test, complete data would be required for at least 45 patients per group. Based on the dropout rates of the above two reports (14%<sup>12</sup> and 5%<sup>15</sup>), the dropout rate will be assumed to be 5%–14%. In addition, more recent chemotherapy regimens that many institutions can adopt such as gemcitabine with nab-paclitaxel and irradiation with S-1 could improve

**Table 1** Observation and follow-up schedule

Timing of evaluation	Before registry	Stenting day	Stenting day +1	Preoperative day	B/A operation
Day	-14~-1	0	1	2~179	180±30
Consent	✓	-	-	-	-
Background	✓	-	-	-	-
Imaging test	✓	-	-	*	✓
Pathological evidence	✓	-	-	-	-
Symptom	✓	✓	✓	✓	✓
Laboratory data	✓	✓	✓	†	✓
Adverse event	-	✓	✓	✓	✓

\*As needed.

†About every 2 weeks.

B/A, before and after.



the preoperative prognosis. Therefore, assuming a 10% dropout rate of enrolled patients, our recruitment goal is a total of 100 patients. In addition, we set the maximum number of included patients per hospital to 25 to reduce institutional bias.

### Statistical analysis

We will calculate the 95% CIs of the incidence of preoperative biliary events in each group and analyse whether the difference between them is within the non-inferiority margin (10%) using the Wald method. The categorical and continuous data will be expressed as proportions and means $\pm$ SD, respectively. Categorical data will be examined using the  $\chi^2$  test or Fisher's exact test. The Mann-Whitney *U* test will be used to compare quantitative data. Kaplan-Meier analysis with the log-rank test will be used to analyse the rate of preoperative biliary events and time to RBO. The results will be considered significant at values of  $p < 0.05$ .

### Data management and monitoring

All sampled data will be linked and anonymised and stored in a password-protected server as described above (NorthNet), which is accessible only by the permitted physicians according to internal information governance rules. The data will be analysed after completion of the study, and no interim analysis is planned. Monitoring will be performed by an independent monitor for every participating institution, and the results including unintended effects of the trial interventions or trial conduct will be reported to the research representative and the director of Hokkaido University Hospital. Severe adverse events will be immediately reported to the research representative and the director of Hokkaido University Hospital.

### Study timeline

This study started in September 2020, and enrolment will be completed by March 2024. A 6-month follow-up period is required after enrolment, and an additional 6-month period for data collection, confirmation and analysis is also necessary. Therefore, the final completion date of this study will be 31 March 2025 at the latest.

### Ethics and dissemination

This study was approved by the Institutional Review Board of Hokkaido University Hospital (approval number: 018-0017; approval date: 17 March 2020) and the director of each participating institution (Hokkaido University Hospital, Yokohama City University Medical Center, Mie University, Kagawa University, Shizuoka Cancer Center, Sapporo City General Hospital, Gifu University, Sapporo Medical University, Kagoshima University, Wakayama Medical University, Asahikawa Medical University, IMS Sapporo Digestive Disease Center General Hospital and Teine Keijinkai Hospital). This study was reviewed and approved by the Hokkaido University Certified Review Board (CRB1180001). If there is a need to modify the protocol during the study period, we will immediately

notify the Hokkaido University Certified Review Board and each institutional review board for approval and publish the results on the UMIN and jRCT websites. The results will be submitted for presentation at an international medical conference and are expected to be published in a peer-reviewed journal.

### Patient and public involvement

All authors involved in treatment/assessment have years of clinical experience in treating pancreatic cancer, including biliary drainage, chemotherapy/chemoradiotherapy and related adverse events. The leading pancreaticobiliary physicians and endoscopists (MK, KK, KS, HI, TI, MI, YM and AK) contributed to the development of the research questions based on their current knowledge of treatments and interventions for pancreatic cancer.

Patients will be questioned and assessed about their body conditions including appetite, body weight and body temperature and complaints throughout each observational period of the study. This will allow us to develop an appropriate preoperative biliary drainage method using a SEMS. This study will include 100 patients who are scheduled to undergo preoperative chemotherapy/chemoradiotherapy with pancreatectomy for primary pancreatic cancer. The aforementioned items and intervention burden will be assessed by the participating pancreaticobiliary physicians and endoscopists, but not by the patients themselves. The study results will be disseminated to the study participants through patient symposia and associations without lucrative purposes or organisations for patients with pancreatic cancer.

### DISCUSSION

Secure biliary drainage is essential during NAC/NACRT for patients with pancreatic cancer and obstructive jaundice. According to previous reports regarding transpapillary biliary decompression, a SEMS is the most reliable tool for its accomplishment.

We assumed that the stent patency of a PCSEMS was similar to that of a USEMS and an FCSEMS. To simply and clearly investigate this compared with the standard USEMS, we will perform a non-inferiority study. If evidence of the non-inferiority of a PCSEMS to a USEMS during NAC/NACRT is provided, both endoscopists and patients will benefit from a wide range of choice of a USEMS, an FCSEMS and a PCSEMS based on the individual situation such as biliary stricture severity and surgeon preference.

Regarding the effect of preoperative SEMS placement on the surgical procedure, several previous studies indicated that biliary SEMS does not adversely affect pancreatectomy, namely, pancreaticoduodenectomy from the perspective of postoperative complications, 30-day mortality, length of stay and biliary anastomotic leak, although there were minor negative effects such as longer operative times.<sup>24-26</sup> However, it is unclear whether there were differences between a USEMS and a PCSEMS,

especially after NAC/NACRT. Thus, through this study, we will obtain new information about the differences between the effects of a USEMS and a PCSEMS on perioperative and postoperative characteristics.

Meanwhile, in the current situation in which no standard NAC/NACRT has been established, a limitation of this study is that we could not determine a NAC/NACRT protocol.

In conclusion, this study will provide a new scientific insight into the choice of a SEMS during NAC/NACRT.

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**Contributors** Contributors MK and KK designed the study, and MK drafted the protocol. KS, HInoue, HK, Hlshiwatari, SK, TI, MY, SH, MI, YM, YN and AK edited the protocol. KK conducted the statistical design. NS supervised and edited the protocol.

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**Competing interests** None declared.

**Patient and public involvement** Patients and/or the public were involved in the design, conduct, reporting or dissemination plans of this research. Refer to the Methods section for further details.

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