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ORIGINAL ARTICLE

Long-term follow-up of a randomized trial of biliary drainage in perihilar cholangiocarcinoma

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Abstract

Background and aims: The DRAINAGE trial was a randomized controlled trial comparing preoperative endoscopic (EBD) and percutaneous biliary drainage (PTBD) in patients with potentially resectable, perihilar cholangiocarcinoma (pCCA). The aim of this study was to compare the long-term outcomes.

Methods: Patients were randomized in four tertiary referral centers. Follow-up data were available for all included patients. Primary outcome was overall survival (OS). Secondary outcomes were readmissions, and re-interventions not including in-trial interventions.

Results: A total of 54 patients were randomized; 27 in both groups. Median follow-up for both groups was 62 months (95% CI 54–70). The median OS was 13 months (95% CI 7.9–18.1) in the EBD and 7 months (95% CI 0.0–17.2) in the PTBD group (P = 0.28). Twenty (37%, n = 8 EBD vs n = 12 PTBD, P = 0.43) of 54 patients were readmitted at least once, mostly due to drainage-related complications (n = 13, 24%). Of note, 14 out of the 54 patients died within the trial. A total of 76 drainage procedures (32 EBD and 44 PTBD) were performed in 28 patients. The median number of stent or drain placements was 2 (2–4) for the EBD group and 2 (1–3) for the PTBD group (P = 0.77).

Discussion: Although this follow-up study represented a small cohort, no long-term differences in survival, readmissions, and drainage procedures for EBD and PTBD were found, even when comparing the resected and unresected group. However, this study demonstrates the complexity of biliary drainage for patients with potentially resectable pCCA, even in tertiary referral centers.

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Introduction

Perihilar cholangiocarcinoma (pCCA) is a rare disease with a poor prognosis. Surgery with curative intent offers the only chance of long-term overall survival (OS), with 5-year OS rates of 43% after radical resection.[1,2] Unfortunately, most patients present with metastatic or locally advanced disease, which leaves only a minority of 20% eligible for resection.[1] The work-up prior to resection usually consists of biliary drainage, liver volume measurement (or calculation) and/or liver function tests and, if necessary, portal vein embolization.[3] The goal of biliary drainage is to decrease morbidity and mortality due to postoperative liver

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failure.[4–7] Biliary drainage however, comes with a high risk of complications itself[8–10] and the optimal drainage method remains a matter of debate.[8,11,12]

The DRAINAGE trial, which ran from 2013 to 2016 was a multicenter randomized controlled trial (RCT) comparing preoperative endoscopic (EBD) and percutaneous biliary drainage (PTBD) in patients with potentially resectable pCCA.[8,13] The trial included 54 patients and was terminated at 50% accrual because of higher mortality in the PTBD group (11% EBD versus 41% PTBD). Post-drainage related complications were comparable between both groups (67% EBD versus 63% PTBD). In addition, 15 (56%) patients treated with initial EBD required additional PTBD, whereas one (4%) patient required EBD after PTBD. For the initial study analysis, patients were followed until 90 days after surgery.

The INTERCPT study, a second RCT that compared PTBD and EBD in suspected malignant biliary hilar obstruction, was prematurely terminated due to slow accrual.[11,14] Only 13 patients were included. This study also showed high morbidity and mortality rates. Post-drainage related complications were comparable between both groups (75% EBD versus 80% PTBD). In addition, eight patients died within 3 months follow-up (50% EBD versus 80% PTBD).

No other RCTs or prospective cohort studies comparing EBD and PTBD have been published. Therefore, no long-term follow-up studies comparing EBD and PTBD in potentially resectable pCCA patients are available. Short-term complications found in both the DRAINAGE trial and INTERCPT study have a significant impact on long-term OS. Therefore, the primary objective of present study was to compare OS after EBD and PTBD for potentially resectable pCCA in the DRAINAGE trial.

Methods

Study population

The DRAINAGE trial was a multicenter randomized controlled trial including patients with potentially resectable pCCA requiring biliary drainage prior to a planned major hepatectomy.[8,13]

Follow-up after trial ending

Follow-up data until dead or last follow-up of all patients included in the DRAINAGE trial were included in this study. For patients who underwent resection, follow-up data were collected starting from the trial endpoint.[8] Data included survival, disease recurrence or progression, presence of (seeding) metastases and adjuvant or palliative chemotherapy. In addition, the number of drainage procedures, drainage complications and readmissions after the end of DRAINAGE trial follow-up were included.

Outcomes

Primary outcome was OS according to initial biliary drainage type. Secondary outcomes were disease free survival (DFS) or progression free survival (PFS), the number of readmissions, days of readmission, number of re-interventions after ending of the initial trial, metal stent placements, permanent external drains, and drainage related complications. Readmissions included all in-hospital admissions (short stay or day treatment admissions for planned stent revisions and emergency department visits without admission were excluded). Unplanned stent placements were placements or revisions due to dislocation or leaking drains, recurrent biliary obstruction due to stent obstruction, dysfunction, or replacements during unplanned readmissions. Planned stent placements were defined as all scheduled stent/drain exchanges and revisions.

Statistical analysis

Normally distributed continuous variables were presented as mean ± standard deviation (SD) and, non-normal distributed continuous variables as median with interquartile range. Comparisons between EBD and PTBD were analyzed using chi-square tests for proportions, Mann–Whitney U test for medians and independent sample T test for means. OS, disease free survival, and progression free survival were calculated using the Kaplan–Meier method. Survival curves were compared using the log-rank test. OS was measured from date of randomization to date of death or last follow-up. PFS was calculated from the day of chemotherapy start until the day of disease progression or last radiological imaging. DFS was calculated from the day of resection until the day of recurrent disease or last radiological imaging. The reverse Kaplan–Meier based method was used to calculate median follow-up. Analysis were performed according to an intention-to-treat principle. A P-value of <0.05 was considered statistically significant. Data were analyzed using IBM SPSS statistics, version 25.0 (IBM Corp). Survival curves were displayed using GraphPad Prism 8.

Results

Trial treatment and patient characteristics

A total of 54 patients were included in the DRAINAGE trial, twenty-seven patients in each arm. Out of 54 patients, 12 (22%) did not undergo an explorative laparotomy due to occult metastasis (n = 3), local tumor progression (n = 3), clinical deterioration (n = 2), benign disease (n = 1), or pre-operative mortality (n = 3). 42 patients were operated of whom 19 (45%) patients underwent exploration without resection and 23 (55%) underwent resection. This included 12 patients out of the EBD (44%) and 11 patients out of the PTBD (41%) group. During the trial, the median number of stent or drain placements was $2^{2,3}$ for the EBD group and $2^{2,3}$ for the PTBD group. A flow diagram of the study is displayed in Fig. 1. All baseline characteristics are displayed in Table 1.

Overall survival

Follow-up data were available for all 54 patients. 47 patients (87%) died during follow-up and median follow-up of patients

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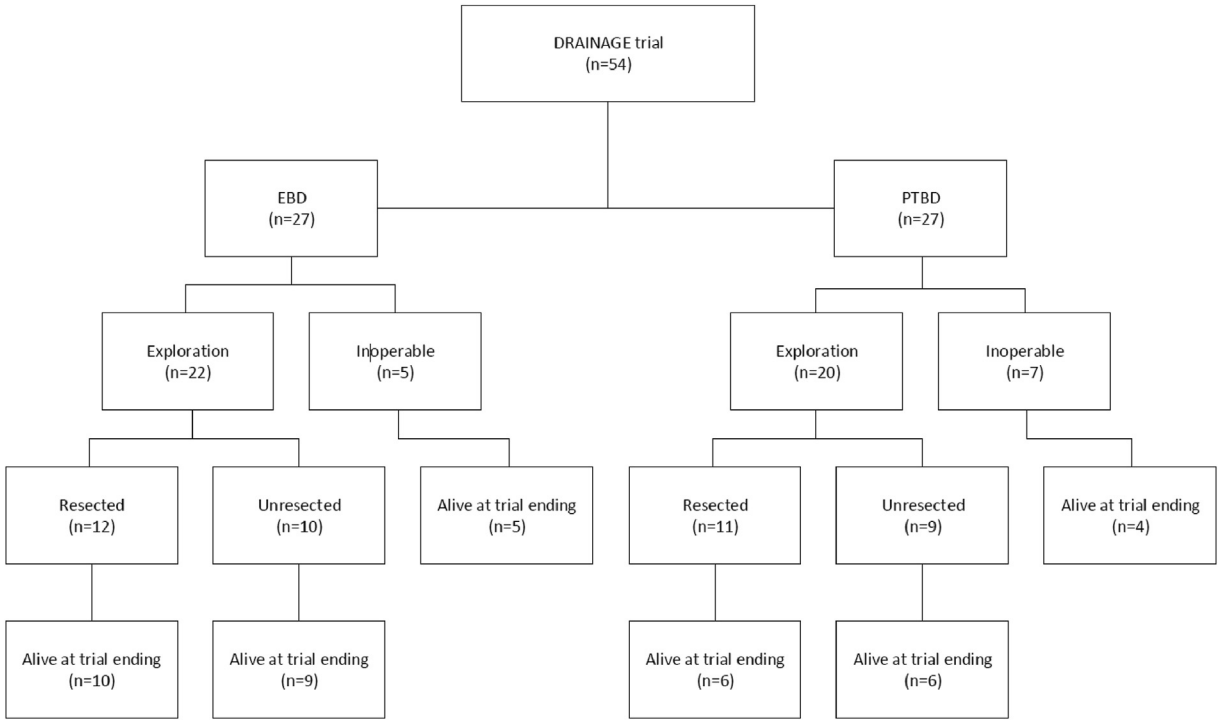

Figure 1 Flowchart of patients in the DRAINAGE trial

alive at last follow-up was 62 months (95% CI 54–70). This was 65 months (95% 59–71) in the EBD and 56 months (95% CI 35–77) in the PTBD group. Median OS from randomization was not significantly different between study arms; 13 months (95% CI 7.9–18.1) in the EBD and 7 months (95% CI 0.00–17.2) in the PTBD group (P = 0.28) (Fig. 2). The 1-, 3- and 5-year OS rates were 52%, 26% and 14% after initial EBD and 44%, 19% and 11% after initial PTBD, respectively.

When the group was further divided in a resected (n = 23) and unresected (n = 31) subgroup, OS was not significantly different between drainage types. In the resected group, median OS was 15 months (95% CI 2.6–27.5) in the EBD and 17 months (95% CI 0–35.6) in the PTBD group (P = 0.75). This included seven patients with 90-day post-operative mortality (n = 2 EBD and n = 5 PTBD). In the unresected group, median OS was 11 months (95% CI 7.3–14.7) in the EBD group and 7 months (95% CI 3.1–10.9) in the PTBD group, respectively (P = 0.31).

Recurrence and disease-free survival, progression, and progression free survival

Two out of the 23 (9%) resected patients received adjuvant chemotherapy. During follow-up, eleven patients (48%, n = 8 EBD and n = 3 PTBD (P = 0.41)) had disease recurrence. One of these patients received adjuvant chemotherapy. Ten patients who underwent resection had local recurrence (n = 7 EBD and n = 3 PTBD) and one patient (EBD group) had peritoneal recurrence. Three of these eleven patients received palliative chemotherapy. For the patients who underwent resection, median time to recurrence was 15 months (95% CI 9.5–20.5). The median time to recurrence was not significantly different between EBD and PTBD group; 15 months (95% CI 7.6–22.4) and 17 months (95% CI 10.6–23.4), respectively (P = 0.42).

Eight out of 31 (26%) patients who did not undergo a resection received palliative chemotherapy. Five out of eight patients (63%, n = 2 EBD, n = 3 PTBD (P = 1.0)) had progression after chemotherapy. For the overall group, median time to progression was 9 months (95% CI 0–20.0). The median time to progression was not significantly different between groups; 33 months (95% CI could not be executed) for the EBD group vs 9 months (95% CI 0–23.4) for the PTBD group (P = 0.24). All secondary outcomes are displayed in Table 2.

Readmissions and stent revisions

Twenty of 54 patients (37%, n = 8 EBD vs n = 12 PTBD, P = 0.43) were readmitted at least once after trial ending, 13 patients due to drainage-related complications (24%, n = 7 EBD and n = 6 PTBD, P = 0.25) (Table 3). Note that 14 out of these 54 patients died within the trial. The median number of readmissions was $1^{[1,2]}$. There were no differences between groups; $1^{[1-3]}$ for the EBD group and $1^{[1,2]}$ for the PTBD group (P = 0.50). The median time of hospitalization after readmission was also not significantly different; for the EBD group this was 10 (2–27) days and for the PTBD group this was $13^{[7-23]}$ days (P = 0.72).

In the complete cohort, a total of 76 drainage procedures with stent or drain placements were performed in 28 patients after trial ending. This concerned, 23 procedures in patients who

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Table 1 Baseline characteristics

	Total (n = 54)	EBD (n = 27)	PTBD (n = 27)
Age (years)	69.2 (61.2–73.5)	66.9 (60.8–72.9)	69.8 (64.1–73.5)
Male patients	36 (67%)	18 (67%)	18 (67%)
ECOG performance status[c]			
0	19 (35%)	9 (33%)	10 (37%)
1	20 (37%)	9 (33%)	11 (41%)
2	12 (22%)	6 (22%)	6 (22%)
Bismuth-Corlette classification			
1	1 (2%)	1 (4%)	0
2	4 (7%)	3 (11%)	1 (4%)
3A	22 (41%)	10 (37%)	12 (44%)
3B	11 (20%)	4 (15%)	7 (26%)
4	16 (30%)	9 (33%)	7 (26%)
DRAINAGE trial (intention to treat)	54 (100%)	27 (100%)	27 (100%)
DRAINAGE trial (per protocol)	54 (100%)	21 (78%)	33 (122%)
Exploratory laparotomy	42 (78%)	22 (81%)	20 (74%)
Resection[a]	23 (43%)	12 (44%)	11 (41%)
resection margin			
R0	9 (45%)	4 (40%)	5 (50%)
R1/R2	11 (55%)	6 (60%)	5 (50%)
T stage			
T2	11 (55%)	5 (50%)	6 (60%)
T3	7 (35%)	4 (40%)	3 (30%)
T4	2 (10%)	1 (10%)	1 (10%)
Lymph node status			
N0	8 (40%)	2 (20%)	6 (60%)
N1	12 (60%)	8 (80%)	4 (40%)
Differentiation			
Well differentiated	2 (10%)	0	2 (20%)
Poorly differentiated	18 (90%)	10 (100%)	8 (80%)
Benign disease[b]	4 (7%)	3 (11%)	1 (4%)

[a] Resection details excluding patients with benign disease (total, n = 20).
[b] n = 3 resected, EBD = endoscopic biliary drainage, PTBD = percutaneous biliary drainage.
[c] Age at inclusion.

Table 2 Secondary outcomes

	Total (n = 54)	EBD (n = 27)	PTBD (n = 27)	P value[a] (EBD vs PTBD)
Chemotherapy				
Adjuvant	2 (9%)	0	2 (7%)	0.211
Palliative	8 (26%)	5 (19%)	3 (11%)	0.406
Recurrence	11 (48%)	8 (30%)	3 (11%)	0.087
Local recurrence	10 (43%)	7 (26%)	3 (11%)	1.000
Peritoneum	1 (4%)	1 (4%)	0	
Progression after chemotherapy	5 (16%)	2 (7%)	3 (11%)	1.000

[a] P-values based on complete case analysis unless unknown is displayed. Statistical analysis using chi square test. EBD = endoscopic biliary drainage, PTBD = percutaneous biliary drainage.

underwent resection and 53 procedures in patients wo did not undergo a resection. The median number of stent or drain placements per patient was 2.[1–4] A total of 32 drainage procedures were performed in 13 patients of the EBD group and 44 drainage procedures were performed in 15 patients of the PTBD group. The median number of stent or drain placements was 2[2–4] for the EBD group and 2[1–3] for the PTBD group ($P = 0.77$). For the resected patients, stent or drain placements all consisted of PTBD replacements due to the Roux-Y construction present after resection, making endoscopic access more challenging. In this group, no double balloon enteroscopy-assisted EBD procedures were performed. Out of all 76 drainage procedures, 48 (63%) were planned and 28 (37%) were unplanned. In the EBD group 13 of 32 (41%) procedures were unplanned. In the PTBD group, 15 of 44 (34%) procedures were unplanned.

Self-expandable metal stents (SEMS) were placed in 20 (37%) patients (n = 7 EBD vs n = 12 PTBD, $P = 0.08$). Five patients (9%) received permanent external drainage. In 13 patients, SEMS placement was the first stent procedure after trial ending. In eight (15%) patients stent in stent placement after initial SEMS was necessary. Presents a follow-up figure of all 54 patients, including stent revisions, metal stent placement (adjuvant or palliative) chemotherapy and recurrent disease.

Discussion

The present long-term follow-up data of a randomized trial on preoperative biliary drainage in perihilar cholangiocarcinoma showed no difference in terms of survival, readmissions and additional drainage procedures between patients who underwent endoscopic or percutaneous biliary drainage. Poor survival was observed in the overall group and there was a high rate of unplanned post-trial readmissions mostly due to stent-related complications.

The poor survival in the patients who underwent resection could partly be attributed to the high perioperative mortality, both after initial biliary drainage and after surgical resection. In addition, approximately half of the patients who underwent resection had recurrence within one year. The survival of patients with unresectable disease observed in this study was also poor. Only a small number of patients received palliative

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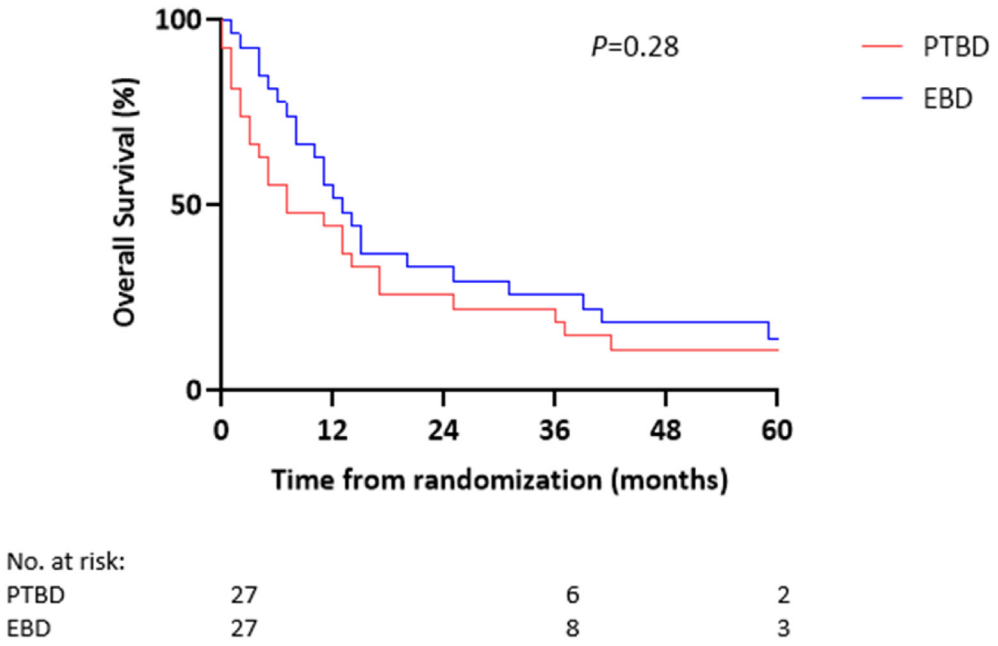

Figure 2 Kaplan–Meier curve of overall survival after PTBD and EBD for overall pCCA cohort

chemotherapy with moderate PFS as a result, reflecting the poor tumor biology of pCCA.

Most available studies comparing preoperative EBD and PTBD in patients with pCCA only described patients who eventually underwent resection and excluded patients with unresectable disease or patients with inadequate biliary drainage or clinical deterioration after biliary drainage. Such studies are prone to selection bias. The present, unselected cohort of patients from a randomized trial represent a unique group, but also makes comparison of results with previous retrospective studies difficult.[9,10,15] A retrospective study comparing EBD and PTBD in 196 patients with resectable pCCA found a median disease specific survival of 44 versus 37 months and a recurrence free survival of 27 versus 24 months.[16] Another propensity score matched study with 245 patients with resectable pCCA found a median OS of 38 months for both EBD and PTBD.[17]

Three recently published systematic reviews on EBD versus PTBD in the preoperative setting included a total of 14 different, mainly retrospective cohort studies. These reviews found no statistically difference in post-operative mortality. However, an increased incidence of implantation metastasis in the PTBD group was found (OR = 0.35, 95% CI: 0.23–0.53, $P < 0.001$). EBD was found to be associated with fewer 5-year recurrences and better 5-year OS, which could possibly be attributed to the fact that patients with PTBD had more advanced disease.[9,10,15] In our study, only one patient had peritoneal recurrence, which was located at the cross-over PTBD puncture track and therefore appeared to be an implantation metastasis. In addition, the median disease-free survival of 15 months in the present study was shorter compared to results found in these reviews and two other studies investigating recurrence patterns in patients with pCCA.[18,19]

Taking a closer look at the differences between EBD and PTBD in unresected patients, the literature shows comparable results. A recent study described 87 patients with unresectable pCCA who underwent initial EBD and PTBD.[20] They found a median number of 1.0 (EBD) and 3.5 (PTBD) hospital readmissions, which is comparable to the results found in our unresectable EBD cohort but not for the PTBD cohort. They also found that 70% of the patients required multiple procedures with similar results for EBD and PTBD which is comparable to our study.

Another interesting finding of the present study is that only ten patients received chemotherapy (eight palliative and two adjuvant). Most of the patients had a poor performance status and were therefore not able to receive palliative chemotherapy. In addition, in the Netherlands, adjuvant chemotherapy was until recently only available in trial setting (ACTICCA-1 study, NCT02170090). Which could explain this small number.

Better techniques and stent technology to ensure adequate drainage without complications are necessary, and therefore several new approaches are currently being investigated. For example, a stent can be placed through endoscopic retrograde cholangiography above the papilla with the retrieval thread in the duodenum (inside stent). A study including 106 patients with malignant strictures found 8% post-drainage related complications[21] instead of the approximately 30% expected with the current stents.[22] Another study including 41 patients with malignant perihilar strictures receiving an inside stent, found 10% drainage-related complications but also an in-hospital mortality rate of 7.3%.[23] In addition, additional therapy (e.g., endobiliary

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Table 3 Secondary outcomes

	Total (n = 54)	EBD (n = 27)			PTBD (n = 27)			*P* value[a] (EBD vs PTBD)
		total	Unresected (n = 15)	Resected (n = 12)	Total	Unresected (n = 16)	Resected (n = 11)	
Re-admissions	20 (37%)	8 (30%)	4 (27%)	4 (33%)	12 (44%)	7 (44%)	5 (45%)	0.425
Number of re-admissions								1.000
1	14 (26%)	6 (22%)	3 (20%)	3 (25%)	9 (33%)	5 (31%)	4 (36%)	
2 or more	6 (11%)	2 (7%)	1 (7%)	1 (8%)	3 (11%)	2 (13%)	1 (9%)	
Number or re-admissions (median)	1 (1–2)	1 (1–3)	1 (1–3)	1 (1–3)	1 (1–2)	1 (1–2)	1 (1–3)	0.504
Days of hospitalization after readmission[b]	12 (3–24)	10 (2–27)	3 (2 – x)	10 (4–23)	13 (3–23)	13 (7–23)	11 (2–24)	0.715
Readmission due to:								0.254
Drainage related problems	13 (24%)	7 (26%)	4 (27%)	3 (25%)	6 (22%)	4 (25%)	2 (18%)	
Ascites	2 (4%)	1 (4%)	0	1 (8%)	1 (4%)	0	1 (9%)	
Liver abscess	3 (6%)	0	0	0	3 (11%)	2 (13%)	1 (9%)	
Other	2 (4%)	0	0	0	2 7%)	1 (6%)	1 (9%)	
Stent placement after trial								
Patients	28 (52%)	13 (48%)	10 (67%)	3 (25%)	15 (56%)	13 (81%)	2 (18%)	0.802
Stent/drain placements (median)	2 (1–4)	2 (2–4)	2 (2–4)	2 (1 – x)	2 (1–3)	2 (1–2)	8 (7 – x)	0.770#
Planned (median)	1 (1–2)	1 (1–2)	1 (1–3)	1 (1–1)	1 (1–2)	1 (1–2)	5 (5–5)	0.816#
Unplanned (median)	1 (1–3)	1 (1–3)	1 (1–2)	2 (1 – x)	2 (1–3)	1 (1–2)	3 (2 – x)	0.641#
SEMS	20 (37%)	7 (26%)	7 (47%)	0	13 (48%)	12 (75%)	1 (9%)	0.079
Permanent external drainage	5 (9%)	4 (15%)	2 (13%)	2 (17%)	1 (4%)	0	1 (9%)	
Stent in SEMS	8 (15%)	3 (11%)	3 (20%)	0	5 (19%)	4 (25%)	1 (9%)	1.000
Number of drainage procedures								0.898
1	8 (15%)	3 (11%)	2 (13%)	1 (8%)	5 (19%)	5 (31%)	0	
2	12 (22%)	6 (22%)	5 (33%)	1 (8%)	6 (22%)	6 (38%)	0	
≥3	8 (15%)	4 (15%)	3 (20%)	1 (8%)	4 (15%)	2 (13%)	2 (18%)	

[a] P-values based on complete case analysis unless unknown is displayed. Statistical analysis using chi square test but # Mann–Whitney U test.
[b] Median, in case of multiple readmissions, only the first readmission was taken. EBD = endoscopic biliary drainage, PTBD = percutaneous biliary drainage, SEMS = self-expandable metallic stent.

radiofrequency ablation) prior to stenting could prolong stent patency and therefore outcome.[24,25] However, this might be more applicable in the palliative setting. There are also several new percutaneous options being investigated. For example percutaneous trans hepatic stenting with plastic or (fully covered) metal stents.[26] Large prospective studies are necessary to investigate and proof its superiority to current methods.

This study has several limitations. First, due to a relatively small cohort of only 54 patients, some analyses were subject to small number of patients or low number of events. Besides, for this study an overall survival primary endpoint was chosen although this was not the primary endpoint of the initial DRAINAGE trial. Therefore, numbers are probably underpowered. In addition, these comparisons are based on an intention to treat principle, which should in theory lead to a decrease in bias. However, 16 out of the 54 patients (30%, 15 out of the 27 patients in the EBD group (56%)) of the patients required crossover treatment during the DRAINAGE trial, which could have led to a skewed distribution.

In conclusion, this study aimed to provide insight into the long-term outcomes of an unselected group of patients with potentially resectable pCCA. Although numbers of patients might not be sufficient, no long-term differences in terms of survival, readmissions, and drainage procedures for EBD and PTBD were found, even when comparing the resected and unresected group. For this study cohort, OS was poor and a high

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rate of unplanned readmissions mostly due to stent-related complications were observed. This study highlights the urgent need for improvement and standardization in the care for patients with pCCA.

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Conflict of interest

None to declare.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.hpb.2022.10.009.

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