Nationwide practice and outcomes of endoscopic biliary drainage in resectable pancreatic head and periampullary cancer

Dutch Pancreatic Cancer Group; Latenstein, Anouk E J; Mackay, Tara M; van Huijgevoort, Nadine C M; Bonsing, Bert A; Bosscha, Koop; Hol, Lieke; Bruno, Marco J; van Coolsen, Marielle M E; Festen, Sebastiaan

Published in:
Hpb

DOI:
10.1016/j.hpb.2020.06.009

Publication date:
2021

https://doi.org/10.1016/j.hpb.2020.06.009 HPB

ORIGINAL ARTICLE

Nationwide practice and outcomes of endoscopic biliary drainage in resectable pancreatic head and periampullary cancer

Anouk E.J. Latenstein[1,*], Tara M. Mackay[1,*], Nadine C.M. van Huijgevoort[2], Bert A. Bonsing[3], Koop Bosscha[4], Lieke Hol[5], Marco J. Bruno[6], Marielle M.E. van Coolsen[7], Sebastiaan Festen[8], Erwin van Geenen[9], Bas Groot Koerkamp[10], Gerrit J.M. Hemmink[11], Ignace H.J.T. de Hingh[12], Geert Kazemier[13], Hans Lubbinge[14], Vincent E. de Meijer[15], I. Quintus Molenaar[16], Rutger Quispel[17], Hjalmar C. van Santvoort[16], Tom C.J. Seerden[18], Martijn W.J. Stommel[19], Niels G. Venneman[20], Robert C. Verdonk[21], Marc G. Besselink[1,#], Jeanin E. van Hooft[2,#] for the Dutch Pancreatic Cancer Group

[1]Department of Surgery, [2]Department of Gastroenterology and Hepatology, Cancer Center Amsterdam, Amsterdam UMC, University of Amsterdam, Amsterdam, [3]Department of Surgery, Leiden University Medical Center, Leiden, [4]Department of Surgery, Jeroen Bosch Hospital, 's Hertogenbosch, [5]Department of Gastroenterology and Hepatology, Maasstad Hospital, [6]Department of Gastroenterology and Hepatology, Erasmus MC University Medical Center, Rotterdam, [7]Department of Surgery, Maastricht University Medical Centre, Maastricht, [8]Department of Surgery, Onze Lieve Vrouwe Gasthuis, Amsterdam, [9]Department of Gastroenterology and Hepatology, Radboud University Medical Center, Nijmegen, [10]Department of Surgery, Erasmus MC University Medical Center, Rotterdam, [11]Department of Gastroenterology and Hepatology, Isala, Zwolle, [12]Department of Surgery, Catharina Hospital, Eindhoven, the Netherlands, [13]Department of Surgery, Cancer Center Amsterdam, Amsterdam UMC, Vrije Universiteit Amsterdam, Amsterdam, [14]Department of Gastroenterology and Hepatology, Tjongerschans, Heerenveen, [15]Department of Hepatobiliary Surgery and Liver Transplantation, University Medical Center Groningen, University of Groningen, Groningen, [16]Department of Surgery, Regional Academic Cancer Center Utrecht, St Antonius Hospital Nieuwegein, Utrecht, [17]Department of Gastroenterology and Hepatology, Reinier de Graaf Ziekenhuis, Delft, [18]Department of Gastroenterology and Hepatology, Amphia Hospital, Breda, [19]Department of Surgery, Radboud University Medical Center, Nijmegen, [20]Department Gastroenterology and Hepatology, Medisch Spectrum Twente, Enschede, and [21]Department of Gastroenterology and Hepatology, Regional Academic Cancer Center Utrecht, St Antonius Hospital Nieuwegein, Utrecht, the Netherlands

Abstract

Background: Guidelines advise self-expanding metal stents (SEMS) over plastic stents in preoperative endoscopic biliary drainage (EBD) for malignant extrahepatic biliary obstruction. This study aims to assess nationwide practice and outcomes.

Methods: Patients with pancreatic head and periampullary cancer who underwent EBD before pancreatoduodenectomy were included from the Dutch Pancreatic Cancer Audit (2017–2018). Multivariable logistic and linear regression models were performed.

Results: In total, 575/1056 patients (62.0%) underwent preoperative EBD: 246 SEMS (42.8%) and 329 plastic stents (57.2%). EBD-related complications were comparable between the groups (44/246 (17.9%) vs. 64/329 (19.5%), p = 0.607), including pancreatitis (22/246 (8.9%) vs. 25/329 (7.6%), p = 0.387). EBD-related cholangitis was reduced after SEMS placement (10/246 (4.1%) vs. 32/329 (9.7%), p = 0.043), which was confirmed in multivariable analysis (OR 0.36 95%CI 0.15–0.87, p = 0.023). Major postoperative complications did not differ (58/246 (23.6%) vs. 90/329 (27.4%), p = 0.316), whereas postoperative pancreatic fistula (24/246 (9.8%) vs. 61/329 (18.5%), p = 0.004; OR 0.50 95%CI 0.27–0.94, p = 0.031) and hospital stay (14.0 days vs. 17.4 days, p = 0.005; B 2.86 95%CI –5.16 to –0.57, p = 0.014) were less after SEMS placement.

Conclusion: This study found that preoperative EBD frequently involved plastic stents. SEMS seemed associated with lower risks of cholangitis and less postoperative pancreatic fistula, but without an increased pancreatitis risk.

Received 15 May 2020; accepted 18 June 2020

Correspondence

Jeanin E. van Hooft, Gastroenterology and Hepatology, C2-115, Cancer Center Amsterdam, Amsterdam UMC, University of Amsterdam, Meibergdreef 9, 1105, AZ, Amsterdam, the Netherlands. E-mail: j.e.vanhooft@amsterdamumc.nl (J.E. van Hooft)

[*] Shared first authorship.

[#] Shared senior authorship.

Correspondence
Anouk E.J. Latenstein, Department of Surgery, Cancer Center Amsterdam, Amsterdam UMC, University of Amsterdam, Amsterdam, the Netherlands. E-mail: a.e.latenstein@amsterdamumc.nl (A.E.J. Latenstein)

Introduction

Patients with resectable pancreatic head and periampullary cancer may require preoperative endoscopic biliary drainage (EBD) due to extrahepatic bile duct obstruction. Early surgery is, however, preferred, as this is associated with fewer perioperative complications compared to preoperative EBD.[1] Indications for EBD include cholangitis, severe jaundice, long waiting times for surgery, and the use of neoadjuvant therapy, which is a rapidly emerging indication for longer-term EBD.[2–4]

Historically, EBD is performed by placement of a plastic stent which has to be replaced every three months to prevent stent occlusion. In the recently updated European Society of Gastrointestinal Endoscopy Clinical Guideline, self-expanding metal stent (SEMS) placement is recommended in case of preoperative EBD of malignant extrahepatic biliary obstruction.[2] A potential downside of SEMS placement could be the increased risk of post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis.[5] Plastic stents are still frequently used, however, possibly because of lower upfront costs. Nationwide studies assessing clinical practices and outcomes of EBD with SEMS or plastic stents in pancreatic head and periampullary cancer are lacking.

The aim of this study was to assess the use of SEMS on a nationwide scale in daily clinical practice in patients with pancreatic head and periampullary cancer undergoing preoperative EBD and to determine the relation between type of stent and EBD-related complications and postoperative outcomes.

Methods

Patients and design

This nationwide, retrospective cohort study included all patients with a pancreatic ductal adenocarcinoma, distal cholangiocarcinoma, duodenal adenocarcinoma, and ampulla of Vater adenocarcinoma who underwent pancreatoduodenectomy (PD) between January 2017 and December 2018 after EBD in the Netherlands. In general, biliary drainage was considered indicated in patients with clinical suspicion of cholangitis (characterized by fever, abdominal pain and/or jaundice), severe jaundice (bilirubin concentration $\geq$250 µmol/L), or mild jaundice (>25 µmol/L) before commencing neoadjuvant chemotherapy. EBD was also indicated for bilirubin <250 µmol/L if the waiting time for surgery exceeded 3 weeks and it was anticipated that the bilirubin might be above $\geq$250 µmol/L at time of surgery. In the Netherlands, endoscopy is always performed by a gastroenterologist and local protocols are followed for procedures concerning EBD and stent placement. Endoscopic ultrasound for obtaining pathological material is performed prior to ERCP and stent placement. Type of stent depends on the expertise and preference of the gastroenterologist. Prevention of post-ERCP pancreatitis exists of rectal nonsteroidal anti-inflammatory drug administration and in case of manipulation of the pancreatic duct, a 5 Fr plastic stent is placed in the pancreatic duct. Patients with percutaneous biliary drainage were excluded. Patients were identified from the Dutch Pancreatic Cancer Audit (DPCA), a nationwide, mandatory, prospective audit of pancreatic surgery. Data were registered by the surgeons of each center. Since 2017, several variables containing information about preoperative EBD and stents were added to the DPCA. All 17 pancreatic centers in the Netherlands performing pancreatic surgery participate in this audit. Annually, each center is required to perform at least 20 PDs. Data are registered anonymously and evaluated retrospectively. This study is reported in accordance with the STROBE guidelines.[6]

Data collection

Patient, tumor, and treatment characteristics were collected. Center of stent placement was not registered, but center of surgery (pancreatic center) was. Therefore, pancreatic centers represent stent placements from the center itself and from regional centers referring to the pancreatic center. Dates of the final multidisciplinary team (MDT) meeting in pancreatic centers and of drainage were available as well as type of stent and EBD-related complications. No other data about stent replacement were available. Postoperative outcomes were postoperative complications, in-hospital mortality, length of hospital stay, and readmissions within 30 days after discharge.

Definitions

Data from patients with pancreatic head and periampullary cancer were pooled in this study. Pancreatic centers were divided according to volume in <40 or $\geq$40 PDs annually. Site of origin was categorized into pancreas, distal bile duct, ampulla of Vater, duodenum, or other. Type of stent was SEMS versus plastic stent. SEMS were categorized into fully covered SEMS and uncovered SEMS. Neoadjuvant therapy was chemo(radio)therapy, mostly

given within a randomized trial. Preoperative pathological confirmation was obtained by duodenoscopy with biopsy, ERCP with brush, or endoscopic ultrasound guided puncture of the primary tumor. PD included pylorus-preserving PD, pylorus-resecting PD, and classical Whipple. EBD-related complications included pancreatitis, cholangitis, stent occlusion, perforation of the bile duct or duodenum, and hemorrhage. These complications were registered accordingly to judgement of the local physicians. It was documented whether reinterventions (radiological or endoscopic) were performed for any EBD-related complication. All postoperative complications during hospital admission or up to 30 days after resection were also registered. Major postoperative complications were defined as a Clavien-Dindo score $\geq$3.[7] Pancreatic surgery specific complications (i.e. postoperative pancreatic fistula, delayed gastric emptying, post-pancreatectomy hemorrhage, and chyle leak) were defined by the International Study Group on Pancreatic Surgery (ISGPS) and scored in three groups of severity.[8–11] Bile leakage was scored accordingly as was defined by the International Study Group of Liver Surgery.[12] Grade B and C graded complications were considered clinically relevant. Reintervention for a postoperative complication was categorized as an endoscopic, radiological, or surgical intervention. Exact details about the type of reintervention were not registered.

Statistical analysis

Missing data (range 0–24%) were imputed by multiple imputation with predictive mean matching in which 25 dummy sets were created. Age, sex, hospital of treatment, date of drainage, and date of MDT meeting were not imputed, because only a selected number of variables could be imputed. Patients with missing data in age, sex and hospital of treatment were excluded for further analyses. Baseline characteristics were presented using descriptive statistics. Normally distributed continuous data were compared using a Students t-test and presented as means with standard errors (SE). Non-normally distributed continuous data were compared using the Mann Whitney U test and presented as medians with interquartile ranges (IQR). Categorical data were presented as frequencies with percentages and compared using the Chi-square test or with the Fisher's exact test if the expected count was less than 5. To determine the association between type of stent and EBD-related complications or postoperative outcomes that differed statistically significantly between the plastic stent and SEMS group, multivariable logistic or linear regression models were performed, adjusted for patient characteristics, differences in baseline data, and other potential risk factors per specific outcome. Postoperative outcomes were also adjusted for hospital volume. The patient characteristics were age, sex, body mass index (BMI), and American Society of Anesthesiologists (ASA) score. Potential risk factors were found for postoperative pancreatic fistula, specifically BMI, pancreatic texture, and pancreatic duct diameter.[13] The results were reported as the odds ratio (OR) with corresponding 95% confidence interval (CI) in logistic regression or as the regression coefficient (B) with corresponding 95% CI in linear regression. All p-values were based on a 2-sided test and p-values of <0.05 were considered statistically significant. Data were analyzed using IBM SPSS Statistics for Windows version 25 (IBM Corp., Armong, N.Y., USA) and R version 3.4.3 (cran.r-project.org).

Results

In total, 1056 patients underwent PD for pancreatic head and periampullary cancer in 2017 and 2018 (Fig. 1). In 655 patients (62.0%) preoperative biliary drainage was performed, of whom 73 patients were excluded because the method of drainage was unknown or occurred percutaneously due to ERCP failure or technical impossibilities to perform EBD (e.g. after gastric bypass). Of the remaining 582 patients, 7 patients were excluded because of missing data in age, sex, and hospital of treatment. The final cohort undergoing EBD existed of 575 patients (54.4%). Missing data were randomly distributed between the pancreatic centers. Baseline characteristics after multiple imputation are demonstrated in Table 1. All 17 pancreatic centers performed $\geq$20 PDs annually, of which 8 centers performed $\geq$40 PDs annually.

Type of stent

SEMS were placed in 246 of 575 patients (42.8%) and plastic stents in 329 patients (57.2%). The use of SEMS varied from 0 to 77.1% between pancreatic centers (Supplemental Fig. 1,

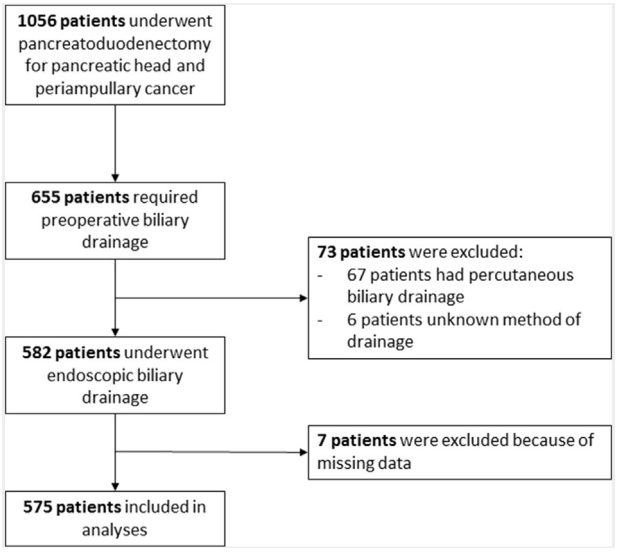

Figure 1 Flow chart of endoscopic biliary drainage in patients who underwent pancreatoduodenectomy for pancreatic head and periampullary cancer in 2017 and 2018 in the Netherlands

Table 1 Baseline characteristics

Variable	All patients (n = 575), n (%)	SEMS[a] (n = 246), n (%)	Plastic stents (n = 329), n (%)	Pooled p-value
Age, mean (SE)	68 (0.4)	68 (0.6)	67 (0.6)	0.117
Male	315 (54.8)	136 (55.3)	179 (54.4)	0.784
BMI[a], mean (SE)	25.3 (0.2)	24.9 (0.3)	25.6 (0.3)	0.074
ASA score[a]				**0.001**
I and II	419 (72.9)	162 (65.9)	257 (78.1)	
III and IV	156 (27.1)	84 (34.1)	72 (21.9)	
Comorbidity				0.098
Liver cirrhosis	10 (1.7)	7 (2.8)	3 (0.9)	
Pancreatitis	24 (4.2)	7 (2.8)	17 (5.2)	
Site of origin				**0.008**
Pancreas	310 (53.9)	155 (63.0)	156 (47.4)	
Distal bile duct	152 (26.4)	57 (23.2)	96 (29.2)	
Ampulla of Vater	99 (17.2)	30 (12.2)	68 (20.7)	
Duodenum or other	14 (2.4)	5 (2.0)	9 (2.7)	
Diameter pancreatic duct, mean (SE)	4.6 (0.1)	4.8 (0.2)	4.4 (0.2)	0.095
Preoperative cytological or histological examination				0.328
Endoscopy with biopsy	201 (35.0)	95 (38.6)	106 (32.2)	
ERCP[a] and brush	289 (50.3)	115 (46.7)	174 (53.2)	
Other	13 (2.3)	4 (1.6)	10 (3.0)	
Type stent				NA
Covered		196 (79.7)		
Uncovered		50 (20.3)		
Neoadjuvant therapy	48 (8.3)	31 (12.6)	17 (5.2)	**0.011**
Hospital volume				**<0.001**
<40 PDs annually	201 (35.0)	55 (22.4)	146 (44.4)	
≥40 PDs annually	374 (65.0)	191 (77.6)	183 (55.6)	
Time to surgery[b], days, median (IQR)	32.0 (22.0–48.0)	27.0 (21.0–41.0)	37.5 (25.0–53.0)	**<0.001**
Pancreatic texture during surgery				**0.001**
Normal/soft	331 (57.6)	121 (49.2)	209 (63.5)	
Fibrotic/hard	244 (42.4)	125 (50.8)	119 (36.2)	

Bold numbers indicate statistical significance; numbers in the SEMS and plastic stent group do not always equal the total cohort, because of rounding due to the imputation.
[a] SEMS: self-expandable metal stents, BMI: body mass index, ASA score: American Society of Anesthesiologists score, NA: not applicable, ERCP: endoscopic retrograde cholangio- and pancreatography, PD: pancreatoduodenectomie.
[b] Only in patients without neoadjuvant chemotherapy and based on non-imputed data: 414 patients in overall group, 240 patients in plastic stent group, and 174 in SEMS group.

$p < 0.001$). Of all SEMS, 196 were covered (79.7%) and 50 were uncovered (20.3%). Timing of stent placement relative to the date of the MDT meeting was analyzed in 493 patients (non-imputed data). The majority of patients (n = 343, 69.6%) had EBD before being discussed in the MDT meeting of a pancreatic center. From these 343 patients, 215 (62.7%) received plastic stents compared to 64 out of 150 patients (42.7%) after the MDT meeting in a pancreatic center ($p < 0.001$).

Patients with SEMS had higher ASA scores, more often a fibrotic/hard pancreatic texture during surgical exploration, were more often treated with neoadjuvant therapy, and the site of origin was more often the pancreas compared to patients with plastic stents (Table 1). Of all patients with neoadjuvant therapy, 31 patients (64.6%) received a SEMS. Time to surgery after stent placement was significantly shorter for patients with SEMS compared to patients with plastic stents after excluding patients

with neoadjuvant therapy (non-imputed data: 27.0 (21.0–41.0) vs. 37.5 (25.0–53.0) days, p < 0.001).

Endoscopic biliary drainage-related complications

The rate of any complication after EBD was comparable in both stent groups (44 patients (17.9%) vs. 64 patients (19.5%) for SEMS and plastic stents respectively, p = 0.607). EBD-related cholangitis occurred less often in patients with SEMS compared to plastic stents (10 patients (4.1%) vs. 32 patients (9.7%), p = 0.043, Table 2). Post-ERCP pancreatitis occurred in 22 patients (8.9%) with SEMS and 25 patients (7.6%) with plastic stents (p = 0.387). Reintervention (endoscopic or radiological) was required in 22 patients (8.9%) of the SEMS group and 32 patients (9.7%) of the plastic stent group (p = 0.584). In multivariable logistic regression, adjusted for patient characteristics (i.e. age, sex, BMI, and ASA score), site of origin, and neoadjuvant therapy, SEMS were associated with a lower OR of cholangitis (OR 0.36 95% CI 0.15–0.87, p = 0.023, Fig. 2a) compared to plastic stents. The rate of any complication after EBD, pancreatitis, cholangitis, perforation, hemorrhage, occlusion, and reintervention for complications did not differ between the covered and uncovered SEMS (See Supplementary Table 1).

Postoperative outcomes after pancreatoduodenectomy

Patients with SEMS and plastic stents had similar rates of major postoperative complications (58 patients (23.6%) vs. 90 patients (27.4%), p = 0.316, Table 3). Major postoperative complications occurred in all 43 patients who had EBD-related cholangitis (100%) and in 181 patients who did not have EBD-related cholangitis (34.0%, p < 0.001). The proportion of patients with postoperative pancreatic fistula grade B–C (i.e. clinically relevant fistula) was lower in patients with a SEMS compared to plastic stents (24 patients (9.8%) vs. 61 patients (18.5%) respectively, p = 0.004). After adjustment for patient characteristics, hospital volume, neoadjuvant therapy, site of origin, pancreatic duct diameter, and pancreatic texture, the use of SEMS was still associated with a significantly lower risk on postoperative pancreatic fistula (OR 0.50 95% CI 0.27–0.94, p = 0.031, Fig. 2a).[13] Patients with SEMS had a shorter mean length of hospital stay than patients with plastic stents (14.0 days (SE 0.6) vs. 17.4 days (SE 1.0) respectively, p = 0.005). In multivariable linear regression, adjusted for patient characteristics, hospital volume, site of origin, neoadjuvant therapy, pancreatic texture, and major postoperative complications, length of hospital stay was almost three days shorter in patients who received a SEMS (B −2.86 95% CI -5.16–0.57, p = 0.014) compared to patients with a plastic stent (Fig. 2b).

Discussion

This nationwide study shows that in 2017 and 2018 in the Netherlands, SEMS were placed in less than half of all patients who received EBD prior to pancreatoduodenectomy. The rate of overall EBD-related complications were similar between SEMS and plastic stents, but patients receiving SEMS had a lower odds of cholangitis, less postoperative pancreatic fistula, and a shorter postoperative hospital stay. No association between SEMS and post-ERCP pancreatitis rate could be demonstrated, neither in the small subgroup analysis of patient that received a covered SEMS.

As demonstrated in a multicenter randomized controlled trial including 196 patients, early surgery without preoperative biliary drainage in patients with cancer of the pancreatic head is the preferred treatment, because routine preoperative biliary drainage increased the rate of complications from 39% to 74%.[1] Still, preoperative EBD was performed in 54.4% of all patients who underwent PD in this study. Unfortunately, the exact indication for stent placement could not be assessed because this variable was not registered in the audit. Data from the Surveillance, Epidemiology, and End Results (SEER) tumor registry showed that in 2004–2007 the rate of preoperative EBD was 40%.[14] The nationwide audit from Germany showed a preoperative EBD percentage of 38.9% for pancreatic ductal adenocarcinoma in 2014–2016.[15] Monocenter studies showed that respectively 47.6% (2005–2016) and 55% (2006–2016) initially

Table 2 Complications related to endoscopic biliary drainage

Variable	All patients (n = 575), n (%)	SEMS[a] (n = 246), n (%)	Plastic stents (n = 329), n (%)	Pooled p-value
Any complication	107 (18.6)	44 (17.9)	64 (19.5)	0.607
Pancreatitis	47 (8.2)	22 (8.9)	25 (7.6)	0.387
Cholangitis	43 (7.5)	10 (4.1)	32 (9.7)	**0.043**
Perforation	16 (2.8)	3 (1.2)	13 (4.0)	0.120
Hemorrhage	23 (4.0)	8 (3.3)	15 (4.6)	0.365
Occlusion	38 (6.6)	11 (4.5)	27 (8.2)	0.173
Reintervention	54 (9.4)	22 (8.9)	32 (9.7)	0.584

Bold numbers indicate statistical significance; numbers in the SEMS and plastic stent group do not always equal the total cohort, because of rounding due to the imputation.
[a] SEMS: self-expandable metal stents.

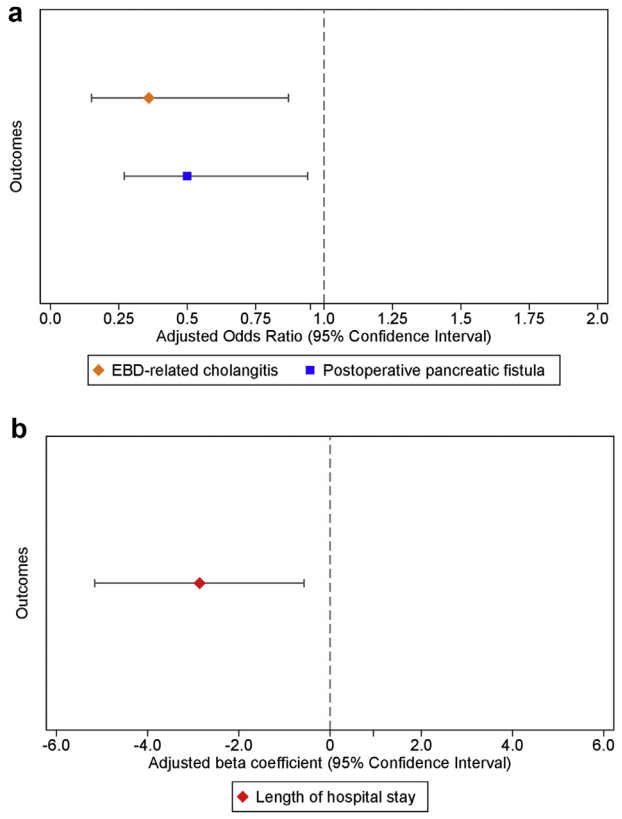

Figure 2 Multivariable regression analysis to assess the association between type of stent and outcomes. **a. Results of multivariable logistic regression analysis to assess the association between type of stent and EBD-related cholangitis and postoperative pancreatic fistula.** Odds ratio of EBD-related cholangitis is adjusted for patient characteristics (i.e. age, sex, BMI, and ASA score), site of origin, and neoadjuvant therapy. Odds ratio for postoperative pancreatic fistula adjusted for patient characteristics (i.e. age, sex, BMI, and ASA score), hospital volume, neoadjuvant therapy, site of origin, pancreatic duct diameter, and pancreatic texture. **b. Results of multivariable linear regression analysis to assess the association between type of stent and length of hospital stay.** The beta coefficient of length of hospital stay is adjusted for patient characteristics (i.e. age, sex, BMI, and ASA score), hospital volume, site of origin, neoadjvant therapy, pancreatic texture, and major postoperative complications

underwent preoperative biliary drainage.[16,17] The relatively high percentage of preoperative drainage in the current study might be a reflection of lack of awareness of the proper indication as stated in the guidelines.[2]

tThe European guideline published in 2018 explicitly recommends the use of SEMS in patients who undergo preoperative EBD.[2] This recommendation is mainly based on a meta-analysis that showed significantly lower rates of endoscopic reinterventions and postoperative pancreatic fistula in patients treated with SEMS compared to plastic stents (3.4% vs. 14.8% and 5.1% vs. 11.8%, respectively).[18] This study shows, however, that over 50% of all patients still received a plastic stent. Which is particularly remarkable as currently neoadjuvant chemo(radio)therapy is increasingly administered to patients with pancreatic cancer. In the Netherlands both the recently completed PREOPANC-1 trial (NL3525; https://www.trialregister.nl/trial/3525) and the ongoing PREOPANC-2 trial (NL7094; https://www.trialregister.nl/trial/7094) advise the use of (fully covered) SEMS prior to start of neoadjuvant treatment.[19] Naturally, the percentage of patients with neoadjuvant therapy was higher in the SEMS group, but still a considerable proportion of patients with neoadjuvant therapy received a plastic stent (35%). Even though data revealed that delay until start of neoadjuvant treatment was shorter in patients with a SEMS and stent patency was longer.[3,20] There could be several reasons for these relatively high percentages of plastic stents in all patients and the subgroup with neoadjuvant therapy. First, most patients received a stent before being discussed in the MDT meeting in a pancreatic center (69.6%). If drainage is performed before staging, a plastic stent is often preferred by the radiologist as scattering from the metallic stent might hamper adequate interpretation of tumor staging. After staging, but before pathological confirmation, as well plastic as fully covered SEMS could be placed. In this scenario the European guideline recommends against uncovered SEMS, because these cannot be removed without surgery.[2] Second, the higher costs of initial SEMS placement compared to plastic stent placement probably also play a major role in the current findings. Dutch costs for initial stent placement for palliation including secondary procedures in case of initial failure were €1973 for a SEMS and €1042 for a plastic stent ($p = 0.001$).[21] However, cost-effectiveness of SEMS placement has been demonstrated in patients who received neoadjuvant therapy (United States' costs of the index ERCP, procedural adverse events, and adverse events from stent occlusion based on actual hospital charges: fully covered SEMS €36.978 vs. uncovered SEMS €37.304 vs. plastic €35.937), as the stent itself is more expensive, but SEMS have higher patency rates and render less adverse events.[3,22] Finally, the new guideline was published in September 2018 and therefore the implementation time was short, however, the results of the Dutch randomized trial were already published in 2016 and were given much attention in the Netherlands.[2,23] As it is known that implementation of new or updated guidelines often requires several years and is affected by multiple factors, e.g. quality of guidelines and characteristics of health care professionals such as age and country of training.[24,25] Even in a small and organized country as the Netherlands, it has been shown that one year after implementation guideline compliance in pancreatic cancer was poor.[24] This is also shown for other countries and cancer types.[26–28] A nationwide implementation strategy addressing both pancreatic centers and regional referral networks might increase the use of SEMS, as recommended by the European guideline, and is currently carried out within the PACAP-1 trial.[29]

Table 3 Postoperative outcomes

Variable	All patients (n = 575), n (%)	SEMS[a] (n = 246), n (%)	Plastic stents (n = 329), n (%)	Pooled p-value
Major postoperative complication	148 (25.7)	58 (23.6)	90 (27.4)	0.316
Any complication during hospital admission/30 days after surgery	363 (63.1)	161 (65.4)	202 (61.4)	0.397
Postoperative pancreatic fistula, grade B/C	85 (14.8)	24 (9.8)	61 (18.5)	**0.004**
Delayed gastric emptying, grade B/C	110 (19.1)	39 (15.9)	72 (21.9)	0.100
Post pancreatectomy hemorrhage, grade B/C	33 (5.7)	11 (4.5)	23 (7.0)	0.236
Bile leakage, grade B/C	25 (4.3)	13 (5.3)	12 (3.6)	0.351
Chyle leak, grade B/C	44 (7.7)	18 (7.3)	25 (7.6)	0.776
Pneumonia	34 (5.9)	18 (7.3)	16 (4.9)	0.245
Wound infection	89 (15.5)	41 (16.7)	48 (14.6)	0.487
Intensive care unit admission	49 (8.5)	20 (8.1)	29 (8.8)	0.652
Reintervention	141 (24.5)	54 (22.0)	87 (26.4)	0.211
Endoscopic	26 (5.2)	13 (5.3)	14 (4.3)	0.553
Radiological	109 (19.0)	40 (16.3)	69 (21.0)	0.164
Reoperation	40 (7.0)	15 (6.1)	25 (7.6)	0.529
In-hospital mortality	8 (1.4)	4 (1.6)	4 (1.2)	0.603
Length of hospital stay, mean (SE)	16.0 (0.6)	14.0 (0.6)	17.4 (1.0)	**0.005**
Readmission within 30 days after discharge	80 (13.9)	32 (13.0)	48 (14.6)	0.598

Bold numbers indicate statistical significance; numbers in the SEMS and plastic stent group do not always equal the total cohort, because of rounding due to the imputation.
[a] SEMS: self-expandable metal stents.

Several baseline characteristics differed between patients in the SEMS and plastic stent groups. Differences in pancreatic texture and site of origin were probably related to neoadjuvant therapy. The higher ASA score of patients with SEMS remains unexplained. The moment of registration of the ASA score is unknown. It could be that in patients with neoadjuvant therapy the ASA score increases during treatment and that this score is registered after treatment shortly before resection. More patients with a SEMS received neoadjuvant therapy and it might be speculated that this (partly) causes the higher ASA score.

In this study, a similar rate of overall EBD-related complications was found in the SEMS and plastic stent groups, but patients receiving plastic stents had statistically significantly more EBD-related cholangitis compared to patients receiving SEMS. This might also be the explanation for the longer time to surgery in patients with a plastic stent. Surprisingly, the percentage of reinterventions was not higher in the plastic stent group. This could have been caused by an under registration, as the DPCA is a surgical audit in which gastroenterological variables may be registered less accurate.

It has been shown in previous studies that the frequency of EBD-related pancreatitis was higher in patients with SEMS as compared to plastic stents.[23,30] SEMS and particularly fully covered SEMS could hamper pancreatic duct out flow as compared to plastic stents which could increase the risk of post-ERCP pancreatitis.[31] In this nationwide study, it was not demonstrated that the post-ERCP pancreatitis rate was higher in patients with a SEMS, which was also confirmed by several other studies.[32,33] Currently, the multicenter SPHINX trial in the Netherlands is assessing whether an endoscopic sphincterotomy prior to biliary fully covered SEMS placement could decrease the incidence of post-ERCP pancreatitis (NL5130; https://www.trialregister.nl/trial/5130).

Major postoperative complications were similar between the SEMS group and plastic stent group. These results were comparable to the results of a meta-analysis.[18] Literature is contradictive about the association between type of stent and postoperative pancreatic fistula.[18,23,34] In the current cohort, after adjustment for patient characteristics (i.e. age, sex, BMI, and ASA score), hospital volume, neoadjuvant therapy, and other risk factors (i.e. BMI, pancreatic texture, and pancreatic duct diameter; in accordance with the alternative fistula risk score) in multivariable analysis, the odds of postoperative pancreatic fistula was statistically significantly lower for patient who received a SEMS.[13] It is thought that the higher odds of postoperative pancreatic fistula is related to pancreatic texture. The current binary classification of pancreatic texture does not cover all variations in pancreatic texture. After expansion of the SEMS, the pancreatic duct experiences more pressure and therefore fibrosis of the pancreatic texture increases. More fibrosis is likely related to less postoperative fistula.

The length of hospital stay was approximately three days shorter in patients who received a SEMS as compared to a plastic stent which is clinically relevant, because it reflects improved

recovery and may result in decreased hospital costs. This has not been previously described.[35] Although not completely clear this might be related to an increased rate of postoperative pancreatic fistula grade A, which is not covered in the Clavien Dindo score $\geq$3, and hence a longer time to functional recovery after surgery with plastic stents.

This study had several limitations. First, the retrospective character of this study causes missing information about for example center of stent placement, exact indication for EBD, severity of EBD-related complications, details about reinterventions for EBD-related complications, and stent replacement. Currently, to improve DPCA data quality even further, gastroenterological variables and definitions of EBD-related complications are critically reviewed by gastroenterologists and surgeons from the Dutch Pancreatic Cancer Group. Second, only patients who underwent a PD were included and therefore selection bias might have been introduced. Therefore, patients who had serious complications due to preoperative EBD and were not able to undergo surgery were not registered in the DPCA. This proportion of patients might be, however, negligible as in a randomized setting there was only 1 out of 120 patients who did not undergo surgery after initial preoperative EBD due to stent related complications.[1,23] The main strength of this study is the mandatory, nationwide aspect of the DPCA including data on all pancreatic resections in the Netherlands. A previous study reported a high quality of DPCA data.[36]

In conclusion, this nationwide study found that EBD prior to pancreatoduodenectomy still frequently involved plastic stents. SEMS placement seemed to be associated with lower risks of cholangitis, less postoperative pancreatic fistula, and a shorter postoperative hospital stay but not with an increased risk of pancreatitis. A nationwide implementation strategy addressing both pancreatic centers and regional referral networks might increase the use of SEMS, as recommended by the European guideline.

Acknowledgements

The authors thank all participants of the Dutch Pancreatic cancer Audit for their dedicated data collection.

Funding

The Dutch Pancreatic Cancer Project, including the Dutch Pancreatic Cancer Audit, received funding from the Dutch Cancer Society (KWF Kankerbestrijding; grant no. UVA2013-5842).

Conflict of Interest

None declared.

References

1. van der Gaag NA, Rauws EAJ, van Eijck CHJ, Bruno MJ, van der Harst E, Kubben FJGM *et al*. (2010) Preoperative biliary drainage for cancer of the head of the pancreas. *N Engl J Med* 362:129–137.
2. Dumonceau J-M, Tringali A, Papanikolaou I, Blero D, Mangiavillano B, Schmidt A *et al*. (2018) Endoscopic biliary stenting: indications, choice of stents, and results: European society of gastrointestinal endoscopy (ESGE) clinical guideline – updated October 2017. *Endoscopy*, 910–930.
3. Gardner TB, Spangler CC, Byanova KL, Ripple GH, Rockacy MJ, Levenick JM *et al*. (2016) Cost effectiveness and clinical efficacy of biliary stents in patients undergoing neoadjuvant therapy for pancreatic adenocarcinoma in a randomized controlled trial. 84: 460–466.
4. Adams MA, Anderson MA, Myles JD, Khalatbari S, Scheiman JM. (2012) Self-expanding metal stents (SEMS) provide superior outcomes compared to plastic stents for pancreatic cancer patients undergoing neoadjuvant therapy. *J Gastrointest Oncol* 3:309–313.
5. Seo DW, Sherman S, Dua KS, Slivka A, Roy A, Costamagna G *et al*. (2019) Covered and uncovered biliary metal stents provide similar relief of biliary obstruction during neoadjuvant therapy in pancreatic cancer: a randomized trial. *Gastrointest Endosc* 90:602–612. https://doi.org/10.1016/j.gie.2019.06.032 [Internet] e4. Available from:.
6. Von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche C, Vandenbroucke JP. (2007) Strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. *BMJ* 335.
7. Dindo D, Demartines N, Clavien P-A. (2004) Classification of surgical complications. *Ann Surg* 240:205–213 [Internet]. Available from: http://content.wkhealth.com/linkback/openurl?sid=WKPTLP:landingpage&an=00000658-200408000-00003.
8. Bassi C, Marchegiani G, Dervenis C, Sarr M. (2016) Pancreas the 2016 update of the International Study Group (ISGPS) definition and grading of postoperative pancreatic fistula: 11 Years after. *Surgery* 161:584–591. https://doi.org/10.1016/j.surg.2016.11.014 [Internet]. Available from:.
9. Wente MN, Bassi C, Dervenis C, Fingerhut A, Gouma DJ, Izbicki JR *et al*. (2007) Delayed gastric emptying (DGE) after pancreatic surgery: a suggested definition by the International Study Group of Pancreatic Surgery (ISGPS). *Surgery* 142:761–768.
10. Wente MN, Veit JA, Bassi C, Dervenis C, Fingerhut A, Gouma DJ *et al*. (2007) Postpancreatectomy hemorrhage (PPH)-An international study group of pancreatic surgery (ISGPS) definition. *Surgery* 142:20–25.
11. Besselink MG, Van Rijssen LB, Bassi C, Dervenis C. (2017) Pancreas Definition and classification of chyle leak after pancreatic operation : a consensus statement by the International Study Group on Pancreatic Surgery. *Surgery* 161:365–372.
12. Koch M, Garden OJ, Padbury R, Rahbari NN, Adam R, Capussotti L *et al*. (2011) Bile leakage after hepatobiliary and pancreatic surgery: a definition and grading of severity by the International Study Group of Liver Surgery. *Surgery* 149:680–688.
13. Mungroop TH, van Rijssen LB, van Klaveren D, Smits FJ, van Woerden V, Linnemann RJ *et al*. (2019) Alternative fistula risk score for pancreatoduodenectomy (a-FRS). *Ann Surg* 269:937–943.
14. Jinkins LJ, Parmar AD, Han Y, Duncan CB, Sheffield KM, Brown KM *et al*. (2013) Current trends in preoperative biliary stenting in patients with pancreatic cancer. *Surgery* 154:179–189.
15. Bolm L, Petrova E, Woehrmann L, Werner J, Uhl W, Nuessler N *et al*. (2019) The impact of preoperative biliary stenting in pancreatic cancer: a case-matched study from the German nationwide pancreatic surgery registry (DGAV StuDoQ|Pancreas). *Pancreatology*. https://doi.org/10.1016/j.pan.2019.09.007 [Internet]. Available from:.
16. De Pastena M, Marchegiani G, Paiella S, Malleo G, Ciprani D, Gasparini C *et al*. (2018) Impact of preoperative biliary drainage on

postoperative outcome after pancreaticoduodenectomy: an analysis of 1500 consecutive cases. *Dig Endosc* 30:777–784.

17. Endo Y, Noda H, Watanabe F, Kakizawa N, Fukui T, Kato T *et al*. (2019) Bridge of preoperative biliary drainage is a useful management for patients undergoing pancreaticoduodenectomy. *Pancreatology* 19:775–780. https://doi.org/10.1016/j.pan.2019.06.013 [Internet]. Available from:.
18. Crippa S, Cirocchi R, Partelli S, Petrone MC, Muffatti F, Renzi C *et al*. (2016) Systematic review and meta-analysis of metal versus plastic stents for preoperative biliary drainage in resectable periampullary or pancreatic head tumors. *Eur J Surg Oncol* 42:1278–1285. https://doi.org/10.1016/j.ejso.2016.05.001 [Internet]. Available from:.
19. Versteijne E, van Eijck CHJ, Punt CJA, Suker M, Zwinderman AH, Dohmen MAC *et al*. (2016) Preoperative radiochemotherapy versus immediate surgery for resectable and borderline resectable pancreatic cancer (PREOPANC trial): study protocol for a multicentre randomized controlled trial. *Trials* 17:1–8. https://doi.org/10.1186/s13063-016-1262-z [Internet]. Available from:.
20. Nakamura K, Sho M, Akahori T, Nagai M, Nishiwada S, Nakagawa K *et al*. (2019) A comparison between plastic and metallic biliary stent placement in patients receiving preoperative neoadjuvant chemo-radiotherapy for resectable pancreatic cancer. *World J Surg* 43: 642–648. https://doi.org/10.1007/s00268-018-4820-6 [Internet]. Available from:.
21. Walter D, Van Boeckel PGA, Groenen MJ, Weusten BLAM, Witteman BJ, Tan G *et al*. (2015) Cost efficacy of metal stents for palliation of extrahepatic bile duct obstruction in a randomized controlled trial. *Gastroenterology* 149:130–138. https://doi.org/10.1053/j.gastro.2015.03.012 [Internet]. Available from:.
22. Ballard D, Rahman S, Ginnebaugh B, Khan A, Dua K. (2018) Safety and efficacy of self-expanding metal stents for biliary drainage in patients receiving neoadjuvant therapy for pancreatic cancer. *Endosc Int Open* 6:E714–E721.
23. Tol JAMG, Van Hooft JE, Timmer R, Kubben FJGM, Van Der Harst E, De Hingh IHJT *et al*. (2016) Metal or plastic stents for preoperative biliary drainage in resectable pancreatic cancer. *Gut* 65:1981–1987.
24. Van Rijssen LB, Van Der Geest LGM, Bollen TL, Bruno MJ, Van Der Gaast A, Veerbeek L *et al*. (2016) National compliance to an evidence-based multidisciplinary guideline on pancreatic and periampullary carcinoma. *Pancreatology* 16:133–137.
25. Davis DA, Taylor-Vaisey A. (1997) Translating guidelines into practice. A systematic review of theoretic concepts, practical experience and research evidence in the adoption of clinical practice guidelines. *Can Med Assoc J* 157:408–416.
26. Worhunsky DJ, Ma Y, Zak Y, Poultsides GA, Norton JA, Rhoads KF *et al*. (2015) Compliance with gastric cancer guidelines is associated with improved outcomes. *JNCCN J Natl Compr Cancer Netw* 13: 319–325.
27. Keikes L, van Oijen MGH, Lemmens VEPP, Koopman M, Punt CJA. (2018) Evaluation of guideline adherence in colorectal cancer treatment in The Netherlands: a survey among medical oncologists by the Dutch colorectal cancer group. *Clin Colorectal Cancer* 17:58–64. https://doi.org/10.1016/j.clcc.2017.10.007 [Internet]. Available from:.
28. Visser BC, Ma Y, Zak Y, Poultsides GA, Norton JA, Rhoads KF. (2012) Failure to comply with NCCN guidelines for the management of pancreatic cancer compromises outcomes. *HPB* 14:539–547.
29. MacKay TM, Smits FJ, Latenstein AEJ, Bogte A, Bonsing BA, Bos H *et al*. (2020) Impact of nationwide enhanced implementation of best practices in pancreatic cancer care (PACAP-1): a multicenter stepped-wedge cluster randomized controlled trial. *Trials* 21:1–18.
30. Liu P, Lin H, Chen Y, Wu Y-S, Tang M, Liu C. (2018) Comparison of metal and plastic stents for preoperative biliary drainage in resectable and borderline resectable periampullary cancer: a meta-analysis and system review. *J Laparoendosc Adv Surg Tech* 28:1074–1082.
31. Kawakubo K, Isayama H, Nakai Y, Togawa O, Sasahira N, Kogure H *et al*. (2012) Risk factors for pancreatitis following transpapillary self-expandable metal stent placement. *Surg Endosc* 26:771–776.
32. Olsson G, Frozanpor F, Lundell L, Enochsson L, Ansorge C, Del Chiaro M *et al*. (2017) Preoperative biliary drainage by plastic or self-expandable metal stents in patients with periampullary tumors: results of a randomized clinical study. *Endosc Int Open* 5:E798–E808.
33. Song TJ, Lee JH, Lee SS, Jang JW, Kim JW, Ok TJ *et al*. (2016) Metal versus plastic stents for drainage of malignant biliary obstruction before primary surgical resection. *Gastrointest Endosc* 84:814–821. https://doi.org/10.1016/j.gie.2016.04.018 [Internet]. Available from:.
34. Sun C, Yan G, Li Z, Tzeng CM. (2014) A meta-analysis of the effect of preoperative biliary stenting on patients with obstructive jaundice. *Medicine* 93:1–8.
35. Mullen JT, Lee JH, Gomez HF, Ross WA, Fukami N, Wolff RA *et al*. (2005) Pancreaticoduodenectomy after placement of endobiliary metal stents. *J Gastrointest Surg* 9:1094–1105.
36. Van Rijssen LB, Koerkamp BG, Zwart MJ, Bonsing BA, Bosscha K, van Dam RM *et al*. (2017) Nationwide prospective audit of pancreatic surgery: design, accuracy, and outcomes of the Dutch Pancreatic Cancer Audit. *HPB* 19:919–926.

Appendix A1. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.hpb.2020.06.009.