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ORIGINAL ARTICLE

Hepatopancreatoduodenectomy –a controversial treatment for bile duct and gallbladder cancer from a European perspective

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Abstract

Background: Hepatopancreatoduodenectomy (HPD) is an aggressive operation for treatment of advanced bile duct and gallbladder cancer associated with high perioperative morbidity and mortality, and uncertain oncological benefit in terms of survival. Few reports on HPD from Western centers exist. The purpose of this study was to evaluate safety and efficacy for HPD in European centers.

Method: Members of the European-African HepatoPancreatoBiliary Association were invited to report all consecutive patients operated with HPD for bile duct or gallbladder cancer between January 2003 and January 2018. The patient and tumor characteristics, perioperative and survival outcomes were analyzed.

Results: In total, 66 patients from 19 European centers were included in the analysis. 90-day mortality rate was 17% and 13% for bile duct and gallbladder cancer respectively. All factors predictive of perioperative mortality were patient and disease-specific. The three-year overall survival excluding 90-day mortality was 80% for bile duct and 30% for gallbladder cancer (P = 0.013). In multivariable analysis R0-resection had a significant impact on overall survival.

Conclusion: HPD, although being associated with substantial perioperative mortality, can offer a survival benefit in patient subgroups with bile duct cancer and gallbladder cancer. To achieve negative resection margins is paramount for an improved survival outcome.

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Introduction

Concomitant liver and pancreatic head resection including the duodenum, that is hepatopancreatoduodenectomy, HPD, has been proposed for bile duct and gallbladder cancers extending into both the liver and pancreas in order to achieve tumor clearance. Reports from Eastern centers have shown relatively low perioperative mortality although high morbidity rate with acceptable long-term survival for this complex procedure.[1,2] The use of HPD is however controversial and is not universally considered.

Because of its infrequent use, little has been reported from Western centers on HPD for bile duct and gallbladder cancers.[3–5] Due to various reasons, such as differences in population and nature of the disease process, reported experience differs between Eastern and Western centers. For example, the perioperative mortality after resection of perihilar cholangiocarcinoma seems to be higher in Western as compared to Eastern centers.[6]

The aim of this retrospective case-series study was to describe the outcomes after HPD for bile duct and gallbladder cancer in European centers through a collaborative effort within the European-African Hepato-Pancreato-Biliary Association (E-AHPBA).

Methods

Members of the E-AHPBA were invited to participate and report all consecutive patients operated with HPD for bile duct or gallbladder cancer between January 2003 and January 2018. HPD was defined as a combination of liver resection, resection of extrahepatic bile ducts, and pancreatic resection, either as pancreaticoduodenectomy or total pancreatectomy. The primary endpoint of this study was 90-day morbidity and mortality rates. The secondary endpoints were R0-resection rate and overall 3-year survival stratified according to type of primary cancer (bile duct or gallbladder cancer).

Participating centers reported their data through an online questionnaire (Caspio®) containing predefined case report forms. Postoperative complications were scored and classified using the Clavien-Dindo classification of surgical complications.[7] Major complications were defined as Clavien-Dindo grade 3–4. Ninety-day mortality (Clavien-Dindo 5) was calculated separately. The definitions of the recommended International Study Group on Pancreatic Surgery (ISGPS) and 2016 update of International Study Group on Pancreatic Fistula (ISGPF)[8] were used to score postoperative pancreatic fistula, delayed gastric emptying[9] and post-pancreatectomy haemorrhage.[10] Postoperative bile leakage and liver failure were defined according to the International Study Group of Liver Surgery.[11,12] The wording 'two-stage procedure' was in the present study used to describe a procedure when the pancreatic and liver resections were performed at two different occasions not separated more than 2 months in time.

Resection margins, including transection and circumferential margins, were classified as follows: R0 (distance, margin to tumor $\geq$ 1 mm), R1 (distance, margin to tumor < 1 mm) and R2 (macroscopically positive margin). Complications and mortality were all recorded up to 90 days postoperatively. Tumor stage was described according to the American Joint Committee on Cancer (AJCC) TNM 7th edition system.[13]

Statistical analysis

Summary statistics were presented as whole numbers and percentages for categorical variables, or as medians with interquartile ranges (IQRs) for continuous variables, unless otherwise stated. A Mann–Whitney U-test was used to compare continuous data, and Fischer's exact test was used for categorical data. Kaplan–Meier analysis was used to estimate survival from the time of operation. Overall survival was calculated from the time of operation. To analyze the effect of patient, tumor and procedure specifics on survival, uni- and multivariable Cox proportional hazards models were used for independent variables. A P-value less than 0.05 was considered statistically significant. Statistical analysis was performed using R (R Core Team (2016). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/).

Ethics

The study protocol was approved by the regional ethics board in Stockholm, Sweden. All participating centers were individually responsible to obtain adequate ethical approval according to national/local legislation before inclusion of patients.

Results

Patient characteristics and operative data

Sixty-six patients who underwent HPD for bile duct or gallbladder cancer from 19 European centers were included. The median number of patients submitted from each center was 2.[1–6]

Table 1 Clinical and surgical data

Characteristic	Value
Number of patients	66
Age (years)	60 (54–67)
Female gender	30 (46)
Body mass index (kg/m^2)	25 (23–27)
Preoperative albumin (g/l)	36 (31–40)
Preoperative bilirubin (μmol/l)	16 (8–36)
Preoperative biliary decompression	40 (61)
Type of decompression	
None	26 (39)
ERCP	29 (44)
PTBD	5 (8)
Both	6 (9)
Portal vein embolization	10 (15)
ASA (3–4)	11 (19)
Preoperative chemotherapy	5 (8)
Planned HPD procedure	36 (54)
Type of liver resection	
2 segments	17 (26)
Left hemihepatectomy	6 (9)
Right hemihepatectomy	21 (32)
Right hepatic trisectionectomy	22 (33)
Concomitant resection of segment 1	21 (32)
Major liver resection	49 (74)
Total pancreatectomy	7 (11)
Arterial resection and reconstruction	2 (3)
Portal vein resection and reconstruction	10 (15)
Two-stage procedure	3 (4)
Operative time (ml)	520 (438–600)
Intraoperative blood loss (ml)	1000 (650–1600)
Intraoperative blood transfusion	30 (54)
Diagnosis	
Bile duct cancer	35 (53)
Gallbladder cancer	31 (47)
T-stage	
1	3 (5)
2	16 (25)
3	22 (34)
4	24 (37)
N classification (pN1)	46 (70)
M classification (pM1)	11 (17)
Major complication (Clavien-Dindo 3–4)	33 (50.0)
Liver failure grade B or C	9 (14)
Bile leakage, grade B or C	18 (27)
Pancreatic fistula grade B or C	13 (20)
Delayed gastric emptying	20 (30)
Post-pancreatectomy hemorrhage grade B or C	6 (9)
Re-laparotomy within 90 days	10 (15)
Need for interventional radiology	26 (39)
Main reason for intervention/re-laparotomy	
Bile leak	16 (55)
Bleeding	4 (14)
Fluid collection	4 (14)
Other	5 (17)
Initial hospital stay (days)	23 (15–35)
Readmission within 90 days	10 (16)
Death within 90 days	10 (15)
Adjuvant chemotherapy	18 (27)
Positive resection margin	13 (20)

The clinical characteristics of all patients are presented in Table 1 and divided according to indication for surgery (bile duct or gallbladder cancer) in Table 2. A larger proportion of patients with bile duct cancer needed biliary decompression (80%) and this was primarily achieved by ERCP with PTBD being required/preferred in only few patients. Portal vein embolization was used to increase future liver remnant in only 10 patients (15%) in the cohort. Of the 10 patients requiring re-laparotomy, 7 also underwent interventional radiology procedures. The ratio of the future liver remnant volume to the total functional liver volume for patients undergoing major liver resections (resection of ≥3 Couinaud's segments) was 37 (32–42)% and 40 (35–45)% for the bile duct cancer group and gallbladder cancer group, respectively.

In about half of the cases (46%) HPD was not planned before surgery. In these cases, the operative strategy was changed due to the results of intraoperative frozen section. Three and 4 patients underwent pancreatectomy because of gross peripancreatic lymph node tumor involvement in the bile duct cancer group and gallbladder cancer group, respectively. The other patients had pancreatectomy because of longitudinal spread of cancer in the hepatoduodenal ligament. Three patients with bile duct cancer were operated in two steps. Two patients had the liver operation first and the pancreatoduodenectomy 7 and 15 days later and one patient a reverse approach with a 48-day delay between the two procedures. Major hepatectomy (≥3 liver segments) was significantly more common in the bile duct cancer group as compared to the gallbladder cancer group (91% vs 55%, p = 0.001) and vascular resections and reconstructions were relatively uncommon (18% of patients). Only 17 (49%) patients with bile duct cancer underwent a caudate lobe excision. Total pancreatectomy was performed in 7 patients aiming at preventing potential pancreatic fistula morbidity.

Table 2 Clinical and surgical data stratified according to cancer type

	Bile duct cancer	Gallbladder cancer	p
Number of patients	35	31	
Age (years)	60 (54–67)	61 (55–67)	0.918
Female gender	11 (31)	19 (61.3)	0.025
Body mass index (kg/m^2)	24 (23–26)	25 (23–29)	0.331
Preoperative albumin (g/l)	36 (33–40)	33 (30–39)	0.209
Preoperative bilirubin (μmol/l)	21 (11–65)	10 (6–25)	0.018
Preoperative biliary decompression	28 (80.0)	12 (38.7)	0.001
Type of decompression			0.003
None	7 (20)	19 (61)	
ERCP	20 (57)	9 (29)	
PTBD	3 (9)	2 (7)	
Both	5 (14)	1 (3)	
Portal vein embolization	6 (17)	4 (13)	0.739
ASA (3–4)	5 (15)	6 (25)	0.499
Preoperative chemotherapy	2 (6)	3 (10)	0.659
Planned HPD procedure	22 (63)	14 (45)	0.216
Type of liver resection			0.001
2 segments	3 (9)	14 (45)	
Left hemihepatectomy	6 (17)	0 (0)	
Right hemihepatectomy	14 (40)	7 (23)	
Right hepatic trisectionectomy	12 (34)	10 (32)	
Concomitant resection of segment 1	17 (49)	4 (13)	0.003
Major liver resection	32 (91)	17 (55)	0.001
Total pancreatectomy	5 (14)	2 (6)	0.433
Arterial resection and reconstruction	1 (3)	1 (3)	1
Portal vein resection and reconstruction	6 (17)	4 (13)	0.739
Two-stage procedure	3 (9)	0 (0)	0.241
Operative time (ml)	560 (500–620)	470 (380–534)	0.003
Intraoperative blood loss (ml)	1050 (700–1500)	1000 (650–1700)	0.469
Intraoperative blood transfusion	14 (48)	16 (62)	0.419
T-stage			<0.001
1	3 (9)	0 (0)	
2	14 (41)	2 (6)	
3	12 (35)	10 (32)	
4	5 (14)	19 (61)	
N classification (pN1)	18 (51.4)	28 (90.3)	0.001
M classification (pM1)	6 (17.1)	5 (16.1)	1
Major complication (Clavien-Dindo 3–4)	22 (62.9)	11 (35.5)	0.048
Liver failure grade B or C	8 (22.9)	1 (3.2)	0.030
Pancreatic fistula grade B or C	9 (26)	4 (13)	0.483
Bile leakage, grade B or C	13 (37)	5 (16)	0.031
Delayed gastric emptying	14 (40)	6 (19)	0.107
Post-pancreatectomy hemorrhage grade B or C	3 (9)	3 (10)	1
Re-laparotomy within 90 days	6 (17)	4 (12)	0.739
Need for interventional radiology	16 (46)	10 (32)	0.318

Table 2 (*continued*)

	Bile duct cancer	Gallbladder cancer	p
Main reason for intervention			0.292
Bile leak	12 (67)	4 (36)	
Bleeding	1 (6)	3 (27)	
Fluid collection	2 (11)	2 (18)	
Other	3 (17)	2 (18)	0.475
Initial hospital stay (days)	23 (18–36)	18 (15–33)	0.083
Readmission within 90 days	8 (24.2)	2 (6.5)	0.759
Death within 90 days	6 (17)	4 (13)	0.739
Adjuvant chemotherapy	9 (26)	9 (29)	0.789
Positive resection margin	9 (26)	4 (13)	0.228

Pathologic variables

In the gallbladder cancer group there was a higher proportion of patients (93%) with T3 and T4 cancers as compared to the bile duct cancer group (49%, P = 0.0001). The gallbladder cancer group also had a higher incidence of regional lymph node metastases (P = 0.001). R0 resection was achieved in 74% of bile duct cancer and 87% of gallbladder cancer patients (P = 0.228). R1 was noted as a positive radial margin in the hepatoduodenal ligament (n = 9), proximal bile duct (n = 3) and liver transection margin (n = 1). The 11 patients classified as M1 had positive lymphnodes either at the coeliac trunk or aortocaval window on final pathology.

Morbidity and mortality (perioperative/surgical outcomes)

Overall postoperative morbidity was high with 50% of patients in the cohort experiencing major complications (Clavien-Dindo grade 3–4) with a higher rate in the bile duct cancer group (63%), as compared to the gallbladder cancer group (35%, p = 0.048). The majority of interventions were for bile leakage. Postoperative liver failure was significantly higher in the bile duct cancer group as compared to the gallbladder cancer group (23% vs 3%, p = 0.030). Grade B and C pancreatic fistula was reported in 13 patients (20%). Ninety-day mortality was 15% (n = 10) for the entire group. The cause of death was multiorgan failure (n = 3), disease recurrence (n = 2), pulmonary embolism (n = 1), liver failure (n = 1), bilateral adrenal infarction (n = 1), sepsis (n = 1). For one patient, the cause of death was not reported. Of the patients who died within 90 days of the operation, one patient dying of multiorgan failure was reported to have had liver failure, and two patients had had a pancreatic fistula, of which one died of multiorgan failure and one died of disease recurrence. Higher BMI, ASA grade 3–4, gallbladder cancer diagnosis, T3 or T4 tumors and lymph node positivity were associated with significantly higher mortality on multivariable analysis (Table 3). Uni- and multivariable analysis of factors influencing major morbidity are shown in Table 4.

Survival

The 3-year overall survival rates for the bile duct and gallbladder cancer groups are shown in Fig. 1a and excluding 90-day mortality in Fig. 1b. Patients operated for gallbladder cancer had a significantly poorer oncological outcome when compared to those operated for bile duct cancer when analyzing only 90-day survivors (P = 0.013) but did not reach significance when including all patients (P = 0.086). Recurrence-free survival was significantly worse for gallbladder cancer patients (Fig. 2) (P = 0.018). On multivariable analysis, only positive resection margins at pathology had a significant impact on overall survival (Table 5).

Discussion

The present study is the largest Western case-series on HPD for bile duct and gallbladder cancer. The rarity of the procedure is reflected by the small number of procedures performed at each of the participating centers. The use of HPD is not universal for advanced bile duct and gallbladder cancer due to a high perioperative mortality and a poor long-term survival. A perioperative mortality of 10% was calculated in a review by Zhou et al.,[14] covering almost exclusively results from Eastern centers. In recent years, expert single-center experiences with HPD have shown a very low mortality below a few percent.[1,2] Reports from Western centers on perioperative mortality for HPD for bile duct and gallbladder cancer are scarce.[3] In the present study the 90-day perioperative mortality after HPD was 17% for bile duct cancer and 13% for gallbladder cancer. Differences in mortality rates between Eastern and Western centers have also been shown after resection of perihilar cholangiocarcinoma without HPD where Western centers report a perioperative mortality of 12% as compared to 3% in Eastern centers.[15]

Previous studies on mortality after resection of perihilar cholangiocarcinoma have mainly focused on biliary drainage and the importance of the size of the future liver remnant.[16] Factors associated with better results after perihilar cholangiocarcinoma resection are the frequent use of preoperative portal vein embolization and withholding resection until a normal or near-normal serum bilirubin level is attained using preferably internal biliary drainage.[17] In the present study, almost all patients had normal bilirubin levels before resection, although the proportion

Table 3 Mortality within 90 days of resection

	Univariable analysis			Multivariable analysis		
	HR	95% CI	p	HR	95% CI	p
Age (>70 years)	3.09	[0.80, 11.97]	0.102	1.46	[0.18, 11.54]	0.722
Female gender	0.76	[0.22, 2.71]	0.676			
Body Mass Index>25 kg/m^2	2.86	[0.71, 11.45]	0.137	**12.6**	**[1.62, 97.77]**	**0.015**
Preoperative albumin >30 g/l	0.18	[0.05, 0.72]	0.016	0.45	[0.04, 4.78]	0.505
Preoperative biliary decompression	0.64	[0.19, 2.21]	0.481			
Portal vein embolization	2.56	[0.66, 9.90]	0.173	4.97	[0.64, 38.72]	0.125
ASA (3–4)	3.16	[0.89, 11.24]	0.075	**17.61**	**[1.62, 190.93]**	**0.018**
Planned HPD procedure	0.54	[0.15, 1.92]	0.344			
Major liver resection	3.32	[0.42, 26.20]	0.255			
Operative time >600 min	1.92	[0.43, 8.58]	0.393			
Bile duct cancer	Ref			Ref		
Gallbladder cancer	0.73	[0.21, 2.58]	0.624	**0.06**	**[0.01, 0.62]**	**0.018**
N classification (pN1)	4.25	[0.54, 33.56]	0.17	**30.72**	**[1.03, 918.49]**	**0.048**
T classification 3-4	4.03	[0.51, 31.83]	0.186	**13.29**	**[1.00, 177.53]**	**0.05**
M classification (pM1)	2.22	[0.57, 8.57]	0.249			
Positive resection margin	1.71	[0.44, 6.63]	0.435			
Portal vein resection	2.83	[0.73, 10.96]	0.132	0.97	[0.09, 10.13]	0.978
Pancreatic fistula	1.72	[0.44, 6.64]	0.434			
Pancreatic hemorrhage	3.04	[0.64, 14.38]	0.161	1.88	[0.25, 14.17]	0.539
Liver failure	1.59	[0.34, 7.49]	0.558			

Bold values signify statistical significance at the p<0.05 level.

of patients subjected to portal vein embolization was comparatively low, only 15% of all patients. This could be explained by the small number of patients submitted to hepatic trisectionectomy (Table 1). There was no trend towards increased utilization of portal vein embolization during the study period (results not shown).

Table 4 Major morbidity within 90 days of resection (Clavien-Dindo 3–4)

	Univariable analysis			Multivariable analysis		
	HR	95% CI	p	HR	95% CI	p
Age (>70 years)	2.07	[0.78, 5.47]	0.142	3.03	[0.97, 9.49]	0.056
Female gender	0.77	[0.36, 1.65]	0.505			
Body Mass Index>25 kg/m^2	1.23	[0.58, 2.59]	0.589			
Preoperative albumin >30 g/l	0.66	[0.25, 1.75]	0.401			
Preoperative biliary decompression	1.47	[0.65, 3.33]	0.353			
Portal vein embolization	1.87	[0.75, 4.62]	0.177	1.61	[0.48, 5.37]	0.437
ASA (3–4)	1.15	[0.44, 3.01]	0.783			
Planned HPD procedure	0.61	[0.29, 1.27]	0.188	0.43	[0.18, 1.06]	0.066
Major liver resection	1.77	[0.61, 5.13]	0.294			
Operative time >600 min	2.04	[0.93, 4.46]	0.074	1.62	[0.62, 4.24]	0.329
Bile duct cancer	Ref			Ref		
Gallbladder cancer	0.64	[0.30, 1.38]	0.252	0.59	[0.22, 1.61]	0.306
N classification (pN1)	2.17	[0.88, 5.36]	0.091	1.85	[0.57, 6.03]	0.306
T classification 3-4	0.96	[0.44, 2.09]	0.919			
M classification (pM1)	1.37	[0.56, 3.37]	0.493			
Positive resection margin	2.79	[1.28, 6.06]	0.01	2.14	[0.82, 5.58]	0.118

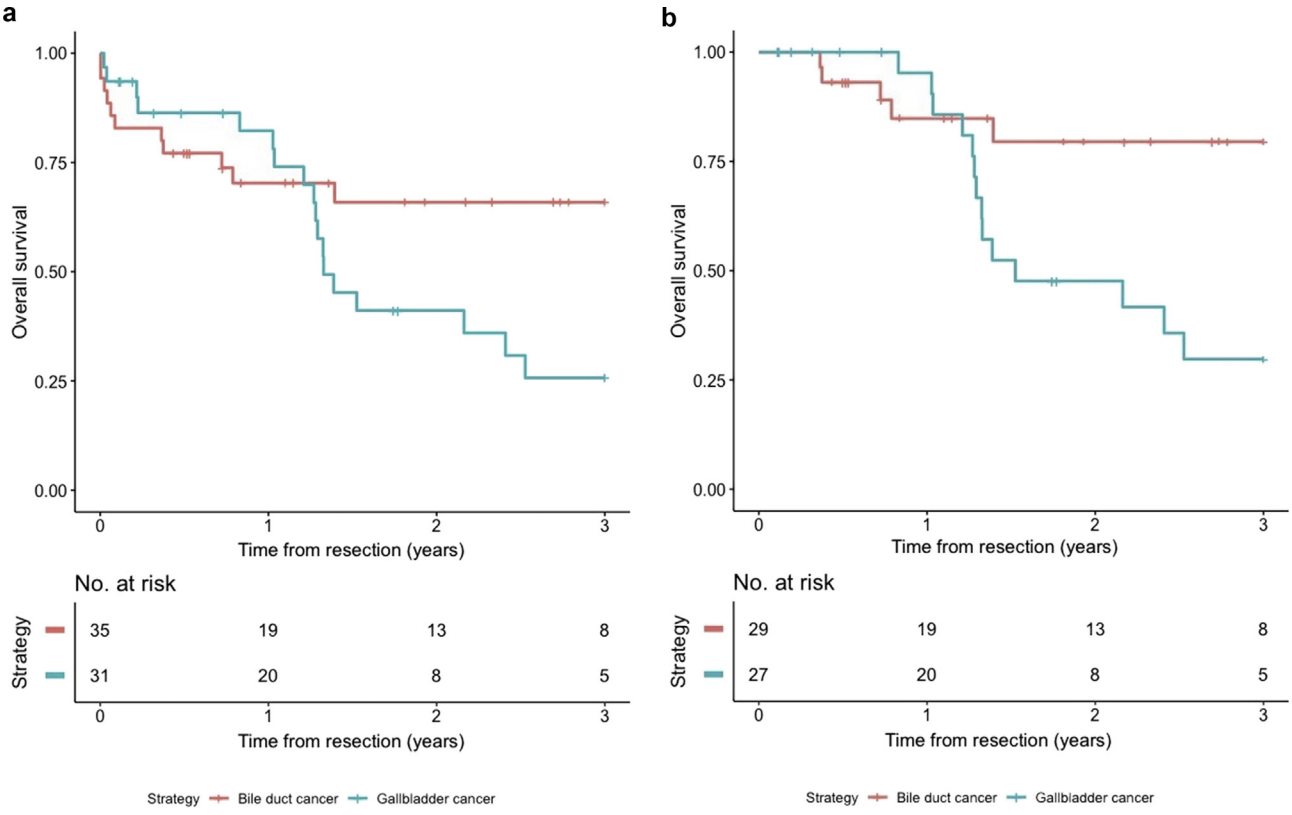

Figure 1 (a) Overall survival after HPD for all patients. (b) Overall survival after HPD excluding 90 -day mortality.

Postoperative liver failure is an important predictor of mortality after resection of perihilar cholangiocarcinoma.[18] In the present study the rate of liver failure was 23% for bile duct cancer patients and 3% for patients with gallbladder cancer. Comparison to other studies is complicated by the use of different definitions of liver failure. In the present study, liver failure was defined as grade B and C according to the International study group of liver surgery.[11] Even lower rates of liver failure have been reported after HPD. In the study by Aoki et al. 52 patients underwent HPD and liver failure occurred in 2 patients only.[2] In the study by Ebata et al. liver failure was recorded in 56 of 85 patients.[1] These large variations reported on postoperative liver failure after HPD are difficult to explain. In the present study, the comparatively low rate of liver failure could be the result of the fewer number of hepatic trisectionectomies performed in carefully selected patients, and that many patients with gallbladder cancer (45%) had resection of two liver segments only.

In the present study, a pancreatic fistula rate of 20% was found. Postoperative pancreatic fistula occurrence is associated with morbidity and mortality after pancreatoduodenectomy. A 20% clinically relevant fistula rate (grade B and C according to ISGP[8]) can be expected.[19,20] Higher frequencies are anticipated in case of a soft pancreatic texture and small pancreatic duct, as can be the case in most patients undergoing HPD.

No impact on perioperative mortality was found due to liver failure or pancreatic fistula in the present study. Actually, factors predictive of mortality were all patient or disease specific. High body mass index has previously been shown to increase morbidity after HPD.[1] Also lymph-node positive and high tumor stage disease increased the risk for mortality. It is plausible that more extensive disease requires more technically demanding procedures increasing the perioperative mortality rate. To decrease the perioperative mortality careful preoperative patient selection is necessary. Comorbidities rather than age seem to influence the risk of mortality. An internationally accepted prospective protocol defining preoperative performance and careful description of the radiological tumor burden in addition to common guidelines on the use of preoperative portal vein embolization and biliary drainage is necessary for a better future selection of which patient group is best served by HPD.

On multivariable analysis, no factor was identified as predictive of major morbidity (Clavien-Dindo grade 3–4) excluding perioperative mortality. A factor almost significantly (P = 0.066) protective for morbidity was if the HPD procedure was planned, that is, if decision to perform HPD was taken before surgery. A planned HPD could reflect a better patient selection in terms of operability. In almost half of the patients, the decision to perform HPD was taken intraoperatively, which was more common for

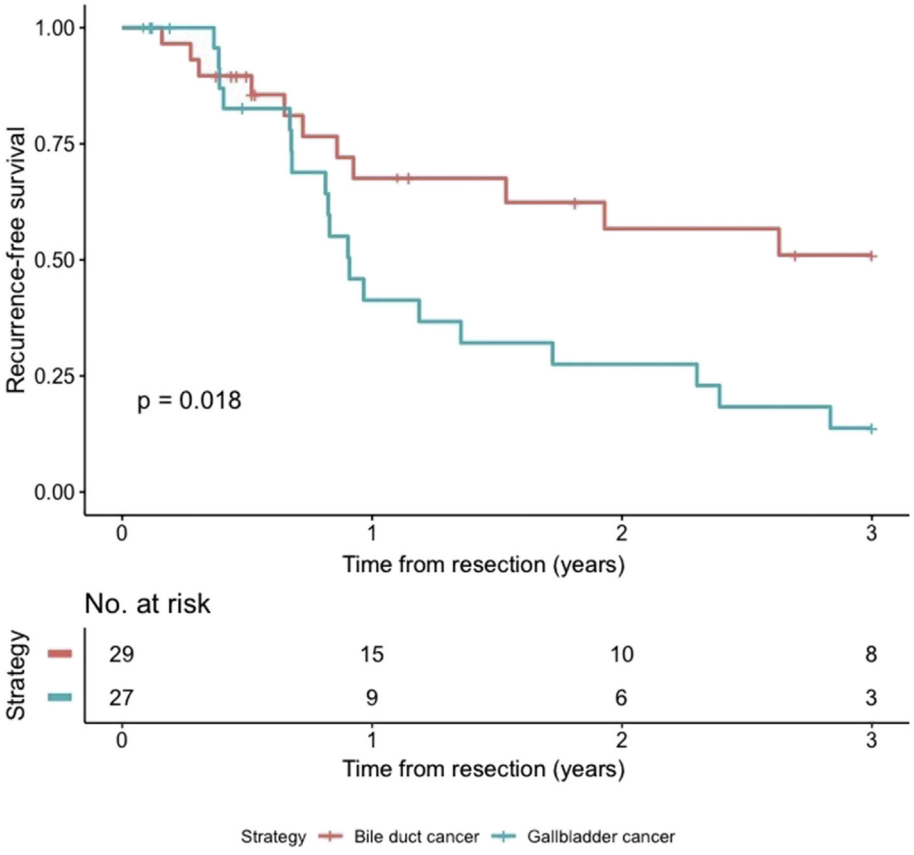

Figure 2 Recurrence-free survival after HPD excluding 90-day mortality.

Table 5 Overall survival for 90-day survivors

	Univariable analysis			Multivariable analysis		
	HR	**95% CI**	**p**	**HR**	**95% CI**	**p**
Age (>70 years)	1.57	[0.36, 6.81]	0.548			
Female gender	1.75	[0.70, 4.38]	0.229			
Body Mass Index>25 kg/m^2	1.11	[0.34, 3.64]	0.864			
Preoperative albumin >30 g/l	0.74	[0.16, 3.38]	0.701			
Preoperative biliary decompression	0.59	[0.24, 1.46]	0.254			
Portal vein embolization	0.9	[0.21, 3.93]	0.891			
ASA (3–4)	1.91	[0.51, 7.08]	0.334			
Planned HPD procedure	**0.42**	**[0.17, 1.04]**	**0.06**	0.42	[0.14, 1.29]	0.13
Major liver resection	**0.27**	**[0.11, 0.67]**	**0.005**	0.43	[0.15, 1.20]	0.106
Operative time >600 min	1.15	[0.31, 4.37]	0.833			
Bile duct cancer	Ref			Ref		
Gallbladder cancer	**3.39**	**[1.22, 9.46]**	**0.019**	2.15	[0.52, 8.93]	0.292
N classification (pN1)	**5.28**	**[1.22, 22.89]**	**0.026**	2.35	[0.45, 12.29]	0.311
T classification 3-4	**3.1**	**[0.90, 10.69]**	**0.073**	1.4	[0.26, 7.60]	0.695
M classification (pM1)	1.01	[0.29, 3.46]	0.991			
Positive resection margin	2.24	[0.80, 6.29]	0.127	**5.17**	**[1.31, 20.33]**	**0.019**

Bold values denote statistical significance at the p<0.05 level.

gallbladder cancer. Intraoperative switch to HPD has been shown to be associated to a decreased recurrence-free survival.[2]

Caudate lobe resection is generally recommended during resection of perihilar cholangiocarcinoma in order to increase the rate of R0 resection and also increase survival.[21] The frequency of caudate lobe resection in the present study was for bile duct cancer only 49%. Reasons for not including the caudate lobe in the resection could be preoperative imaging negating involvement or intraoperative technical challenges.[22]

Overall 3-year survival was 66% for the bile duct cancer group and 26% for the gallbladder cancer group (P = 0.086). When excluding patients with 90-day mortality, the corresponding figures were 80% and 30%, respectively (P = 0.018). Because of the small patients numbers in the present study, the survival data should be interpreted with caution. Previous studies comparing survival after HPD depending on diagnosis have yielded conflicting results. Some studies could not demonstrate any difference between bile duct and gallbladder cancer patients,[2,23–25] while others have shown a lower survival for gallbladder cancer patients.[26,27] The more advanced T-stage for the gallbladder cancers as compared to the bile duct cancers in the present study might be an important reason for the worse survival. The oncological value of HPD for gallbladder cancer can be questioned based on the results of the present study. However, the survival of unresectable patients has been shown to be even worse,[27] indicating a possible benefit of resection, although there have been recent improvements in the oncological treatment of unresectable biliary tract cancer.[28]

Metastatic disease (positive aortocaval or coeliac trunk lymph nodes) was not found significant for decreased overall survival in the present study. However, the number of patients was low. Lymph node invasion beyond the hepatoduodenal ligament is generally considered a contraindication for resection of biliary cancer, but still there exists a chance for long-term survival for patients resected for perihilar cholangiocarcinoma even with positive paraaortal lymphnodes.[17]

In the present study, the survival of bile duct cancer patients was superior to what has previously been reported after HPD. The only factor predictive of survival after multivariable analysis was R0 resection. A majority of R1 margins were at the radial margin in the hepatoduodenal ligament or liver hilum. The negative impact of radial margin positivity for cancer on survival has previously been reported after resection of perihilar cholangiocarcinoma.[29]

The present study has some important limitations. The number of procedures per contributing center was small reflecting a general cautious attitude to the use of HPD in Europe, which would mean that the patients operated were very selected. The number of patients denied HPD and their characteristics and survival is unknown. In addition, general limitations associated with retrospective studies are recall, information, and follow-up bias.

In conclusion, HPD with negative resection margins may confer a survival benefit to a proportion of patients with bile duct and gallbladder cancer. Due to the high perioperative mortality, as described in this multicenter retrospective European study, careful case selection should be ensured. The gravity of this surgery suggests that HPD should only be considered in experienced major HPB surgery centers.

Conflicts of interest

None declared.

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