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Metal stents are safe and cost-effective for preoperative biliary drainage in resectable pancreaticobiliary tumours.

Short Title: SEMS versus Plastic PBD

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Abstract

BACKGROUNDS:

To compare the complication rates and overall costs of self-expandable metal (SEMS) and plastic stents (PS) in clinically indicated preoperative biliary drainage (PBD) prior to a pancreatoduodenectomy (PD).

METHODS:

We conducted an Australian multicentre retrospective cohort study using the databases of four tertiary hospitals. Adult patients who underwent clinically indicated endoscopic PBD prior to PD from 2010-2019 were included. Rates of complications attributable to PBD, surgical complications and pre-operative endoscopic re-intervention were calculated. Costing data was retrieved from our Financial department.

RESULTS:

Among the 157 included patients (mean age 66.6 ± 9.8 years, 45.2% male), 49 (31.2%) received SEMS and 108 received PS (68.8%). Baseline bilirubin was 187.5 ± 122.6 µmol/L. Resection histopathology showed mainly adenocarcinoma (93.0%).

Overall SEMS was associated less complications (12.2% vs 28.7%, P=0.02) and a lower pre-operative endoscopic re-intervention rate (4.3 vs 20.8%, P=0.03) compared with PS. There was no difference in post-PD complication rates.

On multivariate logistic regression analysis, stent type was an independent risk factor of PBD complication (OR of SEMS compared to PS 0.24, 95% CI 0.07-0.79, P=0.02) but not for any secondary outcome measures.

Upfront material costs were $56USD for PS and $1991USD for SEMS. Accounting for rates of complications, average costs were similar ($3110USD for PS and $3026USD for SEMS).

CONCLUSION:

In resectable pancreaticobiliary tumours, SEMS for PBD was associated with reduced risk of overall PBD-related complications and pre-surgical endoscopic reintervention rates and was comparable to PS in terms of overall cost.

Key Words

Pancreatoduodenectomy, Pancreaticoduodenectomy, Biliary Drainage, Pancreatic Cancer, Metal Stents

Article

INTRODUCTION

Obstructive jaundice is the most common and significant sequelae of pancreaticobiliary masses.[1] There is conflicting evidence regarding whether preoperative biliary drainage (PBD) should be performed for resectable pancreatic head cancer.[2] Furthermore, there is uncertainty regarding the efficacy and safety of PBD in malignant obstructive jaundice compared to direct surgery (DS).[3,4] Despite controversy, PBD remains in guidelines for certain indications.[5] Although 10mm diameter self-expandable metal stents (SEMS) are currently recommended for PBD,[5] plastic stents (PS) remain widely in practice[6,7] due to concerns over cost-effectiveness with SEMS.[8] The clinical benefits of SEMS over PS and optimum duration for PBD remains controversial. A 2016 prospective study demonstrated over a four-week period of PBD, patients who received SEMS had lower rates of PBD-related complications compared to those who received PS.[9] However, this was not replicated in both a 2016 randomised trial and 2019 retrospective study with significantly different mean PBD durations with both demonstrating no difference in PBD-related complications.[6,7] A 2018 meta-analysis of four trials showed that SEMS usage in PBD had significantly lower rates of re-intervention and cholangitis.[10] However, in the same meta-analysis, SEMS were associated with higher rates of pancreatitis. Cholecystitis has also been reported post-SEMS insertion.[11] Further evidence is required to establish improved clinical outcomes with SEMS in PBD. Greater focus on healthcare costs associated with stent type is also required.

We conducted a multicentre, retrospective cohort study of adult patients comparing outcomes of SEMS and PS for PBD in resectable pancreaticobiliary malignancies with respect to incidence of PBD-related complications and re-intervention rates. We also performed cost analyses for stent type and PBD-related complications.

METHODS

Study population and data sources

Data was collected from four tertiary hospital centres in Victoria, Australia by using coded searches for pancreatoduodenectomies (PD) (procedures involving the ICD-10 code 0FTG0ZZ) performed from 2010 to 2019. A further subsearch within this cohort for endoscopic retrograde cholangiopancreatography (ICD-10 code 0FJB8ZZ and OFJD8ZZ) was then conducted. These

centres serve a combined catchment area of 3.25 million patients. Each participating centre had a dedicated hepatobiliary department experienced in pancreaticobiliary resections. The study was approved by the Human Research Ethics Committee of Monash Health for all centres (RES-19-0000256A-52970).

We initially included all adult patients who underwent PBD prior to PD for presumed pancreaticobiliary malignancy. We then retrospectively assessed whether PBD was performed for one of the following indications (definitions listed in Table S1): a) cholangitis, b) symptomatic jaundice, c) delayed surgery or d) planned for neoadjuvant chemotherapy, to be consistent with generally accepted guidelines for PBD.[5] We excluded cases where PBD was performed for an indication not listed above and if PBD was not performed endoscopically. The surgical approaches observed in this study were the pylorus-preserving PD and classic Whipple procedure.

Endoscopic preoperative biliary drainage

Endoscopic PBDs were performed by gastroenterologists or hepatobiliary surgeons at the participating centres. Both fully-covered and uncovered SEMS were included, with all varieties included being 10mm diameter. SEMS type was not assessed as different during analysis. Brands and models of stents were dependent on local supply. All cases of PBD were categorised and analysed by initial type of stent inserted. All cases that required re-intervention with re-stenting were performed endoscopically.

Outcome measures

The primary outcome was complication rates related to PBD, including overall rates as a composite of individual complications, up to time of surgery, resulting in reintervention, readmission to hospital or death. The secondary outcomes were rates of endoscopic re-intervention requiring re-stenting prior to surgery, readmission rates for complications related to PBD, length of hospital stay following complication related to PBD, rates of surgical complications, length of intensive care unit stay following surgery, and 90-day mortality rates after surgery. The definitions of complications related to PBD, and surgery are listed in Table S2. To provide a uniform standard of data collection, each centre received the same criteria for complications and other outcomes. To reduce bias, each centre, had two investigators independently evaluate and record complications. Only complications that were recorded by both

investigators were listed as complications in the final dataset. In the event of disagreement, a third investigator made the final decision on inclusion.

Data from each centre was added to REDCap (Vanderbilt University, Nashville, TN). Each centre was able to view and edit their own entered data however only the study coordinators were able to access the entire dataset.

Statistical analysis

Baseline patient demographics, endoscopic adverse events and surgical outcomes were presented using mean and standard deviations for normally distributed continuous variables, median and range for nonnormally distributed continuous variables, and frequency and proportion for categorical variables. Comparisons between groups were performed using the 2-sample *t* test for parametric continuous variables and Wilcoxon rank sum test for nonparametric continuous variables. For categorical variables, Pearson χ^2 test was used for variables with more than two categories and Fisher's exact test was used for binary variables.

A univariate logistic regression analysis was performed, with only those variables with a pre-set cut-off for significance of P value <0.10 used to identify potential predictor variables for the construct of the multivariable model. Multivariate logistic regression analysis was subsequently performed, adjusted for age, gender, stent length, and bilirubin level, which were candidate predictors selected a priori, to assess the risk of PBD-related and surgical complications between the two groups. Collinearity and interactions between concurrent predictors in the adjusted model were tested. A link test was used to assess specification error of the adjusted model. Goodness-of-t for the logistic regression was assessed using a Hosmer and Lemeshow goodness-of-t test. Any missing data was classified as missing completely at random and was removed through a process of pairwise deletion analyses to increase power in our chosen regression models.

Kaplan–Meier estimates were used to depict longitudinal incidence rates of complications during follow-up of both cohorts. Date of PD was defined as the endpoint. Log-rank tests were performed to compare Kaplan-Meier estimates of complication rates.

Statistical significance was determined at P<0.05 and two-sided P values were reported for comparison of all outcome measures. Statistical analysis was performed using Stata V.13 (StataCorp LP, College Station, TX).

Costing

Upfront material and mean admission costs for each PBD-related complication were obtained from the Financial department of our principal centre for FY2013-2019 (data beyond FY2013 was not available). Admission costs were derived from coding as no differentiation was made by our Financial department for de novo and post-procedural complication presentations (i.e. de novo pancreatitis and post-ERCP pancreatitis were not differentiated by the Financial department). Expected costs were derived by multiplying mean admission costs with the observed event rate of each PBD complication.

RESULTS

310 patients underwent PD from 2010 to 2019, of which, 157 underwent clinically indicated endoscopic PBD. Of included patients, 49 received SEMS (31.2%) and 108 received PS (68.8%). Of the 49 SEMS inserted, 44 (89.8%) were fully-covered and five (10.2%) were uncovered SEMS. Baseline demographics and clinical characteristics of the two groups were similar except for stent type in patients who underwent neoadjuvant chemotherapy, stent length and bilirubin level on the day of surgery (Table 1). All patients achieved adequate drainage by time of surgery, defined as greater than 50% reduction in bilirubin from baseline or resolution of symptoms. There was no difference in overall mean reduction in bilirubin from baseline ($\Delta 139.5 \pm 16.6 \mu mol/L$ vs $\Delta 150.4 \pm 12.0 \mu mol/L$, P=0.60).

Two patients who initially received SEMS underwent re-stenting. In both cases, PS were inserted upon re-intervention. 21 patients who initially received PS were re-stented, of which 3 were with SEMS and 18 with PS. There were no recorded cases where patients required a second re-stenting prior to surgery.

There was no difference in mean time to surgery between the SEMS and PS group (50.1 ± 9.6 days vs. 47.2 ± 7.2 days, P=0.82). Tissue characteristics on resection between the groups did not differ (Table S3).

The overall rate of PBD-related complications, which included any patient who developed one or more PBD-related complication, was lower in the SEMS group compared to PS (12.2% vs. 28.7%, P=0.024) (Table 2). Median time to any complication in the PS group was 7 days, as compared with SEMS (11 days, P=0.08) (Figure 1a). Three patients (1.9%) developed more than

one PBD-related complication prior to surgery. There was no difference in individual rates of PBD-related complications between the groups (Figure 1b-d).

Table 3 shows the results of univariate and multivariate logistic regression analyses of risk factors in relation to development of PBD-related complications. Stent type was shown to be an independent risk factor for PBD-related complications with the odds ratio of SEMS compared to PS being 0.24 on multivariate analysis (95% CI, 0.07-0.79, P=0.02). Stent type was not a risk factor for surgical or post-surgical adverse events nor other secondary outcome measures.

Secondary outcomes are described in Table 4. Pre-surgical endoscopic re-intervention rates were lower with SEMS compared to PS (4.3% vs. 20.8%, P=0.03). Median time to endoscopic re-intervention was 9 days in the PS group and 24 days in the SEMS group (P=0.01) (Figure 1e). There was no difference in surgical-related complication rates between the groups. There was no difference in readmission rates at 30 days post-PBD (Figure 1f), readmission length of stay, post-surgical intensive care unit length of stay or mortality rates at 90 days post-surgery.

Full costing data is reported in Table S4. The average upfront material costs were $82AUD for PS and $2900AUD for SEMS. Average costs for admissions with each complication as a principal diagnosis were identified. The predicted cost of using PS and SEMS were similar ($4529AUD PS vs. $4408AUD SEMS).

DISCUSSION

In this multicentre retrospective cohort study, we investigated the impact of patients who received SEMS to those who received PS for PBD prior to PD. We found that PBD with SEMS resulted in lower overall rates of PBD-related complications and endoscopic re-intervention. To our knowledge, for the first time, we report that use of SEMS for PBD was independently associated with lower rates of pre-surgical complications and on formal cost analysis results in no difference in overall cost compared to PS.

Overall complications attributable to PBD were lower with SEMS compared to PS, as reported previously.[9] Although not significant, cholangitis rates were much lower with SEMS compared to PS. Lower rates of cholangitis and stent occlusion with SEMS were important reasons for lower endoscopic re-intervention rates observed in our study. Although pancreatitis and cholecystitis have been associated with SEMS,[10,11] our study demonstrated no difference compared to PS.

We identified on logistic regression analysis that SEMS use was an independent predictor of lower rates of pre-surgical complications. Although this result supports our findings of lower PBD complication rates in patients who received SEMS, there are other important implications for this finding. In our study, similar to other observational studies, the majority of stents initially inserted or utilised for re-insertion were PS. Conventionally, PS occlusion is assumed to occur due to gradual accumulation of biliary sludge, resulting in eventual failure after many weeks.[1,9] Our stent complication Kaplan-Meier curves demonstrate PS fail early after insertion. As such, our data suggests even when resection is planned early, PS use still poses significant risk for stent-related complications.

SEMS and PS may have similar overall costs when used for PBD. Despite initial higher upfront costs of SEMS, after factoring in rates and costs of complications and readmissions, we demonstrated no difference in overall costs between SEMS and PS. Given lower rates of complications and re-intervention, SEMS use upfront for PBD could improve patient experience and reduce burden of admissions on the healthcare system.

Our study was limited by retrospectively assessing the circumstances regarding PBD. How operators chose between SEMS and PS was unknown. Given our demographic findings, we surmise SEMS were chosen if patients were to receive neoadjuvant therapy, however it is not known if other patient factors may have influenced this choice. Similarly, the type of SEMS chosen was unknown. Similarly, the type of SEMS chosen was unknown. Although the majority of SEMS were fully-covered, we included fully-covered and uncovered varieties to reflect current clinical practice where this decision is usually operator driven. We also excluded certain cases of PBD that did not meet current indication guidelines however this may have excluded potentially important unrecognised indications. Although all PDs assessed were performed for presumed malignancy, we tried to reflect real-world practice by including cases where benign disease was revealed on histology post-resection.

Ideal PBD duration has not been established. Previous studies have suggested a minimum four weeks[1,3] however this was not a strict guideline within any of our centres nor has it been in previous studies.[6,7] The mean duration of PBD was similar between our two groups with no difference in post-surgical complication rates. SEMS use itself predicted lower pre-surgical complication rates and stent failure tended to occur early. This may suggest a minimum duration

of PBD may not be necessary and that other factors such as stent type and bilirubin reduction may predict successful outcomes.

PBD remains clinically relevant however further research is required to optimise practice. As previous studies comparing PBD to DS have focused on PS use, head-to-head comparison between PBD with SEMS and DS may yield important results, especially with PD becoming a more centralised, specialist procedure with increasing wait times.

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Disclosure Statement:

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Figure Legend

Figure 1 – Kaplan-Meier Curves for the Primary Outcome, Re-intervention and Readmissions

Panel A shows the overall incidence of PBD-related complications. Panel B shows the incidence of pancreatitis attributed to PBD. Panel C shows the incidence of cholangitis attributed to PBD. Panel D shows the incidence of stent occlusion without cholangitis attributed to PBD. Panel E shows the incidence of pre-surgical re-intervention requiring re-stenting. Panel F shows the incidence of readmissions related to PBD-related complications. All P values are two-sided.

List of Supporting Information

Table S1 – Definitions of the indications for PBD

Table S2 – Definitions of complications

Table S3 – Tissue characteristics on resections

Table S4 – Predicted costs of using PS and SEMS

Table

Table 1 – Baseline demographic and clinical characteristics of the study population

	Obs	PS (N=108)	SEMS (N=49)	P-value
Age – yr (mean ± SD)	157	66.3 ± 9.4	67.2 ± 10.7	0.63
Sex – male (%)	157	62 (57.4%)	24 (49.0%)	0.33
Pre-op tissue diagnosis – yes (%)	151	59 (57.7%)	33 (68.1%)	0.23
Neoadjuvant chemoradiotherapy – yes (%)	152	2 (1.9%)	9 (18.4%)	<0.001
Stent length – cm (median, IQR)	143	7 (5-7)	6 (4-6)	<0.001
Ca19-9 baseline – kU/L (median, IQR)	98	136 (41-325)	196 (49-587)	0.19
Bilirubin baseline – umol/L (median, IQR)	139	182 (102-257)	163 (80-250)	0.33
Bilirubin day of surgery – umol/L (median, IQR)	149	26 (17-46)	16 (12-28)	0.002
ΔBilirubin – umol/L (mean ± SD)	139	150.4 ± 12.0	139.5 ± 16.6	0.60

Interval to surgery post-PBD (mean ± SD)	157	47.2 ± 7.2	50.1 ± 9.6	0.82

Table 2 – Rates of complications related to PBD from time of PBD to time of surgery

	PS (N=108)	SEMS (N=49)	P-value
Overall PBD-related complications – no. (%)	**33 (28.7%)**	**5 (12.2%)**	**0.024**
Pancreatitis – no. (%)	6 (5.9%)	2 (4.3%)	0.68
Cholangitis – no. (%)	14 (12.8%)	2 (4.3%)	0.11
Perforation – no. (%)	0 (0%)	0 (0%)	NA
Haemorrhage – no. (%)	2 (2.0%)	0 (0%)	0.33
Stent occlusion w/o cholangitis – no. (%)	11 (9.8%)	1 (2.1%)	0.09

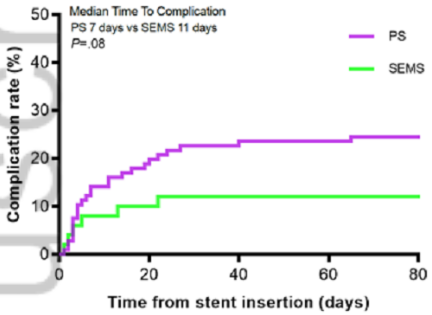
Table 3 – Univariate and multivariate logistic regression analyses for complications related to PBD

	Univariate				Multivariate			
	OR	SE	P-value	95% CI	OR	SE	P-value	95% CI
Age	1.00	0.02	0.79	0.96-1.05	1.00	0.02	0.86	0.96-1.05
Gender	0.85	0.40	0.73	0.34-2.15	0.86	0.38	0.73	0.36-2.03
Bilirubin baseline	0.99	0.02	0.63	0.99-1.00	0.99	0.02	0.91	0.99-1.00
Stent type (SEMS vs. PS)	**0.33**	**0.16**	**0.03**	**0.13-0.85**	**0.24**	**0.15**	**0.02**	**0.07-0.79**
Stent length	0.92	0.09	0.36	0.76-1.10	0.90	0.11	0.39	0.72-1.14
Time from stent to surgery	1.00	0.002	0.102	0.99-1.01				

Table 4 – Secondary outcomes

Complication	PS (N=108)	SEMS (N=49)	P-value
Endoscopic re-intervention pre-surgery – no. (%) **PS** **SEMS**	**22 (20.8%)** **20 (18.8%)** **2 (2.0%)**	**2 (4.3%)** **2 (4.3%)** **0 (0%)**	**0.03**
Overall surgical complications – no. (%)	40 (37.0%)	20 (40.8%)	0.65
Surgical leak[†] – no. (%)	18 (16.8%)	6 (12.8%)	0.83
Pancreatic fistula – no. (%)	25 (23.4%)	6 (12.8%)	0.13
Intraabdominal abscess – no. (%)	14 (12.8%)	8 (17.0%)	0.49
Wound infection – no. (%)	14 (12.8%)	11 (23.4%)	0.10
Bowel ischemia – no. (%)	0 (0%)	0 (0%)	NA
[†]Surgical leaks are defined in Supporting Table 1			

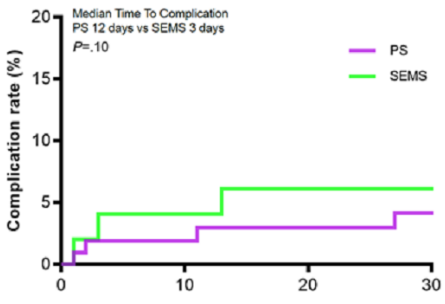
A. Overall PBD-related complications



Number at Risk Table:

Time	0	20	40	60	80
PS	106	86	82	82	81
SEMS	50	46	45	45	45

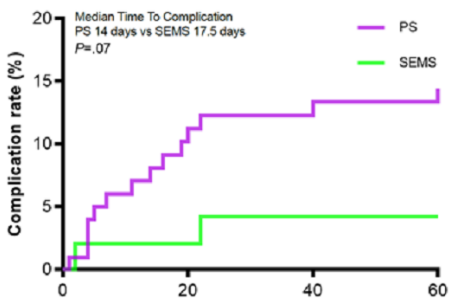
B. PBD-related pancreatitis



Number at Risk Table:

Time	0	10	20	30
PS	106	93	86	83
SEMS	50	47	46	45

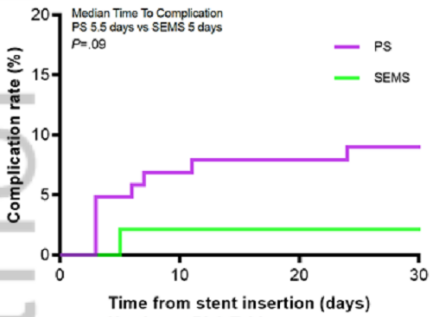
C. PBD-related cholangitis



Number at Risk Table:

Time	0	20	40	60
PS	106	86	82	81
SEMS	50	46	45	44

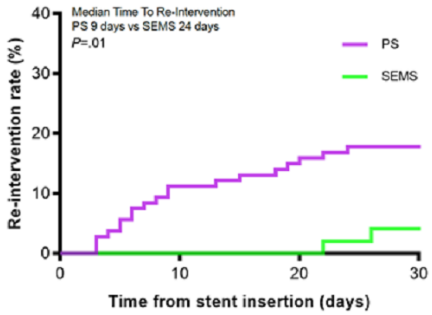
D. PBD-related stent occlusion



Number at Risk Table:

Time	0	10	20	30
PS	106	93	86	83
SEMS	50	46	45	44

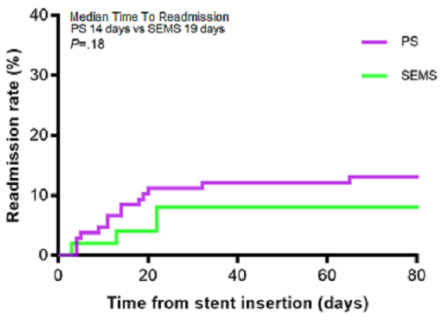
E. Endoscopic re-intervention pre-surgery



Number at Risk Table:

Time	0	10	20	30
PS	107	97	91	89
SEMS	50	50	50	48

F. Readmissions due to PBD-complication



Number at Risk Table:

Time	0	20	40	60	80
PS	107	96	95	95	94
SEMS	50	49	48	48	48

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