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### **Citation**

Keulen, A. M. van, Gaspersz, M. P., Vugt, J. L. A. van, Roos, E., Olthof, P. B., Coelen, R. J. S., ... Koerkamp, B. G. (2022). Success, complication, and mortality rates of initial biliary drainage in patients with unresectable perihilar cholangiocarcinoma. *Surgery*, 172(6), 1606-1613. doi:10.1016/j.surg.2022.06.028

Version: Publisher's Version

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**Note:** To cite this publication please use the final published version (if applicable).



## Success, complication, and mortality rates of initial biliary drainage in patients with unresectable perihilar cholangiocarcinoma



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### ARTICLE INFO

#### Article history:

Accepted 20 June 2022

Available online 18 August 2022

### ABSTRACT

**Background:** The patients with unresectable perihilar cholangiocarcinoma require biliary drainage to relieve symptoms and allow for palliative systemic chemotherapy. The aim of this study was to establish the success, complication, and mortality rates of the initial biliary drainage in patients with unresectable perihilar cholangiocarcinoma at presentation.

**Methods:** In this retrospective multicenter study, patients with unresectable perihilar cholangiocarcinoma who underwent initial endoscopic or percutaneous transhepatic biliary drainage between 2002 and 2014 were included. The success of drainage was defined as a successful biliary stent or drain placement, no unscheduled reintervention within 14 days, and serum bilirubin levels <50 μmol/L (ie, 2.9 mg/dL) or a >50% decrease in serum bilirubin after 14 days. Severe complications, and 90-day mortality were recorded.

**Results:** Included were 186 patients: 161 (87%) underwent initial endoscopic biliary drainage and 25 (13%) underwent initial percutaneous transhepatic biliary drainage. The success of initial drainage was observed in 73 patients (45%) after endoscopic biliary drainage and 6 (24%) after percutaneous transhepatic biliary drainage. The reasons for an unsuccessful initial drainage were: the failure to place a drain or stent in 39 patients (21%), an unplanned reintervention within 14 days in 52 patients (28%), and the bilirubin level >50 μmol/L (or not halved) after 14 days of initial drainage in 16 patients (9%). Severe drainage-related complications occurred in 19 patients (12%) after endoscopic biliary drainage and in 3 (12%) after percutaneous transhepatic biliary drainage. Overall, 66 patients (36%) died within 90 days after initial biliary drainage.

The authors Stefan Büttner and Bas Groot Koerkamp contributed equally.

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<https://doi.org/10.1016/j.surg.2022.06.028>

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**Conclusion:** Initial biliary drainage in patients with unresectable perihilar cholangiocarcinoma had a success rate of 45% and a 90-day mortality rate of 36%. Future studies for patients with perihilar cholangiocarcinoma should focus on improving biliary drainage.

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## Introduction

Perihilar cholangiocarcinoma (pCCA) is the most common malignancy of the bile duct. It arises from the epithelial cells at or near the biliary confluence.<sup>1</sup> Patients with pCCA typically present with painless jaundice due to biliary obstruction caused by the tumor. Relief of biliary obstruction through biliary drainage can resolve jaundice and liver dysfunction as well as improve the wellbeing of patients.<sup>2</sup> Endoscopic retrograde biliary drainage (ERBD) and percutaneous transhepatic biliary drainage (PTBD) are the 2 approaches most frequently used for biliary drainage.

The majority of patients with pCCA have unresectable disease (ie, locally advanced or metastatic) on imaging at the time of presentation.<sup>1,3</sup> The median overall survival (OS) of patients with unresectable disease is about 6 months.<sup>4</sup> Most patients with pCCA die from cholangitis or liver failure due to progressive biliary obstruction rather than widespread metastatic disease.<sup>5</sup> Palliative chemotherapy with gemcitabine plus cisplatin may improve median OS with about 3 months.<sup>6</sup> However, patients are only eligible for systemic chemotherapy with bilirubin below 50  $\mu\text{mol/L}$  (ie, 2.9 mg/dL), which may require drainage.<sup>7</sup>

Most studies have focused on the outcomes of preoperative biliary drainage in patients with resectable pCCA.<sup>8–10</sup> Biliary drainage is even more challenging in patients with unresectable pCCA because of progressive isolation of segmental bile ducts.<sup>11</sup> Patients often have complications after initial biliary drainage (eg, cholangitis), and reinterventions are frequently needed because of inadequate biliary drainage. The goal of initial biliary drainage is to avoid complications and reinterventions, as well as allow for early initiation of systemic chemotherapy. The aim of this study was to evaluate the success, severe complication, and mortality rates of initial palliative biliary drainage in patients with unresectable pCCA.

## Methods

### Study population and data acquisition

Consecutive patients with unresectable pCCA who underwent initial biliary drainage procedure between 2002 and 2014 were retrospectively identified in 2 tertiary referral centers in The Netherlands: Erasmus MC, University Medical Center in Rotterdam, and Amsterdam University Medical Center (AUMC) in Amsterdam. All of the patients were discussed at a multidisciplinary meeting at the tertiary referral center. Initial drainage procedure was performed in one of the tertiary referral centers or in referring hospitals. The patients were considered to have unresectable disease in the event of locally advanced or metastatic pCCA on imaging at the time of presentation or when they were physically unfit for surgery.<sup>1</sup> Metastatic pCCA (ie, AJCC stage IV) was defined as the presence of distant metastases or lymph node metastases beyond the hepatoduodenal ligament (AJCC staging, seventh edition).<sup>12</sup> If no pathological confirmation of suspicious lymph nodes was obtained, positive lymph node metastases were defined on imaging as nodes >1 cm in short-axis diameter, nodes with central necrosis, or an irregular border or hyper-attenuation

compared with portal phase liver parenchyma.<sup>13,14</sup> Locally advanced disease was defined as invasion of surrounding organs or vascular and biliary involvement that precluded an R0 resection with an adequate future liver remnant.<sup>3</sup> The patients with primary sclerosing cholangitis (PSC) were excluded as these patients often undergo biliary drainage procedures before pCCA develops. They were also excluded if a detailed report of the initial drainage procedure was not available.

### Outcomes and definitions

The primary outcome consisted of 3 determinants of successful drainage: successful biliary stent or catheter placement, absence of unscheduled reintervention within 14 days, and serum bilirubin levels <50  $\mu\text{mol/L}$  (ie, 2.9 mg/dL) or a >50% decrease in serum bilirubin after 14 days. A decrease of >50% of serum bilirubin after 14 days was also considered to be successful drainage because the absolute amount of bilirubin after stenting also depends on the serum bilirubin before drainage.<sup>15</sup> A planned reintervention within 14 days (eg, initial external percutaneous biliary drainage followed by stent placement 3 days later, or a plastic stent replaced by a metal stent) was not considered a failure of initial biliary drainage.

The secondary outcomes included drainage related complications, reinterventions, and an OS at 90 days after initial drainage. Drainage-related complications included cholangitis, acute cholecystitis, acute pancreatitis, bile duct injury (perforation and bleeding), duodenal perforation, and cardiopulmonary complications. Cholangitis was defined as both fever (ie, body temperature >38.5°C) and leukocytosis (ie,  $\geq 10 \times 10^9/\text{L}$ ) requiring a reintervention, without clinical or radiological evidence of acute cholecystitis.<sup>10,16,17</sup> Acute cholecystitis was defined as radiologic diagnosis of cholecystitis, in combination with fever and leukocytosis (ie,  $\geq 10 \times 10^9/\text{L}$ ), requiring percutaneous drainage, cholecystectomy, or antibiotics. Acute pancreatitis was defined by abdominal pain and a serum concentration of pancreatic enzymes (amylase or lipase)  $\geq 3$  times the upper limit of normal requiring at least one night of hospitalization.<sup>16</sup> The OS was defined as the time between initial drainage procedure and date of death or date of last follow-up. The primary and secondary outcomes were compared between ERBD and PTBD.

The data on initial biliary drainage were collected from medical records until 90 days after drainage, including the indication for drainage, bilirubin serum levels before and after initial drainage, drainage approach (PTBD or ERBD), type of stent (metal or plastic), drainage-related complications, and survival. If the initial drainage procedure was not performed in one of the tertiary referral centers, data were collected at the referring hospital where initial drainage procedure was performed.

Experienced abdominal radiologists revised the contrast-enhanced computed tomography (CT) and/or magnetic resonance imaging (MRI) performed at the time of presentation. The parameters reassessed on imaging were tumor diameter, Bismuth-Corlette classification,<sup>18</sup> presence of suspected lymph nodes, distant metastases, lobar atrophy, and vascular involvement. The Institutional Review Boards of both centers approved the study, and the need for informed consent was waived.

**Table 1**  
Baseline patient characteristics (n = 186)

Demographics, exam, and laboratory values	Total cohort (% or IQR)	EBD (% or IQR) N = 161	PTBD (% or IQR) N = 25	P value
Age at first presentation, y	72 (62–77)	72 (62–78)	71 (62–75)	.303
≥75 y	73 (39)	65 (40)	8 (32)	.512
Sex, males	105 (57)	90 (56)	15 (60)	.829
BMI, kg/m <sup>2</sup>	25 (23–27)	25 (23–27)	24 (21–28)	.193
WHO performance status*				.923
0	67 (36)	58 (37)	9 (39)	
1	67 (36)	57 (37)	10 (44)	
2	25 (13)	23 (15)	2 (9)	
3	19 (10)	17 (11)	2 (9)	
4	1 (1)	1 (1)		
CA 19.9 (U/ml)†	324 (105–2172)	299 (100–2377)	454 (195–1871)	.660
≥1,000 U/ml	33 (17.7)	28 (34.1)	5 (45.5)	.512
Highest bilirubin predrainage, median‡	248 (138–377)	232 (138–375)	284 (203–384)	.379
<50 μmol/L	6 (4.6)	5 (4.6)	1 (4.5)	1.000
Tumor characteristics on imaging at presentation				
Tumor size, cm	3.0 (2.3–3.9)	3 (2.3–3.9)	2.6 (2.4–4.1)	.880
Size >3 cm	81 (44)	70 (44)	11 (44)	.669
Suspicious lymph nodes on imaging§,				.842
N0	93 (54)	80 (54)	13 (52)	
N1	40 (23)	33 (22)	7 (28)	
N2	40 (23)	35 (24)	5 (20)	
Suspected distant metastases on imaging¶	27 (15)	24 (16)	3 (12)	.772
Any vascular involvement**	129 (69)	110 (77)	18 (75)	.799
PV involvement††	107 (58)	92 (64)	16 (62)	1.000
Unilateral	60 (32)	52 (36)	8 (33)	1.000
Main/Bilateral	47 (25)	40 (28)	7 (29)	
HA involvement‡‡	105 (57)	91 (65)	14 (54)	.647
Unilateral	72 (39)	61 (43)	11 (46)	.654
Main/Bilateral	33 (18)	30 (21)	3 (13)	
Lobar atrophy on imaging§§				.736
None	124 (72)	106 (72)	18 (72)	
Left	9 (5)	7 (5)	2 (8)	
Right	40 (21)	35 (24)	5 (20)	
Bismuth classification [18]¶¶				.760
I	11 (7)	11 (8)		
II	23 (14)	20 (14)	3 (13)	
IIIA	34 (21)	28 (20)	6 (25)	
IIIB	28 (17)	24 (17)	4 (17)	
IV	71 (42)	59 (42)	11 (45)	

Data missing for: 7 patients\*, 93 patients†, 55 patients‡, 13 patients§, 7 patients¶, 19 patients††, 21 patients‡‡, 13 patients§§, 20 patients¶¶.

EBD, endoscopic retrograde biliary drainage; BMI, body mass index; CA 19.9, carbohydrate antigen 19.9; HA, hepatic artery; PTBD, percutaneous transhepatic biliary drainage; PV, portal vein; WHO, World Health Organization.

|| Nodes along the cystic duct, common bile, duct, hepatic artery, and portal vein were classified as N1 and periaortic, pericaval, SMA, and celiac nodes as N2.<sup>12</sup>

\*\* Defined as ≥180° tumor involvement on imaging.

### Statistical analysis

The continuous variables were presented as means with SD if normally distributed or as median with IQR if not normally distributed. The categorical parameters are reported as counts and percentages. The categorical variables were compared with Fisher exact test, whereas continuous variables were compared with Mann-Whitney *U* test. Univariable analyses were performed using logistic regression analyses. The variables with a *P* < .20 in univariable analyses were included in multivariable analysis for mortality. Kaplan-Meier method with log-rank test was used for survival outcomes. The survival status was retrieved from the municipal records. All of the analyses were conducted using IBM SPSS Statistics for Windows (version 21.0; IBM Corp, Armonk, NY).

## Results

### Patient characteristics

A total of 186 drainage naïve patients with unresectable pCCA underwent initial biliary drainage; EBD in 161 patients (87%) and PTBD in 25 patients (13%). Table 1 presents the baseline patient characteristics, which did not differ between approaches. Thirteen

patients (9%) received palliative systemic chemotherapy. Two patients (3%) underwent palliative radiotherapy, and 1 patient (2%) photodynamic therapy. Endoscopic stent placement during initial biliary drainage was most frequently performed with plastic stents in both tertiary referral centers, although the use of metal stents has increased since 2010.

### Initial biliary drainage procedure

In 125 patients (67%) the initial drainage procedure was performed in a tertiary referral center, and in 61 patients (33%) in the referring hospital (Table II). The median serum bilirubin level before initial drainage procedure was 248 (IQR 138–377) μmol/L (ie, 15.1 (IQR 8.1–22.1) mg/dL). Cholangitis was diagnosed in 13 (7%) patients before initial biliary drainage. During initial EBD (*n* = 161), one or more stents were placed in 124 patients (77%), which were plastic stents in 109 patients (68%) and metal stents in 15 patients (9%). There was no association between Bismuth stage and type of stent used (*P* = .760). During initial PTBD procedure (*n* = 25), a drain was placed in 23 patients (92%): an internal-external drain in 20 patients (80%) and an external drain in 3 patients (12%). A plastic stent was placed during 1 initial PTBD (4%).

**Table II**  
Initial biliary drainage characteristics (N = 186)

	Total cohort N = 186	EBD n = 161	PTBD n = 25	P value
Hospital of initial drainage				
Tertiary referral hospital	125 (67)	106 (66)	19 (76)	.367
Referring hospital	61 (33)	55 (34)	6 (24)	
Cholangitis before drainage procedure*	13 (7)	10 (7)	3 (12)	.386
Drain placed at initial PTBD, yes	23 (12)		23 (92)	
Internal-external	20 (11)		20 (80)	
External only	3 (2)		3 (12)	
Papillotomy performed at initial EBD <sup>†</sup>	74 (57)	74 (58)		
Stent placed at initial drainage:	125 (67)	124 (77)	1 (4)	< .001
Plastic	110 (59)	109 (68)	1 (4)	
Metal stent	15 (8)	15 (9)	0	
Lowest bilirubin within 4 wk after initial drainage <sup>‡</sup>	104 (46.5–287)	99 (44–273)	233 (119–393)	.026
Success of initial drainage				
Unsuccessful drainage				
No drain or stent placed	39 (21)	37 (23)	2 (8)	.114
Unplanned reintervention	52 (28)	38 (24)	14 (56)	.002
Inadequate bilirubin decrease <sup>§</sup>	53 (53)	43 (50)	10 (71)	.160
Severe drainage-related complications <sup>††</sup>	22 (12)	19 (12)	3 (12)	1.000
Acute cholecystitis <sup>¶</sup>	0	0	0	
(Worsening of) cholangitis <48 h**	11 (6)	9 (6)	2 (8)	
Acute pancreatitis <sup>  </sup>	5 (3)	5 (3)	0	
Bile duct injury	3 (2)	2 (1)	1 (4)	
Duodenal perforation	1 (1)	1 (1)	0	
Cardiopulmonary complications	2 (1)	2 (1)	0	
Total number of drainage procedures per patient, median (IQR)	3 (2–6)	3 (2–6)	4 (3–7)	.162

Data missing for: 13 patients\*, 33 patients<sup>†</sup>, 86 patients<sup>‡</sup>.

EBD, endoscopic retrograde biliary drainage; PTBD, percutaneous transhepatic biliary drainage.

<sup>§</sup> Serum bilirubin levels >50 μmol/L or a <50% decrease in serum bilirubin within 14 days.

<sup>†</sup> Severe complications were recorded for 90 days after initial drainage.

<sup>¶</sup> Acute cholecystitis was defined as radiologic diagnosis of cholecystitis, in combination with fever and leukocytosis, requiring percutaneous drainage or cholecystectomy.

\*\* Cholangitis was defined as an elevation in temperature >38.5°C and leukocytosis  $\geq 10 \times 10^9/L$ , thought to have a biliary cause, without concomitant evidence of acute cholecystitis, requiring invasive intervention.<sup>10,16,17</sup>

<sup>||</sup> Acute pancreatitis were abdominal pain and a serum concentration of pancreatic enzymes (amylase or lipase)  $\geq 3$  times the upper limit of normal that requires  $\geq 1$  night of hospitalization.

### Success of initial biliary drainage

The success of initial drainage was achieved in 79 patients (43%), 73 patients (45%) after EBD and 6 patients (24%) after PTBD (Figure 1). Reasons for unsuccessful initial drainage were: failure to place a drain or stent in 39 patients (21%), unplanned reintervention within 14 days in 52 patients (28%), and bilirubin level above 50 μmol/L (ie, 2.9 mg/dL) (or not halved) after 14 days in 16 patients (9%) despite drain or stent placement (Figure 1). Irrespective of the reason for failure, 53 patients in the entire cohort (53%) did not reach bilirubin levels <50 μmol/L (ie, 2.9 mg/dL) (or not halved) within 14 days. The time period was not associated with outcomes: success of biliary drainage before 2008 was 39% (19/49) compared to 47% (65/137) after 2008 ( $P = .295$ ).

At initial EBD, no drain or stent was placed (ie, CBD not cannulated or biliary stricture not passed) in 37 patients (23%), 38 patients (24%) needed an unplanned reintervention within 14 days, and another 13 patients (8%) had bilirubin levels >50 μmol/L (ie, 2.9 mg/dL) (or not halved) after 14 days despite stent placement. Irrespective of the reason for failure, a total of 43 patients (50%) in the EBD group did not reach bilirubin levels <50 μmol/L (ie, 2.9 mg/dL) (or not halved) within 14 days.

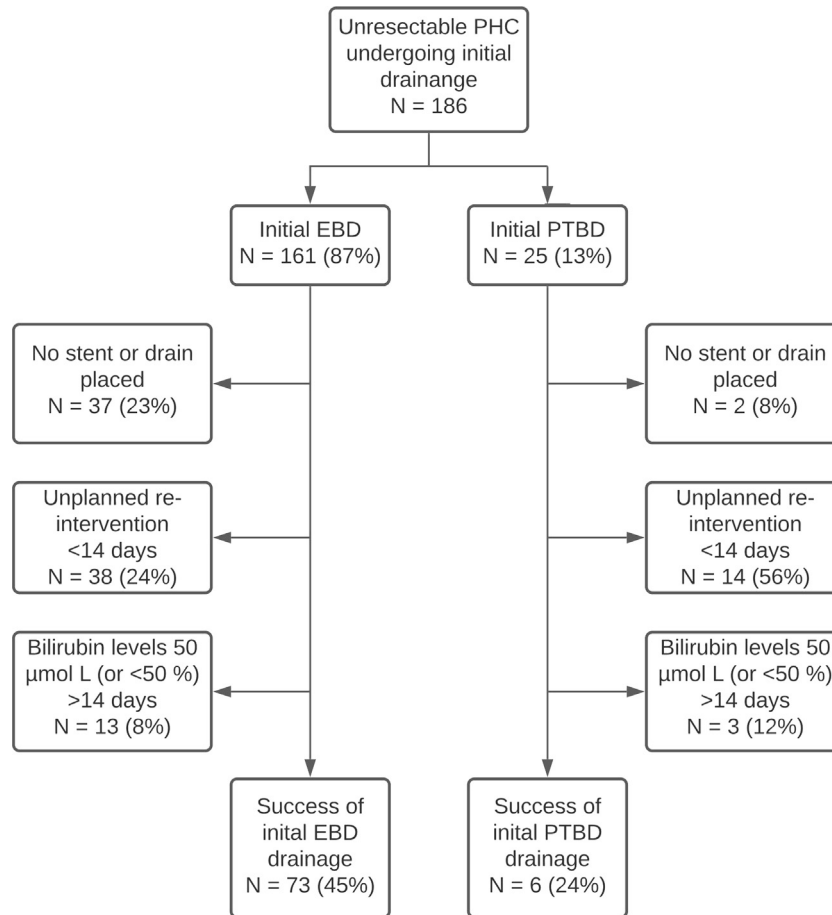
After initial PTBD, success of drainage was observed in 6 (24%) patients; in 2 patients (8%) no drain or stent was placed, 14 patients (56%) needed an unplanned reintervention within 14 days, and 3 patients (12%) had bilirubin levels >50 μmol/L (ie, 2.9 mg/dL) (or not halved) after 14 days despite successful drain placement. Irrespective of the reason for failure, a total of 10 patients (71%) in the PTBD group did not reach bilirubin

levels <50 μmol/L (ie, 2.9 mg/dL) (or not halved) within 14 days. Out of the 25 patients that initially underwent PTBD, 4 patients had an EBD as a second biliary drainage.

Two factors associated with an unplanned reintervention were found; PTBD (OR 4.12, 95% CI: 1.73–9.83,  $P = .001$ ) and portal vein involvement (OR 2.58, 95% CI: 1.12–5.97,  $P = .027$ ; Supplementary Table S1). No factors associated with inadequate drainage (ie, bilirubin levels above 50 μmol/L (ie, 2.9 mg/dL) or not halved) were found. In total, 26 patients (14%) had continued hyperbilirubinemia (median 307, IQR 206–454) but did not undergo a reintervention within 14 days. Twenty-three out of these 26 patients eventually had a second drainage procedure after 14 days at a median of 29 days (IQR 17.5–30). The remaining 3 patients did not undergo a biliary reintervention.

### Severe drainage-related complications after initial biliary drainage

Severe drainage-related complications after initial EBD were observed in 19 patients (12%); 9 patients (6%) developed new onset cholangitis, 5 (3%) acute pancreatitis, 2 (1%) bile duct injury, 1 (1%) duodenal perforation, and 2 (1%) cardiopulmonary complications (Table II). Of the 2 patients with bile duct injuries, 1 patient underwent a reintervention under general anesthesia and the other patient developed sepsis and died. Severe drainage-related complications after initial PTBD were observed in 3 patients (12%); 2 patients (8%) developed cholangitis and 1 patient (4%) a biliary injury.



**Figure 1.** Flowchart success of initial drainage ( $n = 186$ ). EBD, endoscopic retrograde biliary drainage; PHC, perihilar cholangiocarcinoma; PTBD, percutaneous transhepatic biliary drainage.

### Mortality after initial biliary drainage

At the time of last follow-up, 182 patients (98%) had died. No patient was lost to follow-up. The median OS of the entire cohort was 6.7 months (95% CI: 4.9–8.5; [Figure 2](#)). [Figure 3](#) shows the survival curves after initial EBD or PTBD. The 30-day mortality rate after initial drainage for the entire cohort was 11% ( $n = 20$ ) with a 90-day mortality rate of 36% ( $n = 66$ ). The majority of patients with 90-day mortality (77%) had no evidence of metastatic disease. Of the patients with 90-day mortality, 21 patients (32%) had distant metastasis (M1 disease), 8 patients (12%) had main/bilateral involvement of the hepatic artery, 4 patients (6%) had a WHO performance status of 3 or 4, and 20 patients (30%) were  $\geq 75$  years old. However, no statistically significant poor prognostic factors for 90-day mortality were identified in univariate and multivariable analysis ([Supplementary Table S2](#)). In particular, no difference in 90-day mortality was found between the initial EBD and PTBD, or whether EBD patients received a plastic or a metal stent.

### Subsequent biliary drainage procedures

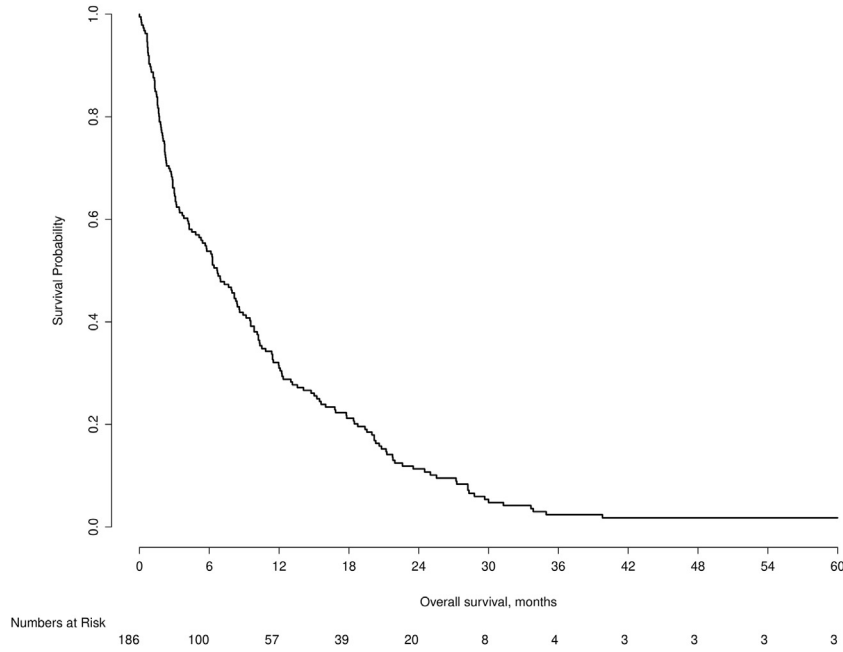
After initial EBD, a second drainage procedure was performed in 125 (78%) patients at some point during palliative care ([Supplementary Figure S1](#)); 107 patients (84%) underwent a second EBD and 21 (16%) underwent a PTBD as a second drainage procedure. After initial PTBD, a second drainage procedure was performed in 24 (96%) patients; 20 patients (83%) underwent another

PTBD, and 4 patients (17%) underwent an EBD as a second drainage procedure. The median period between the initial and second drainage procedure was 10 (5–28) days. The median number of drainage procedures during the entire palliative period was 3 (IQR 2–6), and 66 patients (36%) underwent 5 or more drainage procedures.

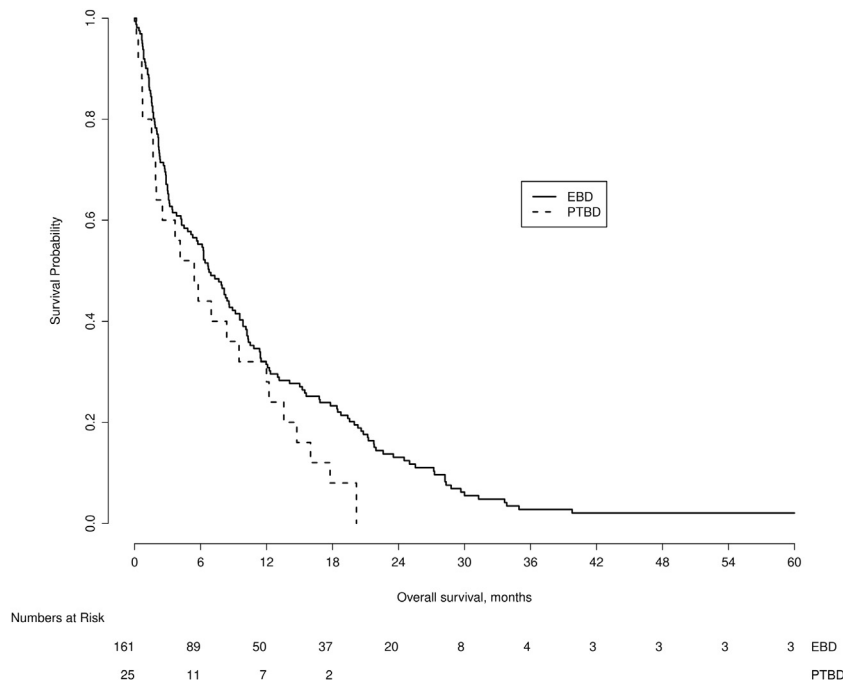
### Discussion

In the present study, we found a success rate of 43% for initial biliary drainage in 186 drainage-naïve patients with unresectable pCCA. The most common reasons for unsuccessful initial drainage were failure to place a drain or stent in 21% and unplanned reinterventions in 28%. Inadequate decrease of bilirubin (ie, below 50  $\mu\text{mol/L}$  [2.9 mg/dL] within 14 days or not halved) was observed in 53% of all treated patients. Observed 90-day mortality was 36%.

These high failure rates are comparable with recently published randomized trials on drainage of malignant biliary obstructions. A randomized trial (the INTERCPT trial) comparing EBD and PTBD for initial biliary drainage in patients with cholestasis and suspicion of malignant hilar obstruction was discontinued early because of lack of accrual.<sup>19</sup> In 2 years, only 13 patients were included. Less than half of all patients achieved the primary endpoint of 50% bilirubin level decrease in 3 weeks. Ninety-day mortality of the entire cohort was 62% (8/13). Biliary drainage has been evaluated mostly in cohorts of pCCA patients eligible for resection to optimize condition before liver resection. In these cohorts, high complication rates have been reported.<sup>20–22</sup> A Dutch randomized controlled trial



**Figure 2.** Survival after biliary drainage for unresectable perihilar cholangiocarcinoma (n = 186).



**Figure 3.** Survival after initial endoscopic retrograde biliary drainage and percutaneous transhepatic biliary drainage for unresectable perihilar cholangiocarcinoma. EBD, endoscopic retrograde biliary drainage; PTBD, percutaneous transhepatic biliary drainage.

(DRAINAGE trial) comparing preoperative EBD to preoperative PTBD in potentially resectable pCCA was prematurely stopped because of increased 90-day mortality in the PTBD group (41% vs 11% in the EBD group,  $P = .03$ ).<sup>23</sup> Severe complications after biliary drainage were common and similar between the groups (PTBD 63% vs EBD 67%). The authors hypothesized that extracting bile from the enterohepatic cycle in severely ill patients with external biliary drainage may have increased mortality in the PTBD group. A review by Kato et al described studies with a variety of definitions to determine

technical and clinical success of biliary drainage for unresectable malignant hilar obstruction.<sup>24</sup> Technical success was often defined as successful stent placement or stent deployment across the obstruction, sometimes confirmed by contrast flow through the stent.<sup>25–28</sup> Clinical success was determined by any up to 75% bilirubin decrease in a time period varying from 1 to 4 weeks.<sup>25–29</sup> A direct comparison of success rates is impossible with this variation in definitions. Moreover, we included “no unplanned reintervention” in our definition of success, which added up to lower success rates.

Inadequate decrease of bilirubin within 2 weeks was observed in 53% of patients. A previous study found that the duration of normalization of bilirubin levels was dependent on the bilirubin level before biliary stenting. Bilirubin levels  $\geq 171$   $\mu\text{mol/L}$  (ie, 10 mg/dL) could take  $>6$  weeks to return to normal levels after drainage.<sup>15</sup> The median bilirubin level before biliary drainage was 248 (IQR 138–377)  $\mu\text{mol/L}$  (ie, 15.1 [IQR 8.1–22.1] mg/dL) for the entire cohort. Therefore, the period of 2 weeks was sufficient to assess successful drainage, but not to determine that bilirubin declined to normal levels.

We found severe drainage-related complications (eg, cholangitis, acute cholecystitis, and acute pancreatitis) in 19 patients (12%) after EBD and in 3 (12%) after PTBD. A randomized controlled trial of patients with unresectable pCCA comparing metal and plastic stents reported postdrainage pancreatitis in 15% and cholangitis in 19%.<sup>30</sup> No patient developed cholecystitis in our study, whereas 3% of patients developed cholecystitis in another randomized controlled trial comparing metal and plastic stents.<sup>31</sup> The difference is partially explained by the differences in definitions. Moreover, pancreatitis, cholecystitis, and cholangitis may be underreported in the present study because of the retrospective study design. Furthermore, prophylactic measures such as pancreatic duct stenting and administration of nonsteroidal inflammatory drugs may have reduced the rate of pancreatitis.

The median OS in our cohort of 6.7 months is similar to reported outcomes in previous studies on EBD in patients with unresectable malignant hilar biliary strictures.<sup>30–32</sup> The 30-day and 90-day mortality rates after initial biliary drainage in our cohort were 11% and 36%. No difference in 90-day mortality was found between initial EBD and PTBD. In the randomized trial comparing plastic and metal stents for unresectable pCCA, the 30-day mortality rate was 29%.<sup>30</sup> In the present study, most of the patients died in the absence of metastatic disease on imaging. Inadequate biliary drainage and complications of biliary drainage, leading to cholangitis and clinical deterioration, appear to be the root cause of 90-day mortality in these patients. Local disease progression with isolation of segmental bile ducts and liver failure is responsible for mortality beyond 90 days.

Resectable pCCA is most often treated with a right or left hemihepatectomy with a bile duct resection and reconstruction, resulting in 90-day mortality rates of 12% in Western centers.<sup>33–35</sup> Most of the patients die from liver failure, typically caused by an inadequate liver remnant and cholangiosepsis. In the present study we found that 90-day mortality after biliary drainage for patients with pCCA who did not undergo resection was even worse with 36%. This difference in mortality is most likely explained by more extensive disease and frailty in the unresectable pCCA group. Moreover, series of patients who underwent resection of pCCA rarely report outcomes of patients with resectable pCCA who did not undergo resection because of clinical deterioration during preoperative biliary drainage. Only the Dutch RCT demonstrated that many patients with resectable pCCA die after preoperative biliary drainage before surgery.<sup>23</sup>

This study had several limitations. Due to the retrospective nature, details related to the biliary drainage procedure were sometimes missing, and complication rates may have been underreported. Mortality, however, was retrieved for all of the patients from municipal records. A few of the patients without a drainage report had to be excluded, which may have led to selection bias. Also, the reason for patients undergoing EBD or PTBD is unknown, potentially leading to selection bias. Finally, although the described cohort is large, the number of patients undergoing initial PTBD was too low to draw statistical conclusions in the comparison with EBD.

Future studies should focus on improving the success rate of initial palliative initial biliary drainage. The need for reintervention

might decrease by more liberal use of metal stents and placement of bilateral stents at initial biliary drainage as recommended by the European Society of Gastrointestinal Endoscopy guidelines.<sup>26,30,36,37</sup> The ongoing TESLA trial (NL9624) investigates initial percutaneous placement of a metal stent that does not cross the ampulla, to avoid contamination of intrahepatic the bile ducts. Randomized trials for initial biliary drainage remain challenging as demonstrated by a multicenter study that was closed early because of lack of accrual.<sup>19</sup>

In conclusion, in patients who were ineligible for resection of pCCA and underwent palliative biliary drainage, we found that the initial biliary drainage had a low success rate of 45% and a high 90-day mortality rate of 36%. Future studies for patients with pCCA should focus on improving biliary drainage.

## Funding/Support

This research did not receive any specific funding from any agencies in the public, commercial, or not-for-profit areas.

## Conflict of interest/Disclosure

The authors have no conflicts of interests or disclosures to report.

## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at [<https://doi.org/10.1016/j.surg.2022.06.028>]

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