



Title	Risk factors for recurrent biliary obstruction following endoscopic biliary stenting in patients with unresectable ampullary cancer : A multicenter retrospective study
Author(s)	Sugiura, Ryo; Kuwatani, Masaki; Kin, Toshifumi et al.
Citation	Journal of Digestive Diseases, 25(5), 310-317 https://doi.org/10.1111/1751-2980.13288
Issue Date	2024-06-20
Doc URL	https://hdl.handle.net/2115/95734
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Type	journal article
File Information	HUSCAP_DDSJ-D-23-00864.pdf



Risk factors for recurrent biliary obstruction following endoscopic biliary stenting in patients with unresectable ampullary cancer

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Author's contribution: R.S. designed the research, performed the research (data acquisition and data analysis), and wrote the manuscript; M.K. performed the research (data analysis) and wrote the manuscript and critical revision; T.K., R.M., Y.I., I.S., K.H., M.Y., Y.M., M.O., H.H., H.Y., M.O., H.N., Y.T., N.E., M.N., H.K., H.I., T.K., and S.K. performed the research (data acquisition) and critically reviewed the manuscript; A.K. supervised the entire research; all authors read and approved the final manuscript.

Funding Information: This work was supported by a research grant from Japan Gastroenterological Endoscopy Society Hokkaido Chapter.

Ethics approval: The present study protocol was in accordance with the ethical guidelines of the 1975 Declaration of Helsinki (revised in 2013). The Institutional Review Board of Hokkaido University Hospital and other cooperative institutes approved the study protocol (022-0072). This study was registered in the UMIN-CTR (clinical trial registration number: UMIN000050406).

Informed consent: Written informed consent was waived due to the retrospective observational nature

of the present study. Informed consent was obtained using an opt-out form.

Conflict-of-interest statement: Author A.K. has received consultant fee from Gadelius Medical and lecture fee from Olympus Medical Systems. The other authors declare no Conflict of Interests.

Acknowledgement: We express our deepest appreciation to the gastroenterological endoscopists at each institution.

Abstract

Background: Unresectable ampullary cancer (AC) is a rare disease entity. The risk factors for recurrent biliary obstruction (RBO) following endoscopic biliary stenting (EBS) for unresectable AC remain unknown. The present study therefore aimed to identify risk factors for RBO following palliative EBS in patients with unresectable AC.

Methods: This multicenter retrospective observational study enrolled consecutive patients with unresectable AC who underwent palliative EBS between April 2011 and December 2021. The primary outcome was risk factors for RBO following palliative EBS via multivariate analysis.

Results: The study analysis comprised a total of 107 patients with a median age of 84 years (interquartile range, 79–88), of whom 63 (58.9%) were men. A plastic stent (PS) or a self-expandable metal stent (SEMS) was placed in 53 and 54 patients, respectively. Functional success was accomplished in 104 patients (97.2%). Of these, RBO occurred in 62 patients (59.6%), with obstruction and complete/partial migration occurring in 47 and 15 patients, respectively. The median time to RBO was 190 days. Multivariate analysis showed that the use of a PS was associated with a higher rate of RBO compared to the use of a SEMS (hazard ratio=2.48; $P<0.01$) and that the presence of bile duct stones/sludge immediately after EBS was an independent risk factor for RBO (hazard ratio=1.99; $P=0.04$).

Conclusions: The use of a SEMS compared to a PS during EBS reduced the time to RBO in patients with unresectable AC. The presence of bile duct stones/sludge immediately after EBS was a risk factor

for RBO.

Keywords: ampullary cancer; endoscopic biliary stenting; plastic stent; recurrent biliary obstruction;
self-expandable metal stent

Introduction

Ampullary cancer (AC) arises from the ampullary complex, which is distal to the confluence of the common bile duct (CBD) and the pancreatic duct. The incidence of AC is reported to be less than 100,000 inhabitants per year and to account for only 0.2% of all gastrointestinal malignancies [1, 2]. Unlike pancreatic and bile duct cancers, which are often at advanced stages by the time patients are symptomatic, jaundice typically develops early in the progression of AC due to obstruction of biliary outflow [3]. Curative surgical resection is reportedly feasible in 95% of patients with AC [4]. Accordingly, cases of unresectable AC are rare.

Endoscopic biliary stenting (EBS) is the standard biliary drainage method in cases of malignant distal biliary obstruction (MDBO). The recent European Society of Gastrointestinal Endoscopy clinical guidelines recommend the use of a self-expandable metal stent (SEMS) during palliative EBS for MDBO due to a lower risk of stent blockage compared to the use of plastic stents (PS) in cases of AC [5] as well as MDBO due to other reasons [6]. However, guidelines for the management of AC are predominantly based studies that comprised a small proportion of patients with AC [5] due to the low incidence, early presentation, and operability of AC. Biliary stents appear be more frequently migrate in patients with AC compared to other cancers due to short anatomical biliary strictures that typically occur in AC. MDBO due to AC differs compared to other malignancies in terms of the anatomical site of origin. Few previous studies have evaluated palliative EBS for MDBO due to AC [7] or periampullary tumors [8]. In addition, the risk factors for recurrent biliary obstruction (RBO) following

EBS in patients with unresectable AC remain unknown. The present study therefore aimed to identify risk factors for RBO following palliative EBS in patients with unresectable AC.

Methods

The present study protocol was in accordance with the ethical guidelines of the 1975 Declaration of Helsinki (revised in 2013). The Institutional Review Board of Hokkaido University Hospital and other cooperative institutes approved the study protocol (022-0072). Written informed consent was waived due to the retrospective observational nature of the present study. Informed consent was obtained using an opt-out form. This study was registered in the UMIN-CTR (clinical trial registration number: UMIN000050406).

Study design

This multicenter retrospective observational study was conducted at 19 institutions in Hokkaido, Japan. Individual databases maintained by each institute were searched for consecutive patients with AC between April 2011 and December 2021. The inclusion criteria of the present study were as follows: 1) patients who were diagnosed with AC by pathological analyses, 2) patients who underwent EBS, and 3) agreement to enrollment in the present study by patient or their families as recorded on the opt-out form. The exclusion criteria of the present study were as follows: 1) patients who underwent curative surgery, 2) patients who underwent endoscopic papillectomy, 3) patients who underwent

endoscopic ultrasound-guided biliary drainage until the initial EBS, 4) patients who underwent insertion of multiple stents, 5) patients with MDBO due to metastatic malignancy, and 6) refusal for enrollment in the present study by patients or their families.

Endoscopic procedures

Written informed consent was obtained from all patients prior to endoscopic retrograde cholangiography and EBS. PS or SEMS were placed across the periampullary stricture under fluoroscopic and endoscopic guidance. EBS was achieved using a 7-Fr, 8.5-Fr, or 10-Fr PS (straight or double-pigtail) or an 8-mm or 10-mm diameter SEMS (fully covered, partially covered, or uncovered). The type of stent used and decision to perform endoscopic sphincterotomy was at the discretion of the endoscopist. If CBD stones or sludge were noted during endoscopic retrograde cholangiography, the decision to perform endoscopic stone extraction was at the discretion of the endoscopist.

Definitions

AC was categorized into two groups according to gross appearance: non-exposed tumor type (bulging papilla covered with a normal duodenal mucosa) and exposed tumor type (bulging papilla overlying cancerous mucosa with or without ulceration). RBO was defined as an exacerbation of jaundice or cholangitis requiring biliary decompression after insertion of a PS or SEMS, as previously described

[9]. RBO was classified according to the underlying cause of migration and occlusion. Stent migration was assessed using a roentgenogram. Complete stent migration was defined as the entire stent migrating into the alimentary tract or bile duct across the biliary stricture. Partial migration was defined as the stent partially migrating from the original drainage position across the biliary stricture to the proximal or distal side of the duct. Functional success was defined as any one of the following: (a) a decrease in serum total bilirubin (T-BIL) from >2.0 mg/dL to ≤ 2.0 mg/dL, (b) a decrease in serum T-BIL by greater than 50% from >2.0 mg/dL within two weeks, (c) a 50% or greater decrease in hepatobiliary enzyme levels in cases with a serum T-BIL of 2.0 mg/dL or less within two weeks, or (d) no subsequent increase in serum T-BIL level of >2.0 mg/dL or hepatobiliary enzymes due to palliative EBS in the case of a decrease in serum T-BIL from >2.0 mg/dL to ≤ 2.0 mg/dL and/or a 50% or greater decrease in hepatobiliary enzyme levels after previous biliary drainage. Adverse events following palliative EBS were assessed according to the severity grading system of the American Society for Gastrointestinal Endoscopy lexicon.¹⁰

Outcome measures

The primary outcome of the present study was risk factors for RBO following palliative EBS. Multivariate analysis included the following variables: age (>84 or ≤ 84 years), sex (male or female), tumor type (exposed tumor or non-exposed tumor type), longest tumor dimension (>16 or ≤ 16 mm), CBD diameter (>17 or ≤ 17 mm), main pancreatic duct diameter (>3.5 or ≤ 3.5 mm), serum T-BIL level

before initial EBS (>3.2 or ≤ 3.2 mg/dL), endoscopic sphincterotomy during palliative EBS (presence or absence), pre-biliary drainage (presence or absence), stent type (SEMS or PS), CBD stones or sludge immediately after palliative EBS (presence or absence), and palliative chemotherapy (presence or absence). The median value of continuous variables was used as the cutoff value when evaluating risk factors for RBO. Secondary outcomes were functional success rate, clinical details of RBO, cumulative rate of RBO, and adverse events.

Statistical analysis

Statistical analyses were performed using EZR, which is a free statistical software [11]. Categorical variables were presented as percentages. Continuous variables were presented as the median and interquartile range (IQR). Categorical variables were compared using Fisher's exact test. The cumulative rates of RBO and survival from the day of EBS were estimated using the Kaplan-Meier method, with differences groups evaluated using the log-rank test. Regarding cumulative rates of RBO, patients were censored for the following reasons: death without RBO, loss from follow-up, stent migration without RBO, scheduled stent exchange, conversion to palliative biliary bypass surgery, or re-intervention due to drainage-related adverse events. Risk factors for RBO following EBS were analyzed using Cox proportional hazard analysis. The selection of variables was performed using a stepwise procedure with the Akaike information criterion (AIC) [12]. *P*-values less than 0.05 were considered statistically significant.

Results

In total, 548 patients with AC were identified at participating institutions during the study period. Of these, 107 patients were included in the study analysis (Figure 1).

Baseline participant characteristics

The present study included 63 men and 44 women with a median age of 84 years (IQR, 79–88 years).

The predominant reason for the unresectability of AC was advanced age and/or decline in activities of daily living (n = 80, 74.1%). Exposed tumor and non-exposed tumor types were observed in 72 patients (67.3%) and 35 patients (32.7%), respectively. The median longest tumor dimension was 16.0 mm (IQR, 12.0–20.0 mm). The median CBD and main pancreatic duct diameters were 17.0 mm (IQR, 14.0–20.5 mm) and 3.5 mm (IQR, 2.0–6.0 mm), respectively. The presence of CBD stones or sludge immediately after EBS was observed in 22 patients (20.6%). Table 1 shows the baseline characteristics of study participants.

Details of EBS and related procedures

Table 2 shows the details of EBS and related procedures. Endoscopic sphincterotomy was performed during EBS in 14 patients (13.1%). A PS and a SEMS were inserted in 53 and 54 patients, respectively.

The predominant types of PS and SEMS used were straight PS (n = 47) and fully covered SEMS (n =

37), respectively. Of the 37 patients that received fully covered SEMS, a dumbbell-shaped fully covered SEMS (BONASTENT M-Intraductal, Standard Sci-Tech Inc., Seoul, Korea) was placed in three patients.

Clinical outcomes

The median follow-up period was 371 days (IQR, 143–627 days). The survival rates after the target EBS are shown in Figure 2a; the median period of survival was 597 days (95% confidence interval, 474–787 days). The survival rates were not significantly different between PS and SEMS groups (median survival day: PS, 625 days; SEMS 495 days; $P = 0.28$; Figure 2b).

Table 3 shows clinical outcomes among study participants. Functional success was obtained in 104 patients (97.2%). RBO occurred in 62 patients (59.6%), with obstruction, complete migration, and partial migration occurring in 47, nine, and six patients, respectively. In the PS group, obstruction, complete migration, and partial migration occurred in 28, two, and five patients. In the SEMS group, obstruction, complete migration, and partial migration occurred in 19, seven, and one patient, respectively. The ratio of stent migration to stent dysfunction was 24.2%. The cumulative incidence of RBO following EBS is shown in Figure 3a. The median time to RBO (TRBO) was 190 days (95% confidence interval, 152–353 days) using the Kaplan-Meier method. The cumulative rate of RBO in patients that received a SEMS was significantly lower than in patients that received a PS ($P < 0.01$; Figure 3b). The median TRBO in patients that received a SEMS and a PS was 315 and 91 days,

respectively. The cumulative rate of RBO did not significantly differ between SEMS types (median TRBO: fully covered SEMS, 410 days; partially covered SEMS, 353 days; uncovered SEMS, 239 days; $P = 0.26$). The cumulative rate of RBO did not significantly differ between the two types of PS (median TRBO: straight PS, 91 days; pigtail PS, 161 days; $P = 0.21$). The cumulative rate of RBO did not significantly differ according to the presence and absence of CBD stones or sludge in patients that received a SEMS. In the PS group, the cumulative rate of RBO was significantly higher in patients with CBD stones or sludge immediately after EBS ($P < 0.01$; Figure 3c), and the median TRBO in patients with and without CBD stones or sludge was 48 and 157 days, respectively.

Among the 42 patients without RBO, 20 patients were lost to follow-up, 16 patients died, two patients underwent scheduled PS change, two patients experienced natural stent dislocation, one patient underwent palliative biliary bypass surgery, and one patient underwent re-intervention due to a drainage-related adverse event (moderate pancreatitis).

Adverse events following EBS occurred in eight patients (7.7%), all of which were pancreatitis (mild in four patients and moderate in four patients). Of these, seven patients received a SEMS and one patient received a PS ($P = 0.06$). Although one patient had functional success due to deployment of a 10-mm diameter fully covered SEMS, moderate pancreatitis developed due to compression of the pancreatic duct by the SEMS. This event was successfully treated by re-intervention (SEMS exchange with a 7-Fr biliary PS one day after initial EBS).

Risk factors for RBO following EBS

Table 4 shows univariate and multivariate analyses of risk factors for RBO following EBS.

According to the results of a multivariate analysis using a stepwise procedure with the AIC, PS (hazard ratio, 2.48; $P < 0.01$) and the presence of CBD stones or sludge immediately after EBS (hazard ratio, 1.99; $P = 0.04$) were independent risk factors for RBO following EBS.

Discussion

The results of the present study demonstrate that SEMS is superior to PS in terms of TRBO. Park et al [7], previously reported that two types of 10-Fr double-pigtail PS were comparable to a 10-mm diameter uncovered SEMS in patients with AC in terms of stent dysfunction time (median 128.5 days and 132.7 days, respectively). Multiple PS and large PS are associated with longer stent dysfunction time than single PS and thick PS [13-15]. In the report by Park et al. [7], the duration of stent dysfunction was not analyzed using the Kaplan-Meier method and the number of patients was very small ($n = 37$), which may have affected the results of their study. The recent European Society of Gastrointestinal Endoscopy clinical guidelines recommended the insertion of a SEMS during EBS in patients with AC [5]. However, these guidelines are limited by the small proportion of patients with AC included in many previous studies. The results of the present study may strengthen these recommendations.

We observed similar TRBO between the three types of SEMS evaluated in the present study (fully covered, partially covered, and uncovered SEMS); however, the numbers of patients that received each type of SEMS were small and the effect of bias could therefore not be fully excluded. In our study, only a few patients received a specialized type of SEMS. Lee et al. [8] previously reported that a 12-mm diameter dumbbell-shaped fully covered SEMS (BONASTENT M-Intraductal) was associated with a longer stent dysfunction time compared to a conventional 10-mm diameter fully covered SEMS in patients with periampullary tumors (median 228 days and 157 days, respectively, $P = 0.048$). Further prospective studies are required to accurately compare the different types of SEMS, including dumbbell-shaped SEMS, in patients with unresectable AC.

In previous studies, stent migration occurred less than stent occlusion in patients with AC [7] and those with periampullary tumors [8] (stent migration rates of 16.7% and 38.1%, respectively). These studies included many patients that received a double-pigtail PS, an uncovered SEMS, or a dumbbell-shaped fully covered SEMS. In the present study, most patients received a straight PS and a conventional fully covered SEMS, which are generally considered to be easy to move with a similar ratio of stent migration. Taken together, these results indicate that stent migration is not the predominant cause of RBO in patients with MDBO due to AC, regardless of stent type.

The presence of CBD stones or sludge during EBS was a risk factor for RBO, particularly in patients that received a PS. PS placement can shave down and fragment CBD stones [16, 17] and therefore increase the amounts of biliary sludge in the bile duct. PS occlusion has been posited to

occur due to the presence of biliary sludge and the formation of bacterial biofilms [18]. Accordingly, PS occlusion may occur more frequently in patients with CBD stones or sludge. On the other hand, the presence of CBD stones or sludge at the time of EBS was not associated with RBO in the SEMS group of the present study. A SEMS has a larger diameter than a PS and CBD stones or sludge may migrate into the gastrointestinal tract through a SEMS, even without endoscopic extraction of biliary stones or sludge.

A previous study reported that curative surgical resection was performed in 95.0% of patients with AC [4], although our study comprised a relatively high proportion of patients with unresectable AC. This difference may be attributable to bias in our study cohort as the participating institutions included a range of medical institutions that was not limited to tertiary medical institutions and high-volume centers.

The present study had several limitations. First, this was a retrospective study. Second, selection bias could not be avoided as the selection of stent type and the strategy for CBD stone or sludge extraction at EBS was at the discretion of the endoscopist. Further, assessment of resectability of AC was conducted at individual institutions. Thirdly, the use of stents and other devices was not standardized across all participating institutions. Therefore, further prospective studies are required to accurately compare the use of different SEMS types in patients with unresectable AC.

In conclusion, a SEMS is superior to PS in terms of TRBO in patients with unresectable AC. The presence of CBD stones or sludge immediately after EBS was a risk factor for RBO, particularly in patients with a PS.

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Tables

Table 1. Baseline characteristics of study participants

Sex (male: female), n	63: 44
Age, median (IQR), years	84 (79–88)
Reason for unresectability of AC, n	
Advanced age and/or decline in ADL	80
Distant metastasis of AC	20
Coexistence of other advanced cancer	4
Mental retardation	1
Unknown	2
Maximum diameter of AC, median (IQR), mm	16.0 (12.0–20.0)
CBD diameter before initial biliary drainage, median (IQR), mm	17.0 (14.0–20.5)
MPD diameter, median (IQR), mm	3.5 (2.0–6.0)
Serum T-BIL before initial biliary drainage, median (IQR), mg/dL	3.2 (1.2–6.1)
CBD stones or sludge immediately after the palliative EBS, n (%)	22 (20.6)

AC, ampullary cancer; ADL, activities of daily living; CBD, common bile duct; EBS, endoscopic

biliary stenting; IQR, interquartile range; MPD, main pancreatic duct; T-BIL, total bilirubin

Table 2. Details of EBS and related procedures

Endoscopic sphincterotomy during palliative EBS, n (%)	14 (13.1)
Stent type (PS: SEMS), n	53: 54
Details of stent, n	
PS, straight type	47
7-Fr	29
8.5-Fr	13
10-Fr	5
PS, double-pigtail type	6
7-Fr	6
SEMS, fully covered type	37
8-mm diameter	2
10-mm diameter	32
Dumbbell-shaped 10-mm diameter	3
SEMS, partially covered type	13
10-mm diameter	13
SEMS, uncovered type	4
10-mm diameter	4

EBS, endoscopic biliary stenting; PS, plastic stent; SEMS, self-expandable metal stent

Table 3. Clinical outcomes

Functional success, n (%)	104 (97.2)
Follow-up period, median (IQR), days	371 (143–627)
RBO, n (%)	62 (59.6)
Cause of RBO, n	
Obstruction	47
Complete migration	9
Partial migration	6
Cause of RBO in patients with a PS, n	
Obstruction	28
Complete migration	2
Partial migration	5
Cause of RBO in patients with a SEMS, n	
Obstruction	19
Complete migration	7
Partial migration	1
Adverse event, n (%)	8 (7.7)
Pancreatitis, n	8

IQR, interquartile range; PS, plastic stent; RBO, recurrence biliary obstruction; SEMS, self-expandable metal stent

Table 4. Univariate and multivariate analyses of risk factors for recurrence of biliary obstruction following palliative endoscopic biliary stenting

	Univariate analysis		Multivariate analysis	
	HR (95% CI)	<i>P</i> -value	HR (95% CI)	<i>P</i> -value
Age, >84 vs. ≤84 years	1.56 (0.94–2.60)	0.08		
Sex, male vs. female	0.97 (0.58–1.61)	0.90		
Exposed tumor vs. non-exposed tumor type	1.12 (0.65–1.92)	0.69		
Longest tumor dimension, >16 vs. ≤16 mm	0.91 (0.55–1.51)	0.70		
CBD diameter, > 7 mm vs. ≤17 mm	0.91 (0.55–1.51)	0.71		
MPD diameter, >3.5 mm vs. ≤3.5 mm	0.78 (0.45–1.36)	0.38		
Serum T-BIL level, >3.2 vs. ≤3.2 mg/dL	0.74 (0.44–1.23)	0.24		
Endoscopic sphincterotomy	1.50 (0.78–2.90)	0.23		
Stent type, PS vs. SEMS	2.15 (1.29–3.58)	<0.01	2.48 (1.46–4.22)	<0.01
CBD stones/sludge, presence vs. absence	1.44 (0.75–2.74)	0.27	1.99 (1.01–3.92)	0.04
Chemotherapy, presence vs. absence	0.73 (0.38–1.41)	0.35	0.60 (0.31–1.18)	0.14

CBD, common bile duct; CI, confidence interval; HR, hazard ratio; MPD, main pancreatic duct; PS, plastic stent; SEMS, self-expandable metal stent; T-BIL, total bilirubin

Figure legends

Figure 1. Study flow chart

Figure 2.

A. Survival rate in all patients.

B. Survival rate according to stent type. The survival rates were not significantly different between plastic stent (PS) and self-expandable metal stent (SEMS) groups ($P = 0.28$).

Figure 3.

A. Cumulative RBO incidence following palliative endoscopic biliary stenting.

B. Cumulative RBO incidence according to stent type. The cumulative RBO rate in patients with a self-expandable metal stent (SEMS) was lower than in patients with a plastic stent (PS) ($P < 0.01$).

C. Cumulative RBO incidence according to the presence or absence of CBD stones or sludge in patients with a PS. The cumulative RBO rate in (a) patients with CBD stones or sludge was higher than in patients with no CBD stones or sludge (b) ($P < 0.01$).

Figure 1

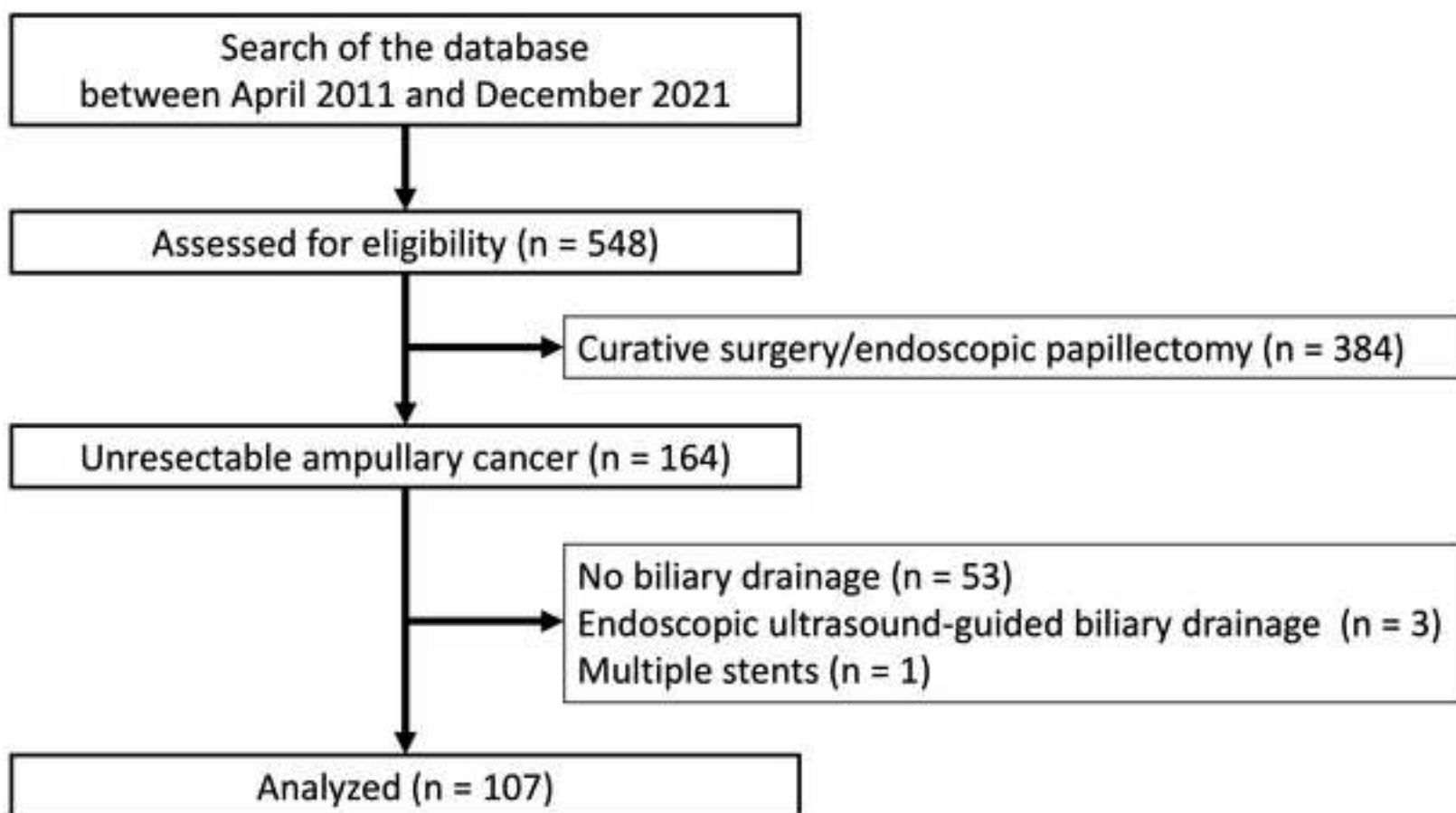
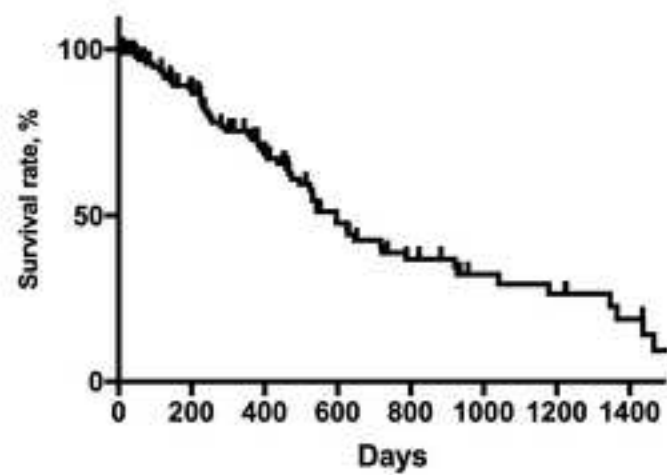


Figure 2

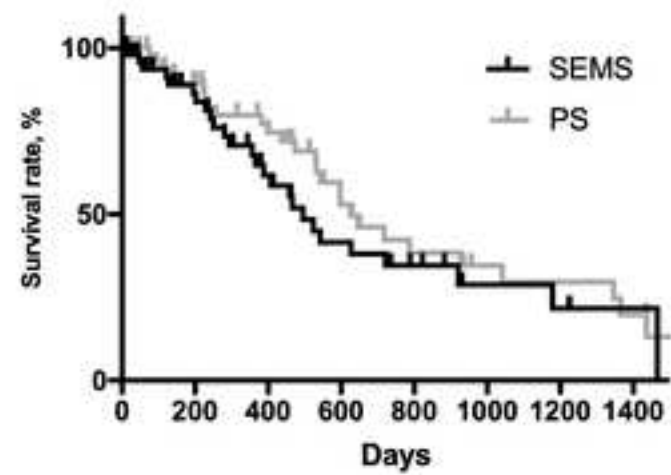
(A)



Number at risk

Days	0	200	400	600	800	1000	1200	1400
Number at risk	104	74	49	28	18	11	9	5

(B)



Number at risk

	Days	0	200	400	600	800	1000	1200	1400
SEMS	54	34	20	12	8	4	3	1	
PS	53	40	29	16	10	7	6	4	

Figure 3

