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Endoscopic sphincterotomy to prevent post-ERCP pancreatitis after self-expandable metal stent placement for distal malignant biliary obstruction (SPHINX): a multicentre, randomised controlled trial

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COMPETING INTERESTS

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ABSTRACT

BACKGROUND

Endoscopic retrograde cholangiopancreatography (ERCP) with fully covered self-expandable metal stent (FCSEMS) placement is the preferred approach for biliary drainage in patients with suspected distal malignant biliary obstruction (MBO). However, FCSEMS placement is associated with a high risk of post-ERCP pancreatitis (PEP). Endoscopic sphincterotomy prior to FCSEMS placement may reduce PEP risk.

OBJECTIVE

To compare endoscopic sphincterotomy to no sphincterotomy prior to FCSEMS placement.

DESIGN

This multicentre, randomised, superiority trial was conducted in 17 hospitals and included patients with suspected distal MBO. Patients were randomised during ERCP to receive either endoscopic sphincterotomy (sphincterotomy group) or no sphincterotomy (control group) prior to FCSEMS placement. The primary outcome was PEP within 30 days. Secondary outcomes included procedure-related complications and 30-day mortality. An interim analysis was performed after 50% of patients (*n*=259) had completed follow-up.

RESULTS

Between May 2016 and June 2023, 297 patients were included in the intention-to-treat analysis, with 156 in the sphincterotomy group and 141 in the control group. Following the interim analysis, the study was terminated prematurely due to futility. PEP did not differ between groups, occurring in 26 patients (17%) in the sphincterotomy group compared with 30 patients (21%) in the control group (RR 0.78, 95% CI 0.49-1.26, p=0.37). There were no significant differences in bleeding, perforation, cholangitis, cholecystitis or 30-day mortality.

CONCLUSION

This trial found that endoscopic sphincterotomy was not superior to no sphincterotomy in reducing PEP in patients with distal MBO. Therefore, there was insufficient evidence to recommend routine endoscopic sphincterotomy prior to FCEMS placement.

SUMMARY BOX

WHAT IS ALREADY KNOWN ON THIS TOPIC

- Post-ERCP pancreatitis (PEP) is the most common complication after endoscopic retrograde cholangiopancreatography (ERCP) with fully covered self-expandable metal stent (FCSEMS) placement in patients with distal malignant biliary obstruction (MBO). Endoscopic sphincterotomy is routinely performed by endoscopists to facilitate stent placement and reduce the risk of PEP by dilating reducing pancreatic sphincter compression. To date, one randomised trial has evaluated the effect of endoscopic sphinterotomy before FCSEMS placement in 74 patients with distal MBO; however, no episodes of PEP occurred in both the sphincterotomy group and the control group either arm of this study.

WHAT THIS STUDY ADDS

- This multicentre randomised, controlled trial comprised the largest population of patients with distal MBO undergoing biliary drainage by ERCP with FCSEMS placement. Endoscopic sphincterotomy prior to FCSEMS placement did not reduce post-ERCP pancreatitis in patients with suspected distal MBO. Other procedure-related complications, such as gastrointestinal bleeding, perforation, cholangitis, and cholecystitis, were comparable between patients who underwent endoscopic sphincterotomy and those who did not.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

- Patients with distal MBO undergoing ERCP with FCSEMS placement had a high risk of post-ERCP pancreatitis of up to 21%. This study found that endoscopic sphinterotomy was not superior to no sphincterotomy in preventing pancreatitis in this group of patients. Future research should explore alternative strategies to reduce this complication.

INTRODUCTION

Endoscopic retrograde cholangiopancreatography (ERCP) with fully covered self-expandable metal stent (FCSEMS) placement has become the preferred approach for biliary drainage in patients with suspected distal malignant biliary obstruction (MBO).[1] However, FCSEMS have been associated with a high incidence of post-ERCP pancreatitis (PEP) of up to 27%.[2-5] This is considered to be the result of pancreatic outflow obstruction caused by the expansive forces of the FCSEMS on the orifice of the pancreatic duct.[3]

Reducing the risk of PEP among patients with MBO holds significant importance in order to prevent potential treatment delay and, subsequently, unfavourable oncological outcomes.[6] Several interventions, including rectal non-steroidal anti-inflammatory drugs (NSAIDs) administration and pancreatic duct (PD) stent placement in case of inadvertent PD cannulation, have become standard clinical practice to reduce the incidence of PEP.[7] Endoscopic sphincterotomy prior to FCSEMS placement has the potential to further reduce the risk of PEP by dilating the orifice of the major duodenal papilla, thereby alleviating pressure on the pancreatic sphincter.[3, 8] Therefore, in addition to its role in facilitating repeated biliary cannulation and stent placement, endoscopic sphincterotomy is routinely performed by many endoscopists.[9-11]

Despite the presumed benefits, endoscopic sphincterotomy carries risks such as bleeding and perforation.[12-14] Although FCSEMS placement may help mitigate these complications[15], current guidelines refrain from making a definitive recommendation to perform endoscopic sphincterotomy before FCSEMS placement as it is uncertain whether the benefits of sphincterotomy outweigh the risks.[1, 7] A previous randomised controlled trial compared endoscopic sphincterotomy before FCSEMS placement with no sphincterotomy in 74 patients with distal MBO. Notably, neither group experienced PEP.[16] This observation contrasts with real-world data from a previous meta-analysis, which showed that pancreatitis was the most common complication following ERCP, with a pooled incidence of 10% across various indications.[17] While observational and retrospective studies did not demonstrate a benefit of endoscopic sphincterotomy in reducing PEP following FCSEMS placement, high-quality prospective data from large trials are scarce.[18-20] Therefore, this study aimed to assess whether endoscopic sphincterotomy prior to FCSEMS placement reduces PEP in patients with suspected distal MBO.

METHODS

Study design and participants

The SPHINX trial is a multicentre randomised controlled, superiority trial comparing endoscopic sphincterotomy prior to biliary FCSEMS placement to no sphincterotomy in patients with suspected MBO. This trial was conducted in 16 Dutch hospitals and 1 Spanish hospital (5 academic and 12 teaching hospitals). Individuals aged 18 years or older with suspected distal MBO and an indication for biliary drainage by ERCP with FCSEMS placement were eligible to participate. Indications for biliary drainage were in accordance with the ESGE guideline and were discussed at a multidisciplinary team

meeting with input from surgeons, gastroenterologists, and oncologists.[1] Patients with suspected distal MBO requiring replacement of a previously placed plastic stent with a FCSEMS were also eligible for the study. Exclusion criteria were benign biliary stenosis, hilar biliary obstruction (i.e., stenosis located within 2 cm of the liver hilum), previous sphincterotomy, prior PD stent placement, haemostasis disorders, and inability to discontinue anticoagulants. All eligible patients were counselled about the risks and benefits of both treatments (endoscopic sphincterotomy vs. no sphincterotomy) by their treating physician and written informed consent was obtained prior to the ERCP procedure. All local study investigators and their study teams were trained on the latest version of the study protocol. The study was monitored at the initiating study site by an independent monitoring board. There was no patient or public involvement in the patient accrual, conduct or reporting of this trial. However, a representative from the patient association holds positions on both the board and scientific committee of the Dutch Pancreatic Cancer Group, who both approved the study design before the start of this study. The study was conducted according to the principles of the Declaration of Helsinki and Good Clinical Practice guidelines and was approved by the Medical Ethics Committee (MEC) of the Amsterdam UMC (location Academic Medical Centre) and by the institutional review boards of each participating centre. The trial protocol was registered in the Dutch National Trial Register (study ID: NL5130).[21]

Randomisation

Patients were randomised in a 1:1 ratio to receive endoscopic sphincterotomy (sphincterotomy group) or no sphincterotomy (control group) during ERCP after successful biliary cannulation was obtained. Centre-stratified permuted block randomisation was used to balance treatment allocation within each centre. The variable sequences of the randomisation blocks were computer-generated by Castor EDC before the start of the trial.[22]

Patients were considered screen failures if they were ineligible for randomisation during ERCP for one of the following reasons: i) unsuccessful biliary cannulation, ii) need for pre-cut or standard ES prior to randomisation, iii) need for prophylactic duct stent placement prior to randomisation, iv) other reason preventing successful biliary cannulation. Patients were enrolled, randomised and followed up by the local study investigators or by the lead study coordinators (EvH, NvH, MG, AO). Patients remained blinded to treatment allocation. The study team, including treating endoscopists, local investigators,

and lead coordinators, were aware of group assignments due to their involvement in the randomisation process.

Procedures

All ERCP procedures were performed by or under direct supervision of a dedicated interventional endoscopist. Patients were randomised during ERCP after successful biliary cannulation was achieved without the need for pre-cut sphincterotomy or prophylactic PD stent placement. In the intervention group, endoscopic sphincterotomy was performed using mixed current according to the ESGE guideline.[23] In both groups, a FCSEMS (Cook Evolution® Biliary Stent - Fully Covered; Cook Ireland Ltd, Limerick, Ireland) with a standardised body diameter of 10 mm and length of 6 cm was used. Alternative stent lengths of 4 cm and 8 cm were allowed if the 6 cm stent length was not suitable (*Supplementary Figure 1*). Rectal NSAIDs were routinely administered before ERCP.[1] Patients were discharged from the hospital at the discretion of the endoscopist on the same day or the day after ERCP according to local clinical practice. Patients were prospectively followed up 7 days and 30 days after ERCP using clinical data from medical records or, if not all relevant data were available, by telephone consultation with the local study investigator or lead study coordinators.

Outcomes

The primary outcome was PEP, defined as acute pancreatitis within 30 days of ERCP according to the modified Cotton criteria: (1) onset of new or worsened abdominal pain requiring new or prolonged hospital admission and (2) an elevation of pancreatic enzyms (amylase and/or lipase) of ≥ 3 times upper limit of normal at more than 24 hours after the procedure.[24, 25] Secondary outcomes included severity of pancreatitis defined according to both the Cotton criteria and Revised Atlanta Classification, technically successful stent placement, ERCP-related morbidity, stent-related morbidity, and 30-day mortality.[24, 26] ERCP-related morbidity included procedure-related gastrointestinal bleeding and perforation, and stent-related morbidity was defined by cholangitis, cholecystitis, stent obstruction, and stent migration. Definitions of associated complications are provided in *Supplementary Box 1*. All adverse events within 30 days, whether or not considered related to the study procedure, were verified by the lead study coordinators (MvG, AO) under the supervision of the principal investigator (JvH). All serious adverse events (SAEs) were reported to the DSMB and MEC for assessment of their potential

relationship to the trial and any implications for patient safety. Furthermore, all SAEs were adjudicated by an independent gastroenterologist (KB) who was unaware of the treatment allocation to ascertain whether SAEs met the predefined outcome criteria for PEP, bleeding, perforation, cholangitis and cholecystitis.

Statistical analysis

This study was designed as a superiority trial, aiming to demonstrate a reduction in the primary outcome in favour of the approach using endoscopic sphincterotomy. The sample size was based on a Dutch multicentre prospective cohort study on the incidence of PEP after FCSEMS placement and a randomised trial investigating the effect of endoscopic sphincterotomy after uncovered SEMS placement for proximal biliary obstruction.[3, 27] The Dutch cohort study reported a PEP rate of 18% and was expected to reflect the patient population in the current study.[3] The randomised trial showed a 69% relative risk reduction in PEP after endoscopic sphincterotomy.[27] A conservative approach was adopted to calculate the sample size, assuming a 16% risk of PEP in the control group with a reduction to 8% after endoscopic sphincterotomy. To detect this 50% risk reduction with a power of 80% at a two-sided α level of 0.05, a sample size of 518 patients (259 patients per group) was needed. The primary analysis included all randomised patients following the intention-to-treat principle. A per-protocol analysis was performed excluding those who did not receive their allocated treatment or had a substantial protocol deviation.

An interim analysis was planned after 50% of patients (*n*=259) had been enrolled and had completed follow-up. An independent Data Safety Monitoring Board (DSMB) assessed whether SAEs were related to the study intervention. Patient recruitment was continued during the DSMB review process if no safety concerns had been identified during the course of the trial. An independent statistician performed the statistical analysis of the interim results. Pre-specified criteria for early termination were (1) the Haybittle-Peto boundary for efficacy and (2) a futility threshold of 10% conditional power; a value below this would indicate that the trial is statistically unlikely to meet the alternative hypothesis of a 50% risk reduction in PEP.[28, 29] Progress of the trial was subject to annual review by the MEC. Both the DSMB and MEC could recommend early termination of the study.

Categorical data are presented as counts and proportions, and continuous data as mean ± standard deviation (SD) or medians with corresponding interquartile ranges (P25-P75), depending on distribution. Categorical data were analysed using Fisher's exact test and continuous data were analysed using Student's t-test or Mann-Whitney *U* test, as appropriate. Primary and secondary outcomes were presented as relative risks (RR) provided with 95% confidence intervals (CI). There were no missing data for the primary and secondary outcomes. Missing data for baseline variables were identified and reported. Post-hoc subgroup analyses were performed to assess whether the effect of endoscopic sphincterotomy differed across subgroups including sex, age, ECOG performance status, PD dilatation, biliary cannulation difficulty, incidental PD cannulation, incidental PD contrast injection, and same-session EUS-guided tissue acquisition. PD dilatation was defined as a diameter of ≥ 5 mm on cross-sectional imaging.[30] Biliary cannulation difficulty was scored by the treating endoscopist on a standardised 3-point Likert scale ranging from easy to difficult. Procedures meeting the established ESGE criteria for difficult cannulation (i.e., > 5 minutes of cannulation time, > 5 cannulation attempts, or inadvertent PD cannulation) were classified as difficult, irrespective of the endoscopist's rating.[23] Age was dichotomised at 70 years, reflecting the median age of our study population. Logistic regression models were used to calculate odds ratios (ORs) and 95% CIs for the association between endoscopic sphincterotomy and PEP within each subgroup. Additionally, potential interaction effects of endoscopic sphincterotomy across subgroups were assessed to evaluate effect modification. Missing data were assumed to be missing at random. Despite the limited extent of missing data (less than 5%), best- and worst-case imputation sensitivity analyses for the sphincterotomy group were conducted to assess its potential impact, as outlined in the *Supplementary Material.* [31, 32] Since both imputation methods indicated a minimal impact of missing data on our results, post-hoc subgroup analyses were conducted using complete case analysis.[33] Statistical analyses with a two-sided p-value <0.05 were considered statistically significant. Data were analysed with the use of SPSS version 29 (IBM Corp., Armonk, New York, USA).

RESULTS

Between 16 May, 2016 and 1 June, 2023, 505 patients were screened for eligibility, of whom 298 were randomised (*Figure 1*). During ERCP, 177 of patients were deemed ineligible for randomisation primarily due to failed biliary cannulation (*n*=30), need for pre-cut sphincterotomy (*n*=94), or need for

prophylactic PD stent placement (*n*=30). One patient was excluded after randomisation due to patient withdrawal. The remaining 297 patients were randomised to the sphincterotomy group (*n*=156) and control group (*n*=141) and included in the intention-to-treat analysis (*Supplementary Table 1)*.

Premature termination

At the interim analysis on 21 October 2022, the DSMB raised no safety concerns in the first 259 patients (50% of the originally planned 518 patients). However, the interim results showed futility, as 23 of 134 patients (17%) in the sphincterotomy group developed PEP compared with 26 of 125 patients (21%) in the control group (RR 0.83, 95% CI 0.50 – 1.37, p=0.46). Consequently, the predictive probability of demonstrating superiority of endoscopic sphincterotomy in the final analysis was 2.5%. In addition, the trial experienced considerable delays in patient enrolment, with only half of the intended patients being randomised after six years, exceeding the originally planned three-year study duration. These findings led the MEC to recommend early termination of the study. Accordingly, the study was stopped on 1 June 2023.

Patient and procedure characteristics

Patients had a median age of 69 (P25-P75, 61-76) years and 160 (54%) were male. Baseline and ERCP procedure-related characteristics were well balanced between the groups (*Table 1*). Pancreatic cancer was the most common aetiology of distal MBO (219 patients [74%]). Of all performed ERCP procedures, 95 (33%) were classified as difficult by the endoscopist. Incidental cannulation and contrast injection of the PD occurred in 89 patients (31%) and 44 patients (15%), respectively.

After randomisation, protocol deviations occurred in 10 patients (6%) in the sphincterotomy group and in 9 patients (6%) in the control group. Two patients did not meet eligibility criteria due to absence of distal MBO, of whom one in the sphincterotomy group due to malignant hilar stenosis and one in the control group with benign aetiology of bile duct stones. In addition, 4 patients in the sphincterotomy group were randomised inadvertently (i.e. prior to successful cannulation) and did not receive endoscopic sphincterotomy owing to inability to reach the papilla (*n*=1), unsuccessful biliary cannulation (*n*=2), and sphincterotomy not deemed feasible (*n*=1). Other protocol deviations included pre-cut sphincterotomy (*n*=1), failed biliary stent placement (*n*=1) and uncovered SEMS placement (*n*=3). In the control group, 6 patients did not receive their assigned treatment due to unsuccessful

biliary cannulation (*n*=2) and the need for pre-cut sphincterotomy (*n*=4). Reasons to perform endoscopic sphincterotomy in the control group after randomisation included difficulties encountered during biliary brush insertion (*n*=2), facilitation of FCSEMS placement (*n*=1) and removal of a suspected obstructing biliary stone (*n*=1). The other deviations in the control group were due to prophylactic placement of a PD stent (*n*=2).

Table 1. Baseline characteristics

	Sphincterotomy group *(N*=156)	**Control group *(N*=141)**
Sex		
Male	86 (55%)	74 (53%)
Female	70 (45%)	67 (48%)
Age, median (P25-P75)	70 (61-77)	69 (61-75)
ECOG performance status [a]		
ECOG 0 - 1	123 (79%)	112 (81%)
ECOG 2 - 3	32 (21%)	27 (19%)
ASA score		
ASA I	16 (10%)	20 (14%)
ASA II	105 (67%)	96 (68%)
ASA III	35 (22%)	25 (18%)
Serum bilirubin (mean in µmol/L, SD)	221 (127)	218 (136)
Indication for ERCP [b]		
Cholestasis	105 (69%)	84 (61%)
Symptomatic jaundice	109 (72%)	104 (75%)
Cholangitis	2 (1%)	3 (2%)
Neoadjuvant therapy	17 (11%)	17 (12%)
Other	7 (5%)	3 (2%)
Aetiology		
Pancreatic cancer	111 (71%)	108 (77%)
Cholangiocarcinoma	23 (15%)	17 (12%)
Metastatic disease	10 (6%)	8 (6%)
pNET	7 (4%)	4 (3%)
Ampullary carcinoma	3 (2%)	1 (0%)
Gallbladder carcinoma	1 (1%)	-
Lymphoma	0	2 (1%)

Benign aetiology	-	1 (0%)
Dilated PD of ≥ 5 mm	95 (63%)	85 (63%)
Preoperative resectability [c]	74 (48%)	50 (36%)
Previous biliary drainage	18 (12%)	18 (13%)
History of pancreatitis	3 (2%)	5 (4%)
ERCP characteristics		
Prophylactic rectal NSAID administration [d]	151 (97%)	133 (94%)
Attempts of biliary cannulation, median (P25-P75)	3 (1-5)	2 (1-5)
Difficulty biliary cannulation [e]		
Easy cannulation	71 (47%)	58 (43%)
Neither easy nor difficult cannulation	34 (22%)	31 (23%)
Difficult cannulation	47 (31%)	46 (34%)
Incidental PD cannulation [f]	50 (33%)	39 (28%)
Number of PD guidewire passages (P25-P75)	0 (0-1)	0 (0-1)
Incidental PD contrast injections [g]	25 (16%)	19 (14%)
Same-session EUS-TA	43 (28%)	40 (28%)

Values are presented as n (%) unless listed otherwise. Percentages might not sum to 100% because of rounding.

P25-P75, quartiles represented by 25th and 75th percentile; ECOG, Eastern Cooperative Oncology Group; ASA, American Society of Anaesthesiologists; ERCP, endoscopic retrograde cholangiopancreatography; pNET, Pancreatic neuroendocrine tumour; PD, pancreatic duct; NSAID; non steroid anti-inflammatory drug; EUS, endoscopic ultrasound; TA, tissue acquisition; U/L, units per litre; µmol/L, micromole per litre.

[a]ECOG status was missing in 3 patients (1 in ES group and 2 in control group).

[b]Patients could have multiple indications for biliary drainage.

[c]Resectability status missing in 3 patients (2 in ES group and 1 in control group).

[d]Standard PEP prophylaxis regimen consisting of pre-procedure rectal NSAID (100 mg diclofenac).

[e]Cannulation difficulty as judged by the endoscopist, ≥ 5 biliary cannulation attempts or ≥ 5 minutes required for cannulation; missing in 10 patients (4 in ES group and 6 in control group).

[f]Incidental PD cannulation and contrast injections missing in 6 patients (3 patients in both groups).

Outcomes

Of all randomised patients, 26 of 156 patients (17%) in the sphincterotomy group and 30 of 141 patients (21%) in the control group developed PEP (RR 0.78, 95% CI 0.49 – 1.26, p=0.37; *Table 2*). Results were similar in the per-protocol population (*Supplementary Table 2*).

Moderate or severe pancreatitis based on the Cotton criteria occurred in 17 of 26 patients (65%) in the sphincterotomy group compared with 13 of 30 patients (43%) in the control group (RR 1.51, 95% CI 0.92 – 2.48).[24] Moderate or severe episodes of pancreatitis according to the revised Atlanta classification occurred in 3 of 26 patients (12%) in the sphincterotomy group compared with 6 of 30

patients (20%) in the control group (RR 0.66, 95% CI 0.22 – 2.00).[26] In total, 2 of 56 patients (4%) with PEP died of severe acute pancreatitis: 1 patient in the sphincterotomy group due to infected pancreatitis and pneumonia and 1 patient in the control group due to multi-organ failure associated with systemic inflammatory response syndrome (SIRS) (*Supplementary Table 3*).

There was no difference in the incidence of GI bleeding and perforation between the sphincterotomy group and control group (both complications occurred in 0 patients (0%) vs. 1 patient (1%), respectively, p=0.48). The one patient in the control group had a small type III perforation according to the Stapfer classification following a complex ERCP procedure with 8 cannulation attempts, including 2 inadvertent PD cannulations.[14] The clinical course was mild with rapid recovery under treatment with intravenous antibiotics. A second patient in the control group with GI bleeding presented with melena within 12 hours of an apparently uneventful ERCP procedure, requiring transfusion and a prolonged hospital stay of 2 days. Cholangitis occurred in 4 patients (3%) in the sphincterotomy group compared with 3 patients (2%) in the control group (RR 1.21, 95% CI 0.27 – 5.29), and cholecystitis in 8 patients (5%) and in 9 patients (6%), respectively (RR 0.80, 95% CI 0.32 – 2.03). No differences were observed in stent-related morbidity, including stent migration and stent re-obstruction. Other procedure-related complications were described in *Supplementary Table 4* and did not differ between groups (*Table 2*).

In total, 10 patients (6%) in the sphincterotomy group died compared with 5 patients (4%) in the control group during the 30-day follow-up (RR 1.81, 95% CI 0.63 – 5.16). Causes of death are described in the Appendix (*Supplementary Table 3*). Post-hoc subgroup analyses for sex, age, ECOG performance status, PD dilatation, biliary cannulation difficulty, incidental PD cannulation, incidental PD contrast injection, and same-session EUS-guided tissue acquisition showed no significant interactions with the effect of endoscopic sphincterotomy (*Figure 2 and Supplementary Table 5*).

Table 2. Primary and secondary outcomes

	Sphincterotomy group (*N*=156)	**Control group (*N*=141)**	**RR (95% CI)**	**P-value**
Primary outcome				
PEP	26 (17%)	30 (21%)	0.78 (0.49 – 1.26)	0.37
Secondary outcomes				
Pancreatitis severity according to Cotton criteria				0.12
Mild	9/26 (35%)	17/30 (57%)	0.61 (0.33 – 1.13)	
Moderate or severe	17/26 (65%)	13/30 (43%)	1.51 (0.92 – 2.48)	
Pancreatitis severity according to revised Atlanta criteria				0.48
Mild	23/26 (89%)	24/30 (80%)	1.11 (0.88 – 1.39)	
Moderate or severe	3/26 (12%)	6/30 (20%)	0.58 (0.16 – 2.10)	
Technical success of stent placement	154 (99%)	138 (98%)	1.02 (0.99 – 1.04)	0.67
ERCP-related morbidity				
Bleeding	0 (0%)	1 (1%)	-	0.48
Perforation	0 (0%)	1 (1%)	-	0.48
Cholangitis	4 (3%)	3 (2%)	1.21 (0.27 – 5.29)	1.00
Cholecystitis	8 (5%)	9 (6%)	0.80 (0.32 – 2.03)	0.80
Other procedure-related complications	3 (2%)	2 (1%)	1.36 (0.23 – 8.00)	1.00
Stent-related morbidity				
Stent migration	4 (3%)	5 (4%)	0.72 (0.20 – 2.64)	0.74
Stent re-obstruction	0 (0%)	2 (1%)	-	0.23
30-day mortality	10 (6%)	5 (4%)	1.81 (0.63 – 5.16)	0.30

Values are presented as n (%). Percentages might not sum to 100% because of rounding.

RR, risk ratio; PEP, post-ERCP pancreatitis; ERCP, endoscopic retrograde cholangiopancreatography.

DISCUSSION

This multicentre, randomised, superiority trial showed that endoscopic sphincterotomy prior to biliary FCSEMS placement was not superior to no sphincterotomy in reducing PEP in patients with suspected distal MBO. There were no differences found between both groups in rates of other procedure-related complications, including bleeding, perforation, cholangitis or cholecystitis. The trial was terminated prematurely due to futility and extended study duration.

At the interim analysis, the incidence of PEP was comparable between the groups. The low predicted probability (2.5%) of a significant effect in favour of endoscopic sphincterotomy for the final analysis was well below the prespecified futility threshold of 10%. Although terminated early, this study involving 297 patients with distal MBO was the largest randomised trial to date comparing endoscopic sphincterotomy with no sphincterotomy prior to FCSEMS placement.

The current study differs from a previous randomised trial conducted by Artifon et al., which compared endoscopic sphincterotomy with no sphincterotomy prior to FCSEMS placement in 74 patients with unresectable distal MBO.[16] There were no cases of post-ERCP pancreatitis in this previous study, contrasting with the current literature and daily practice where post-ERCP pancreatitis is the most common complication following ERCP.[17] However, a significantly higher overall complication rate was reported after endoscopic sphincterotomy (49% in the sphincterotomy group vs. 11% in the control group, $P<0.01$). Specifically, the rates of ERCP-related complications, including bleeding (14%), perforation (11%) and stent migration (16%), were higher compared to our study, where none of the patients in the sphincterotomy group developed bleeding or perforation, and the rate of stent migration was only 4%. Our study used the mixed current technique for endoscopic sphincterotomy, as recommended by the ESGE guideline, whereas Artifon et al. used a pure cut technique, which has been associated with an increased risk of bleeding.[23, 34] In addition, the small sample size (n=37 per group) limits the interpretation and generalisability of their results.[16, 23]

Our findings of no benefit of endoscopic sphincterotomy prior to SEMS placement are in line with previous Japanese studies.[10, 18-20, 35] A randomised trial by Hayashi et al. found that no sphincterotomy was non-inferior to endoscopic sphincterotomy in preventing PEP following partially covered SEMS placement, with PEP rates of 8% vs. 9%, respectively.[35] However, the current study observed an overall high rate of PEP (19%), which may be explained by several patient and procedural factors. First, the current study included a broad patient population with suspected MBO,

encompassing both resectable and unresectable disease, undergoing ERCP with FCSEMS placement. FCSEMS are the preferred stent type in the absence of a definitive histopathological diagnosis, but their complete coverage of the pancreatic duct orifice may have conferred an increased risk of PEP compared to the partially covered SEMS used by Hayashi et al.[35, 36] In addition, the prevalence of difficult cannulation (31%) and inadvertent PD cannulation (30%) in our study was high. These established risk factors for PEP, along with the high proportion of included patients (88%) with a naïve papilla, may have led to the elevated risk of PEP observed in our study.[7] In contrast, while Hayashi et al. did not report on cannulation difficulty, fewer patients had a naive papilla (69%) due to previous drainage, and accidental PD cannulation occurred in only 17% of patients. Furthermore, a key difference limiting direct comparison relates to the use of post-ERCP prophylaxis, as our study adhered to current guidelines by routinely administering prepocedural rectal NSAIDs, whereas the study by Hayashi et al. did not follow this practice.[7, 37]

A similarly high rate of PEP (18%) was reported in a previous Dutch prospective cohort study following FCSEMS placement in patients with resectable periampullary or pancreatic cancer.(3) In both our study and the previous study, meticulous patient follow-up was prioritised to capture all adverse events. Patients were instructed to contact the hospital if they experienced new or worsening abdominal pain of any severity or other signs of clinical deterioration. This high level of vigilance may have contributed to a high detection rate of PEP, including cases with mild symptoms that patients may not otherwise have presented with.

Other potential factors that may have influenced the observed PEP incidence were hospital volume and the complexity of the caseload. Our study observed a wide variation in annual ERCP volume between participating centres. Academic hospitals performed a higher number of procedures (300-1000 per year) compared to teaching hospitals (80-500 per year). While there is no defined minimum threshold for hospital and endoscopist volume, several studies suggest a minimum of 200 annual procedures per hospital and 50 per endoscopist to ensure high-quality ERCP procedures. [38-41]

Furthermore, our patient population represented a difficult caseload as reflected by the high rate of screen failures (*n*=177, 37%) due to failed biliary cannulation, the need for pre-cut sphincterotomy, or PD stent placement. Moreover, nearly one-third of the included patients had a difficult biliary cannulation. These findings are in line with previous research that reported a high incidence of difficult biliary cannulation and cannulation failure in patients with distal MBO.[42] Even in expert hands, biliary

drainage by ERCP remains a challenging procedure, often requiring advanced cannulation techniques and carrying a high risk of adverse events.[43]

Subgroup analyses showed no significant treatment effect of endoscopic sphincterotomy on PEP rates across all subgroups. These findings warrant further exploration of alternative endoscopic techniques to reduce drainage-related complications. Endoscopic ultrasound-guided choledochoduodenostomy (EUS-CDS) may be a promising option and is currently recommended by ESGE in cases where ERCP was unsuccessful.[44] EUS-CDS bypasses both the papilla and the pancreas, thereby minimising the risk of pancreatitis. Future studies should investigate the feasibility and efficacy of EUS-CDS as a primary drainage strategy.

This study has several limitations. First, the study was terminated prematurely after enrolling 297 patients, falling short of the planned sample size of 518 patients. As a result, the study had reduced power to statistically detect the hypothesised 50% reduction in PEP. However, at the interim analysis, the predictive probability of achieving this effect size even if the trial were to continue was low (2.5%), warranting termination for futility. Second, the trial encountered significant delays in patient enrolment, extending the trial beyond the planned 3 years to 6 years with only half the target sample size. This delay was largely due to the substantial proportion of screen failures (37%), the initiation of nationwide competing trials, and logistical constraints. Patients were considered screen failures (e.g. due to failed biliary cannulation or the need for pre-cut sphincterotomy or prophylactic PD stenting) if they could not be randomised during the ERCP procedure. The exclusion of these specific patient group may have limited the generalisability of our results to a broader patient population. An alternative study design would be to randomise patients prior to ERCP, allowing an intention-to-treat analysis to capture all patient outcomes regardless of whether advanced or alternative drainage techniques were used. Additionally, a sensitivity analysis within a per-protocol population could evaluate the specific impact of ES in patients with successful biliary cannulation. Third, the study team including the treating endoscopist, local coordinating investigator, and lead study coordinators, were not blinded to treatment allocation. Endoscopists could not be blinded given their role in performing the ERCP procedure with or without ES. Local study investigators and lead study coordinators managed the randomisation process and conducted patient follow-up. The lead study coordinators verified all

adverse events. The potential risk of detection bias was minimised through blinded adjudication of all SAEs by an independent gastroenterologist. Additionally, predefined and objective criteria for primary and secondary outcomes further reduced potential bias.

Strengths of this study include its multicentre randomised controlled design with the largest sample size to date on this subject. Furthermore, the results can be applied to other hospital settings as patients from both teaching and academic hospitals were included.

In conclusion, this study did not show the hypothesised benefit of endoscopic sphincterotomy before FCSEMS placement in reducing PEP in patients with suspected distal MBO. Conversely, there were no apparent harms from the use of endoscopic sphincterotomy, as no increased risk for other procedure-related complications was observed. However, in the absence of a clear benefit, our findings recommend against endoscopic sphincterotomy prior to FCSEMS placement in the setting of suspected distal MBO.

Contributors

JvH, NB and EvH designed the study. EvH, NvH, MG, and AO coordinated the study and JvH supervised the study. AO, MG, and JEvH had access to the data and AO and MG verified the data. AO and MG analysed and interpreted the data. AO performed the formal statistical analysis. AO and MG wrote the initial draft of the manuscript. All authors critically assessed the study design, included patients in the study, edited the manuscript, and read and approved the final version of the manuscript for submission. JvH is the guarantor of the article.

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Previous presentations

The results of the interim analysis were presented at the Dutch Digestive Disease Days, United European Gastroenterology (UEG) Week 2023 and European Pancreatic Club (EPC) 2024.[45]

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request. Individual patient data will be shared after de-identification and approval by the

study team and Dutch Pancreatic Cancer Group. Furthermore, a data transfer agreement has to be set up before data will be shared. The study protocol is available online without an end date at the Dutch Trial Register (https://www.onderzoekmetmensen.nl/en/trial/21209).

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Figure 1. Flow diagram of study. ERCP, endoscopic retrograde cholangiopancreatography; MBO, malignant biliary obstruction; PD, pancreatic duct; USEMS, uncovered self-expandable metal stent; FCSEMS, fullycovered self-expandable metal stent

Figure 2. Risk of PEP in subgroups. Values are presented as n (%). PEP, post-ERCP pancreatitis, OR, Odds Ratio; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; PD, pancreatic duct; EUS, endoscopic ultrasound; TA, tissue acquisition. [a] 1 missing in sphincterotomy group, 2 in control group; [b] 6 missing in sphincterotomy group, 6 in control group; [c] 4 missing in sphincterotomy group, 6 in control group [d,e] 3 missing in sphincterotomy group, 3 in control group.