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ORIGINAL ARTICLE

Does same session EUS-guided tissue acquisition and ERCP increase the risk of pancreatitis in patients with malignant distal biliary obstruction?

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Abstract

Background: Endoscopic retrograde cholangiopancreatography (ERCP) and endoscopic ultrasonography-guided tissue acquisition (EUS-TA) are increasingly performed in the same session in patients with malignant biliary obstruction. In this retrospective analysis, we investigated adverse events (AE) after same session ERCP and EUS-TA.

Methods: Patients with malignant distal biliary obstruction who underwent EUS-TA and/or ERCP with self-expandable metal stent (SEMS) placement from January 2015 to April 2020 were included. Primary outcome was post-procedural pancreatitis (PPP). Secondary outcomes were other procedure-related AE.

Results: We included 494 patients, of which 118 patients (24%) underwent same session EUS-TA+ERCP, 51 patients (10%) underwent separate session EUS-TA & ERCP, 90 patients (18%) ERCP-only and 235 patients (48%) EUS-TA only. PPP occurred in 22 patients (19%) after same session EUS-TA+ERCP and in 6 patients (12%) after separate EUS-TA & ERCP ($p = 0.270$). When adjusted for other known risk factors (i.e., difficult procedure), the difference in PPP remained non-significant (adjusted odds ratio 1.74 (95%-CI 0.65–4.67, $p = 0.268$). The incidence of other AE was similar, although the overall AE rate was significantly higher after same session EUS-TA+ERCP (36% vs. 20%, $p = 0.030$).

Conclusion: Same session EUS-TA+ERCP did not significantly increase the incidence of PPP, although overall AE were significantly higher. These data warrant further prospective studies.

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Introduction

Malignant obstruction of the distal bile duct is most commonly caused by pancreatic ductal adenocarcinoma (PDAC). PDAC

often presents late and only 20% of patients have a surgically resectable tumor. Chemotherapy is the mainstay of treatment in the other 80% of patients, since it prolongs overall survival in

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both primary resectable and advanced stages of disease.^{1–5} Histopathological confirmation of a malignant biliary obstruction is required prior to initiation of (chemo)therapy. Endoscopic ultrasonography (EUS)-guided tissue acquisition (TA) is recommended by several guidelines to obtain a histopathological sample based on the high diagnostic accuracy (95%) for diagnosing PDAC.^{6,7} In addition, biliary drainage is indicated in the majority of patients as most PDAC are located in the pancreatic head and often lead to obstructive jaundice. In accordance with current guidelines, endoscopic retrograde cholangiopancreatography (ERCP) with biliary self-expandable metal stent (SEMS) placement is the preferred drainage strategy in these patients.⁸ Over the last decade, there has been a tendency to combine EUS-TA and ERCP (EUS-TA+ERCP) in a single session, as this strategy offers advantages such as reducing the number of hospital visits, procedure time, anesthetic requirement, and costs.^{9–12} Data on the safety profile of performing same session EUS-TA+ERCP is however limited. Considering the aggressive course of disease of PDAC, adverse events (AE) are particularly undesirable as it may deteriorate the clinical condition of the patient resulting in delay or even annulment of (chemo)therapy.

EUS-TA is considered a relatively safe procedure with AE being rare, but include post-procedural pancreatitis (PPP), bleeding, and perforation (in 0.44%, 0.10%, and 0.02%, respectively).¹³ ERCP on the other hand is associated with a significant AE rate of which the majority is accounted for by PPP (3.5–9.7%), as well as bleeding (0.3–9.6%), cholecystitis (0.5–5.2%), cholangitis (0.5–3.0%), and perforation (0.08–0.6%).^{8,14}

PPP is common after ERCP and a clear association has been established with procedural factors that represent the degree of pancreatic manipulation during the procedure (e.g. difficult biliary cannulation and pancreatic duct cannulation).⁸ Even though PPP rates in EUS-TA are low, suggesting that pancreatic damage inflicted by EUS-TA alone is generally insufficient to induce PPP, it may well serve as an additional risk factor for PPP in patients undergoing a consecutive ERCP.

Up to date, several monocentric cohort studies have reported conflicting results on the incidence of AE after same session EUS and ERCP procedures for a variety of indications.^{15–19} None of these studies have focused on AE severity in particular. Therefore, the aim of this multicenter retrospective cohort study was to evaluate the incidence and severity of AE, with a focus on PPP, after same session EUS-TA and ERCP in patients with malignant distal biliary obstruction in a tertiary care setting.

Methods

Study design and patients

We performed a multicenter retrospective cohort study in both locations (Academic Medical Center (AMC) and VU Medical

Center) of the Amsterdam University Medical Centers, which are tertiary care centers that have recently merged. This study was conducted according to the STROBE guidelines for reporting observational studies.²⁰ We searched in our endoscopy database for all ERCP and EUS procedures between January 2015 and April 2020 and included consecutive patients with histopathologically confirmed malignant biliary obstruction who underwent: a) EUS-TA and ERCP with biliary SEMS placement in the same session (same session EUS-TA+ERCP group) or b) EUS-TA and ERCP with biliary SEMS placement with at least a 24 h interval (separate EUS-TA & ERCP group). In addition, patients who underwent ERCP with biliary SEMS placement without EUS-TA (ERCP only group) or EUS-TA without ERCP (EUS-TA only group) were included. Only patients who underwent EUS-TA of pancreatic masses were included. In case patients underwent multiple procedures only the first procedure was included for analysis. Exclusion criteria were: EUS without TA, proximal biliary obstruction, previous biliary stent placement, ERCP with unsuccessful biliary cannulation, surgically altered anatomy, and insufficient follow-up data regarding the occurrence of AE within 30 days. The study was approved by the local institutional review board of the Amsterdam University Medical Centers, location Academic Medical Center on February 6th, 2020 and the requirement to obtain informed consent was waived.

Data collection and definitions

Data on demographics, clinical features, radiology and laboratory findings, procedural details, and follow-up were collected retrospectively by two authors (MG and NvdV) using Castor EDC.²¹ In difficult cases the reports and images were independently reviewed by a third author (RvW) and disagreement was solved through discussion. Malignant biliary obstruction was defined as histopathology and/or cytopathology samples, either obtained from the primary tumor or a distant metastasis, showing a malignant tumor. Pancreatic duct (PD) dilation was defined as a PD diameter of >5 mm on preprocedural imaging. Distal biliary obstruction was defined as ≥ 2 cm from the liver hilum on computed tomography (CT) or ERCP. Midazolam/fentanyl was used as conscious sedation during EUS-TA procedures in both centers. In the VU medical center ERCP procedures were performed under midazolam/fentanyl sedation until 2018, while propofol sedation was used hereafter. In the AMC all ERCP procedures in the study time frame were performed under propofol sedation. Endoscopic sphincterotomy prior to SEMS placement was either performed at the discretion of the endoscopist or after allocation to the intervention group in the randomized controlled SPHINX trial, which investigates the effect of endoscopic sphincterotomy to prevent PPP.²² PD manipulation was defined as > 1 guidewire passages and/or contrast injection into the PD. The ESGE guideline classified

procedures as ‘difficult’ in case of >5 min of biliary cannulation attempts, > 5 contact with the papilla or >1 unintended PD cannulation.⁸ Due to the retrospective nature of this study, we were unable to reproduce the difficulty of the procedure according to the ESGE definition. Therefore, procedures were classified as ‘difficult’ when PD manipulation occurred (either guidewire passage or contrast injection), or if more than one attempt was necessary to obtain biliary cannulation. The latter was based on the observation that immediate (one attempt) cannulation success was standardly reported in the endoscopy database, while in case multiple attempts were required the number of attempts was generally not specified.

Primary and secondary outcomes

Our primary outcome was PPP within 30 days, defined according to the Cotton criteria as a combination of abdominal pain, increased serum amylase or lipase levels of at least three times the upper limit of normal (ULN) at more than 24 h after the procedure, requiring hospital admission or a prolongation of planned admission.²³ Secondary outcomes were PPP severity according to the modified Atlanta classification,²⁴ gastrointestinal bleeding, perforation, and cholangitis (defined and graded for severity according to the criteria proposed by Cotton *et al.*),²⁵ and cholecystitis (defined and graded for severity according to the 2018 Tokyo guidelines).²⁶ ‘Early’ AE were directly related to the procedure and included PPP, gastro-intestinal bleeding, perforation, cholecystitis, and AE that were classified as ‘other’.

Statistical analysis

Data were analyzed with the use of IBM SPSS Statistics version 26 (IBM Corp. Released 2019. IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY: IBM Corp). Baseline characteristics were presented as frequencies and proportions for categorical variables and median with corresponding interquartile range (IQR) for continuous variables. Groups were compared using Chi-square test for categorical variables (or Fisher’s exact test when appropriate) and the Kruskal–Wallis test for continuous variables. Univariate logistic regression analysis was performed to identify factors associated with PPP. Risk factors included female sex, more than one guidewire passage into the PD, contrast injection in the PD, PD manipulation (defined as either >1 guidewire passage or contrast injection into the PD), and difficult procedure. To prevent the problem of multicollinearity, meaning that the results of multivariable logistic regression are troubled by two or more predictor variables that are mutually correlated, only the variable ‘difficult procedure’, which also contained PD manipulation, was included. Results were expressed as odds ratios (OR) with 95 percent confidence intervals (95%-CI). A two-sided *p*-value of less than 0.05 was considered statistically significant.

Results

Baseline characteristics

In total, 5557 patients were screened for eligibility, of whom 494 patients were enrolled (Fig. 1). Same session EUS-TA+ERCP was performed in 118 patients (24%), whereas 51 patients underwent separate EUS-TA & ERCP (10%). ERCP only was performed in 90 patients (18%), whereas the majority of patients (*n* = 235, 48%) underwent EUS-TA only. Median age in the total cohort was 69 years (IQR 62–75 years), a majority of the patients were male (*n* = 256, 52%), and 27 patients (6%) had a history of acute pancreatitis. A majority of patients in the same session EUS-TA+ERCP and separate session EUS-TA & ERCP group were diagnosed with PDAC (102 patients [86%] and 43 patients [84%], respectively) and localization in the pancreatic head (92 patients [78%] and 35 patients [69%], respectively). Baseline characteristics of patients in the same session EUS-TA+ERCP and separate session EUS-TA & ERCP group, including a comparison between both groups, are depicted in Table 1. Baseline characteristics of the ERCP only and EUS-TA only group are shown in Supplementary Table S1.

Procedural characteristics

Significantly more patients in the separate EUS-TA & ERCP group underwent a previous attempt for biliary drainage when compared to the same session EUS-TA+ERCP group (39% vs. 7%, *p* < 0.001). Advanced cannulation techniques were performed more frequently in the separate EUS-TA & ERCP group when compared to the same session EUS-TA+ERCP group (63% vs. 41%, *p* = 0.008). In addition, a higher rate of difficult procedures (61% vs. 41%, *p* = 0.016) was observed in the separate EUS-TA & ERCP group. PD manipulation occurred equally in both groups (19% vs. 24%, *p* = 0.880). Significantly more patients (*p* = 0.004) received a fully covered SEMS in the same session EUS-TA+ERCP group (*n* = 109, 92%), whereas uncovered SEMS were more frequently placed in the separate EUS-TA & ERCP group (*n* = 12, 24%). An overview of the procedure characteristics and comparisons between the same session EUS-TA+ERCP and separate EUS-TA & ERCP group are displayed in Supplementary Table S2, whereas the procedure characteristics of the ERCP only and EUS-TA only group are presented in Supplementary Table S3.

Post procedural pancreatitis

The incidence of PPP did not differ significantly between the same session EUS-TA+ERCP group and the separate EUS-TA & ERCP group (19% vs. 12%, respectively, *p* = 0.270, Table 2). The severity of PPP was comparable between both groups with the majority being mild (77% vs. 83%, respectively, *p* = 1.000). Ten percent (*n* = 9) of the patients developed PPP after ERCP only, whereas EUS-TA only caused PPP in 4 patients (2%, Table S4). To adjust for the effect of other known risk factors for PPP, we performed a univariate and multivariable logistic regression

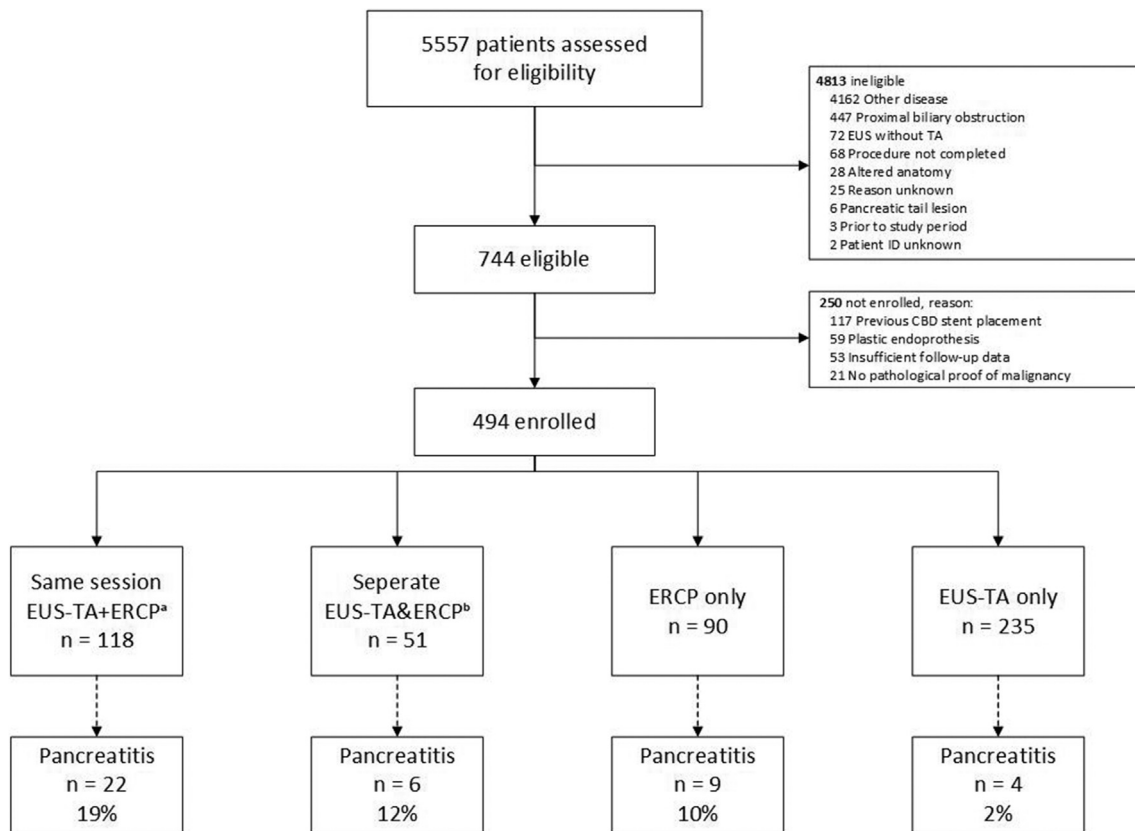


Figure 1 Flow diagram of study participants. ^a Patients who underwent EUS-TA and ERCP in a single session were included in the same session group. ^b Patients who underwent separate EUS-TA and ERCP with a time interval of >24 h were included in the separate group. Abbreviations: CBD, common bile duct; ERCP, endoscopic retrograde cholangiopancreatography; EUS-TA, endoscopic ultrasonography-guided tissue acquisition; N, number

analyses (Table 3). None of the predictor variables reached statistical significance in univariate logistic regression analysis. In multivariable analysis, in which we adjusted for the effect of other possible confounders (i.e., the variable ‘difficult procedure’), same session EUS-TA+ERCP remained a non-significant predictor for the occurrence of PPP (adjusted OR 1.74, 95%-CI 0.65–4.67, $p = 0.268$).

Incidence and severity of other adverse events

The occurrence of bleeding (4% vs. 0%, $p = 0.324$), perforation (2% vs. 0%, $p = 1.000$), cholecystitis (1% vs. 4%, $p = 0.217$), and cholangitis (11% vs. 2%, $p = 0.067$) was similar between the same session EUS-TA+ERCP and separate EUS-TA & ERCP group (Table 2). Cholangitis was caused by spontaneous stent migration in 3 out of 14 patients (21%) in the same session EUS-TA+ERCP group. Although the incidence of early AE was comparable between both groups (25% vs. 18%, $p = 0.271$), overall AE were more frequent in the same session EUS-TA+ERCP group (36% vs. 20%, $p = 0.030$). AE severity was similar in the same session EUS-TA+ERCP and separate EUS-TA & ERCP group, with the majority being moderate or severe (76%

vs. 75%, respectively, $p = 0.712$). An overview of the AE rates in both groups are displayed in Table 2. In the ERCP only group, 24% of the patients developed an AE. Adverse events after EUS-TA only occurred in 2% of the patients. The AE rates in the ERCP only and EUS-TA only group are presented in Table S4.

Discussion

In this study, the incidence of PPP in patients with malignant distal biliary obstruction was similar after same session EUS-TA+ERCP versus separate session EUS-TA & ERCP. The overall AE rate was significantly higher after same session EUS-TA+ERCP. No differences in AE severity were observed.

Several studies previously investigated the safety of same session EUS-TA+ERCP and have reported conflicting results.^{15–19} These studies included more heterogeneous patient populations in comparison to the current study, and did not report on AE severity. One of these studies, published by Lee *et al.*, aimed to identify risk factors for AE after EUS-TA in over 4000 patients and found that ERCP being performed on the same day was an independent risk factor for both overall AE and PPP

Table 1 Baseline characteristics in same session or separate EUS-TA and ERCP

	Same session EUS-TA+ERCP ^a n = 118	Separate EUS-TA & ERCP ^b n = 51	p-value
A. Clinical features			
Male, n (%)	57 (48)	23 (45)	0.702
Age (median in years, IQR)	70 (63–75)	70 (61–75)	0.247
History of pancreatitis, n (%)			0.246 ^c
No	109 (92)	45 (88)	
Acute pancreatitis	2 (2)	4 (8)	
Chronic pancreatitis	4 (3)	1 (2)	
Serum bilirubin (median in $\mu\text{mol/L}$, IQR)	220 (125–324)	155 (74–268)	0.009^d
B. Imaging characteristics			
Lesion size (median in mm, IQR)	30 (23–42)	30 (21–40)	0.885
PD dilation, n (%)	84 (71)	34 (67)	0.698
Diameter of PD (median in mm, IQR)	7 (5–10)	8 (5–9)	0.358
C. Pathological characteristics			
Type of malignancy, n (%)			0.166 ^c
PDAC	102 (86)	43 (84)	
Cholangiocarcinoma	8 (7)	2 (4)	
Ampullary carcinoma	1 (1)	4 (8)	
Metastatic disease	4 (3)	1 (2)	
pNET	3 (3)	1 (2)	
Location of lesion, n (%)			0.535 ^c
Uncinate process	10 (9)	6 (12)	
Head	92 (78)	35 (69)	
Body	7 (6)	4 (8)	
Unknown	9 (8)	6 (12)	

Percentages might not sum to 100% because of rounding.

Abbreviations: ERCP, endoscopic retrograde cholangiopancreatography; EUS-TA, endoscopic ultrasonography-guided tissue acquisition; IQR, interquartile range; Mm, millimeter; N, number; PD, pancreatic duct; PDAC, pancreatic ductal adenocarcinoma; pNET, pancreatic neuroendocrine tumor; $\mu\text{mol/L}$, micromole per liter.

^a Patients who underwent EUS-TA and ERCP in a single session were included in the same session group.

^b Patients who underwent separate EUS-TA and ERCP with a time interval of >24 h were included in the separate group.

^c Fisher's exact test.

^d Statistically significant.

specifically.¹⁹ The patient population in their study was however heterogeneous and included both cystic, solid, as well as benign and malignant lesions, which makes it difficult to draw conclusions. Our study on the other hand focused on patients with a malignant distal biliary obstruction, and thus represents a more

homogenous population. For the same reason, only patients treated with biliary SEMs were included in the study, since these stents have been associated with higher PPP rates than plastic endoprosthesis.²⁷ Excluding patients with plastic stents contributed to a fair comparison between both groups. Another strongpoint of this study was that patients in either group were exposed to the risks of both procedures, only differing in the time interval between the procedures. One relevant difference between both groups was that procedures in the separate EUS-TA & ERCP group appeared technically more demanding, as illustrated by the more frequent use of advanced cannulation techniques, and which could be explained by a higher percentage of referrals for ERCP that previously failed in other hospitals. In addition, we acknowledge that other procedure-related factors (e.g., differences in conscious sedation protocols and differences in endoscopists between EUS-TA and ERCP procedures) might have been misbalanced among the groups, although these factors are unlikely to have substantially influenced our primary study outcome.

Procedural characteristics (e.g., difficult procedure) of an ERCP, and to a lesser extent EUS-TA, are known to have an impact on AE rates.^{8,28} We corrected for this confounding effect by using logistic regression analysis, yet the difference in PPP incidence remained non-significant in multivariable regression analysis. Although a possible confounding effect cannot be excluded, it should be noted that the more technically challenging procedures in the separate EUS-TA & ERCP may have resulted in a higher AE rate in this group. Thus, the difference in AE rates between both groups may in fact be underestimated in this study, and further supports the observation of a higher AE rate in the same session EUS-TA+ERCP group. Another AE that occurred frequently in the same session EUS-TA+ERCP group was cholangitis. This may be explained by the observation that the same session group more often received fully covered SEMs, likely because of not yet histopathologically confirmed malignancy, which are known to have a higher risk of stent migration when compared to uncovered SEMs.^{29,30} No differences in cholecystitis, bleeding or perforation were noted between both groups.

Comparing the post-ERCP AE rates of this cohort to those reported in the current literature is rather difficult due to heterogeneous patient populations.⁸ Our findings are in line with the incidence of PPP (18%) previously reported in a Dutch prospective multicenter study for preoperative biliary drainage in resectable pancreatic cancer.²⁷ The PPP incidence reported in international literature nonetheless appears to be lower, as illustrated by the most recently available systematic review on early AE after ERCP by Andriulli *et al.*, which reported a 7% overall AE rate, although it only included studies published before 2006.¹⁴ As a consequence, it may be possible that the incidence of AE has changed over the years, as illustrated by several large cohort studies published thereafter, both from

Table 2 Adverse events in same session or separate EUS-TA and ERCP

	Same session EUS-TA+ERCP ^a n = 118	Separate EUS-TA & ERCP ^b n = 51	p-value
A. Adverse events			
Pancreatitis, n (%)	22 (19)	6 (12)	0.270
Bleeding, n (%)	5 (4)	–	0.324 ^g
Perforation, n (%)	2 (2)	–	1.000 ^g
Cholecystitis, n (%)	1 (1)	2 (4)	0.217 ^g
Cholangitis, n (%)	13 (11)	1 (2)	0.067 ^g
Other ^c , n (%)	–	1 (2)	0.302 ^g
B. Severity grading			
Pancreatitis severity ^d , n (%)			1.000 ^g
Mild	17 (77)	5 (83)	
Moderate or severe	4 (18)	1 (17)	
Unknown	1 (5)		
AE severity ^e , n (%)			0.712 ^g
Mild	3 (14)	1 (25)	
Moderate or severe	16 (76)	3 (75)	
Fatal	2 (10)	–	
C. Overall AE			
Early AE ^f , n (%)	30 (25)	9 (18)	0.271
Overall AE, n (%)	43 (36)	10 (20)	0.030^h

Percentages might not sum to 100% because of rounding. Abbreviations: AE, adverse event; ERCP, endoscopic retrograde cholangiopancreatography; EUS-TA, endoscopic ultrasonography-guided tissue acquisition; N, number.

^a Patients who underwent EUS-TA and ERCP in a single session were included in the same session group.

^b Patients who underwent separate EUS-TA and ERCP with a time interval of >24 h were included in the separate group.

^c This patient was admitted in a hospital elsewhere for 2 days after the procedure, details are unknown.

^d Pancreatitis severity according to the modified Atlanta criteria.²³

^e Severity of adverse events according to the criteria proposed by Cotton *et al.*²⁴

^f Early adverse events; defined as the occurrence of either post-procedural pancreatitis, clinically relevant gastro-intestinal bleeding, perforation, cholecystitis, or adverse events that were classified as 'other'.

^g The Fisher's exact test was used.

^h Statistically significant.

peripheral hospitals and tertiary centers, which have reported AE rates of 10–12%.^{31–34} The current study reports a relatively high AE rate of 20–36%, and PPP is responsible for the majority of these adverse events and thus warrants a detailed analysis. The overall incidence of PPP in our study ranged from 10 to 19%, which again is relatively high compared to a systematic review of randomized controlled trials from 2015, that found an incidence of 10%, increasing to 14.7% in high risk patients.³⁵ In contrast to this review, our study focused on a specific patient group that required transpapillary biliary stenting with SEMs, which in

Table 3 Predictors for pancreatitis in univariate and multivariable analysis

	Univariate analysis		Multivariable analysis	
	OR	95%-CI	Adjusted OR	95%-CI
Female	0.88	0.39–1.98	–	–
Pancreatic guidewire passages >1	0.56	0.10–3.01	–	–
Pancreatic contrast injection	0.90	0.25–3.30	–	–
Pancreatic duct manipulation ^a	0.93	0.23–3.67	–	–
Difficult procedure ^b	0.99	0.44–2.22	1.08	0.47–2.46
Same session or separate session	1.72	0.65–4.53	1.74	0.65–4.67

Abbreviations: CI, confidence interval; OR, odds ratio.

^a Pancreatic duct manipulation; defined as either >1 guidewire passages into the pancreatic duct or pancreatic injection.

^b Difficult procedure; defined as either PD manipulation (guidewire passage or contrast injection) or > 1 attempt to obtain biliary cannulation.

itself increases the risk of PPP by impairing pancreatic duct outflow. This is especially true in those without PD dilation, which was the case in a significant 40% of patients in our cohort.³⁶ One observation in our study that needs adaptation is that only 7% of patients received a PD stent, while manipulation occurred in 20%, despite PD stent placement being an established method to prevent PPP in these patients.⁸ Furthermore, only 28% of the patients underwent endoscopic sphincterotomy prior to SEMs placement. Although its efficacy to prevent PPP is currently being investigated in a randomized controlled setting, this might have influenced the rate of PPP in our cohort.

This study should be interpreted in light of some limitations. First, its retrospective design makes the results of this study subject to indication and selection bias, meaning that the underlying reasoning to either perform same session or separate procedures may have influenced the reported AE rates. Second, in retrospective study designs the risk of confounding makes it hard to draw firm conclusions on causality. In order to deal with these limitations we corrected for commonly known confounders of PPP by constructing a multivariable logistic regression model. Nevertheless, it was impossible to include all possible risk factors in the logistic regression model due to the relatively small sample size. Third, this study was performed in a tertiary care center. Therefore, the results of this study might not be generalizable to other hospital settings.

In conclusion, same session EUS-TA+ERCP did not significantly increase the incidence of PPP in patients with malignant distal biliary obstruction. Nonetheless, a higher incidence of overall AE was observed in the same session EUS-TA+ERCP group. The limitations of this study however do not warrant immediate discontinuation of this approach, when taking into

account the advantages this strategy offers to both the patient and the healthcare provider. Future prospective multicenter research is needed to further reveal the possible negative effect of same session EUS-TA+ERCP procedures, and should also address the clinical implications of these AE.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.hpb.2022.04.003>.