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Treatment of mid-bile duct carcinoma: Local resection or pancreatoduodenectomy?

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ABSTRACT

Introduction: Whereas distal cholangiocarcinoma (DC) is treated by pancreatoduodenectomy (PD), consensus is lacking on treatment of mid-bile duct carcinoma (mid-BDC) without involvement of the pancreatic head. Both PD or a local resection (LR) of the extrahepatic bile duct with lymphadenectomy are being used. The aim of this study was to compare outcomes after PD and LR for mid-BDC and, for reference, PD for DC.

Methods: Retrospective monocenter study including consecutive patients who underwent LR for mid-BDC (LR), PD for mid-BDC (PD-mid) and PD for DC (PD-distal) between 2000 and 2016. Clinicopathologic characteristics, postoperative outcomes and survival were compared.

Results: A total of 184 patients were included (LR, 22; PD-mid, 38; PD-distal, 124). Postoperative mortality was 0% following LR, 5% (2/22) for PD-mid and 3% (4/124) for PD-distal, $p = 0.542$. Major complications occurred in 5/22 patients (23%), 19/39 (50%) and 46/124 (37%) respectively, $p = 0.103$ (LR versus PD-mid, $p = 0.038$).

Tumor size, differentiation grade and resection margin status were comparable across groups. Median number of resected lymph nodes was 5 (range 3–7), 9 (7–14) and 12 (8–16) respectively, $p < 0.001$. Median overall survival was 46 months (95%CI 10–82), 19 months. (95%CI 11–27), and 29 months (95%CI 23–35) respectively, $p = 0.39$ (LR versus PD-mid, $p = 0.20$). Disease-free survival also did not differ.

Conclusion: LR is an acceptable treatment for selected patients with mid-BDC, showing less morbidity and comparable survival despite smaller lymph node retrieval.

1. Introduction

Surgical resection remains the only curative treatment option for cholangiocarcinoma [1]. The type of resection primarily depends on anatomical localization of the tumor in the biliary tract. Extrahepatic cholangiocarcinoma is typically categorized into perihilar (PHC) and distal cholangiocarcinoma (DC), according to proximal or distal localization in the bile duct [2]. In between, mid-bile duct carcinoma (mid-BDC) may be considered as a separate entity as these are localized below the level of the biliary confluence and above the upper pancreatic border. Usually, mid-BDC is resected the same way as DC by performing pancreatoduodenectomy (PD) with transection of the bile duct high up in the liver hilum. Alternatively, in patients with mid-BDC, local resection (LR) of the extrahepatic bile ducts with locoregional lymphadenectomy may suffice to obtain negative proximal and distal resection margins. This limited resection has lower operative morbidity and may be chosen in selected patients, usually the elderly or poor surgical candidates [3,4]. However, the general assumption is that as lymphatic drainage of the distal area of the bile duct involves lymph nodes located in the peripancreatic fat tissue, not performing a PD may lead to inadequate lymph node assessment and decreased survival [5].

Previous reports provide insufficient evidence on whether LR may be sufficient for patients with a mid-BDC in terms of oncological outcome. Several studies have shown that primary tumor site in the bile duct (mid-BDC or DC) does not influence survival

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[6,7]. Two small studies comparing LR to PD for mid-BDC found comparable survival rates between both groups [4,8].

The aim of this study was to assess whether local bile duct resection alone is an acceptable treatment for patients with mid-BDC, in terms of postoperative morbidity, mortality, overall survival (OS) and disease-free survival (DFS).

Methods

We retrospectively analyzed records of all patients who underwent surgical exploration with curative intent for extrahepatic cholangiocarcinoma between January 2000 and December 2016 at a tertiary referral center (Amsterdam UMC, location AMC).

Patients were included if they underwent resection for extrahepatic cholangiocarcinoma without involvement of the biliary confluence. Patients with a Bismuth-Corlette type I PHC were also included: although formally these tumors are considered 'perihilar', they do not invade the biliary confluence. Final selection of patients was based on postoperative pathological evaluation, excluding patients with benign disease and with tumors not originating from the biliary tract epithelium. Clinicopathologic characteristics, perioperative outcomes and survival were compared across 3 groups: patients with mid-BDC undergoing LR (LR), patients with mid-BDC undergoing PD (PD-mid) and patients with DC undergoing PD (PD-distal). PD-distal patients functioned as a reference group for postoperative outcomes of PD-mid.

The Medical ethics committee of the Amsterdam UMC, University of Amsterdam waived the need for official approval (reference number W19_007#19.025).

Preoperative workup

Standard preoperative evaluation included computed tomography (CT) with intravenous contrast and either endoscopic retrograde cholangiopancreatography (ERCP) or percutaneous transhepatic cholangiography, both with brush cytology if possible.

In the presence of distant metastases and/or lymph node metastases outside the locoregional area, primary tumors were considered unresectable. Hepatic artery involvement or portal vein involvement without reconstructive options implied unresectability. For distal cholangiocarcinoma, resectability was identical as for pancreatic cancer and was determined according to the Dutch Pancreatic Cancer Group (DPCG) definition for resectability [9].

In case of obstructive jaundice, preoperative biliary drainage was performed either by ERCP or percutaneous transhepatic biliary drainage.

Surgical procedures

LR consisted of excision of the extrahepatic bile duct in combination with regional lymphadenectomy of the hepatoduodenal ligament, followed by biliary reconstruction by Roux-en-Y hepaticojejunostomy. For PD, pylorus-preserving resection was the standard surgical procedure, which was extended to a Whipple-procedure when necessary to achieve radical resection. Standard lymphadenectomy in PD consisted of resection of lymph node stations 5, 6, 8a, 12b1, 12b2, 12c, 13a, 13b, 14a, 14b, 17a, and 17b according to the 2014 ISGPS consensus statement [10]. Suspicious lymph nodes outside the standard resection area and lymph node station 8B and 9 were sampled for frozen section prior to resection. A positive lymph node at the level of the celiac trunc (station 9 and/or 8B) was considered a distant metastasis, and generally led to termination of the procedure.

When the surgeon deemed it possible peroperatively to obtain a radical resection without performing a PD, a LR was performed. Negative proximal and distal bile duct margins were obtained as confirmed by routine intraoperative frozen section. In case of a positive bile duct margin as confirmed by frozen section, additional resections were performed. .

Outcomes

Pre- and postoperative outcomes, as well as operative details (including procedures performed, duration of operation) were retrieved from patient charts. Preoperative data included patient characteristics (age, sex, ASA status, preoperative presence of cardiovascular disease, pulmonary disease and diabetes) as well as preoperative management (biliary drainage).

Pathology findings included histological differentiation (well, moderate or poor), lymphangio-invasion, perineural invasion, resection margin status and tumor staging. Microscopic presence of tumor cells within 1 mm of any resection margin was considered an R1 resection, and macroscopic residual tumor an R2 resection. A positive frozen section was always considered an R1 resection unless a re-resection was performed. Standard pathological examination after PD included assessment of the following resection margins: the pancreatic neck margin, the superior mesenteric artery (SMA) margin, the superior mesenteric vein (SMV)/portal vein (PV) margin, the posterior retroperitoneal margin, and the proximal bile duct margin. After local resection, the proximal and distal bile duct resection margins and the circumferential dissection margin were examined. Tumor staging was assessed using the American Joint Committee on Cancer (AJCC) TNM staging for pancreas and hepatobiliary cancers, according to the edition applicable at the time of treatment (6th or 7th edition) [11].

Operative mortality was defined as mortality by any cause within 90 days of surgery. Overall morbidity was defined as the number of patients with one or more (major or minor) complications occurring within 90 days of surgery. Severity of complications were graded according to the Clavien-Dindo classification [12]. Bile leakage was graded according to the International Study Group of Liver Surgery (ISGLS) criteria [13]. Postoperative pancreatic fistula (POPF) was graded according to the updated definition of the International Study Group for Pancreatic Fistula (ISGPF) [14] Hemorrhage was graded according to the ISGPS definition for postpancreatectomy hemorrhage, considering grade B or C PPH as clinically relevant (hemorrhage requiring blood transfusion or (surgical or radiological) reintervention) [15].

OS was calculated from date of surgery until date of death (by any cause). Survival status was confirmed with the Dutch municipal registry in June 2018. DFS was calculated from date of surgery until date of radiologically suspected tumor recurrence, or date of last hospital visit. Patients who died in the postoperative phase (<90 days) were excluded from the survival analyses. Patients were followed until June 2018.

Statistical analysis

Categorical data are presented as numbers and percentages, with statistical comparison made using a Chi square test or Fishers' exact test, as appropriate. Continuous data are presented as mean ± SD, or medians with range, according to the distribution of data. Data with a normal distribution were compared using an independent samples T test or one-way ANOVA. Non-normally distributed data was compared using a Mann-Whitney *U* test or Kruskal Wallis test. Cumulative OS and DFS were calculated using the Kaplan-Meier method. Comparisons were made by univariate log-rank test. The Cox proportional hazards model was used to assess correlation between number of lymph nodes and survival in an univariate analysis. Due to the sample size, multivariate Cox

regression analysis was not performed.

All data analyses were performed using SPSS software, version 24.0.0.1 (IBM Corp., Armonk, New York, USA). A two-sided p-value of <0.05 was considered statistically significant.

Results

Between 2000 and 2016, 184 patients underwent resection with curative intent for mid- or distal cholangiocarcinoma. Of these, 60 patients had a mid-BDC (LR: 22 patients and PD-mid: 38 patients) and 124 patients had DC (PD-distal). Hence, a total of 162 patients underwent PD.

Mean age was 65.1 years (SD ± 11.4), see Table 1. The majority of patients presented with jaundice (168/184 patients, 91.3%), and 163 patients (88.6%) underwent preoperative biliary drainage. Groups were comparable regarding age, ASA classification, comorbidity, BMI, presenting symptoms, and preoperative biliary drainage. A lower proportion of male patients was seen in PD-distal patients (69/124, 55.6%, p = 0.058). Only 8 patients received adjuvant chemotherapy (gemcitabine in 4 patients and gemcitabine + cisplatin in 4 patients), without differences between groups.

Operative details and postoperative outcomes

Mean operative time was shorter in patients undergoing LR: 310 min ± 97.5 versus 378 min ± 98.7 for PD-mid and 340 ± 105 for PD-distal; p = 0.052 (LR versus PD, p = 0.018), see Table 2. In 20/184 patients (10.9%), a vascular resection was performed, with no difference between groups. The majority of vascular resections concerned wedge resections of the portal vein (n = 13). Estimated blood loss was only recorded in 49/184 patients (26.6%), and was therefore not further analyzed.

Operative mortality was 0% (0/22) for LR, 5.3% for PD-mid (2/38 patients), and 3.2% for PD-distal (4/124 patients), p = 0.542 (LR versus PD, p = 0.359). Overall morbidity was 59.1% for LR (13/22 patients), 81.6% for PD-mid (31/38), and 66.1% for PD-distal, p = 0.120 (LR versus PD, p = 0.058). Severe morbidity was 22.7% for LR (5/22 patients), 50% for PD-mid (19/38 patients), and 37.1% for PD-distal (46/124 patients), p = 0.103 (LR versus PD, p = 0.038).

Clinically significant hemorrhage occurred in 0/22 patients (0%) undergoing LR, 8/38 patients (21.1%) for PD-mid, and 10/124 patients (8.1%) for PD-distal, p = 0.016 (LR versus PD, p = 0.010). In accordance with type of surgery, patients undergoing LR did not develop POPF. In patients undergoing PD the rate of POPF was 33.3% (54/162 patients). Delayed gastric emptying (DGE) occurred in 4/22 patients undergoing LR (18.2%) and 60/162 patients undergoing PD (37.0%), p = 0.038. Rates of bile leakage, intra-abdominal abscesses, pneumonia and surgical site infections did not differ between groups.

Length of stay was shorter in the group undergoing LR (median 11 days (IQR 7–15 days), versus 14 days (IQR 11–22) for PD-mid and 12 days (IQR 9–25) for PD-distal; p = 0.049).

Pathological findings

Tumor size was comparable between groups with a median of 20 mm (IQR 15–25 mm) in the LR group, 20 mm (IQR 15–25 mm) for PD-mid and 21 mm (IQR 15–27) for PD-distal, p = 0.708 (see Table 3). Between LR and PD-mid, T-stage was comparable, but PD-distal patients had a higher number of pT3 tumors (p = 0.008).

The median number of lymph nodes resected was 11 (IQR 7–15). This was significantly lower for patients undergoing LR (median of 5 (IQR 3–7), versus 9 for PD-mid (IQR 7–14) and 12 for PD-distal (IQR 8–16), p < 0.001). The number of patients with a pN1 stage was comparable between LR (6/22, 27%) and PD-mid (13/38, 34.2%),

Table 1
Baseline characteristics.

	Missing N (group A/B/C)	Total N = 184 (%)	Group A LR N = 22 (%)	Group B PD-mid N = 38 (%)	Group C PD-distal N = 124 (%)	p-value across 3 groups	p-value LR vs PD-mid
Age (mean ± SD)	0	65.1 ± 11.4	69.1 ± 9.4	65.3 ± 11.8	64.3 ± 11.4	0.182	0.196
Male sex	0	114 (62.0)	18 (81.8)	27 (71.1)	69 (55.6)	0.058	0.353
ASA classification	0						
- I/II		150 (81.5)	20 (90.9)	30 (78.9)	100 (80.6)	0.468	0.231
- III		34 (18.5)	2 (9.1)	7 (21.9)	25 (19.2)		
History of cardiovascular disease	0	39 (21.2)	5 (22.7)	8 (21.1)	26 (21.0)	0.983	0.879
Pulmonary disease	0	14 (7.6)	2 (9.1)	2 (5.3)	10 (8.1)	0.818	0.567
Diabetes	0	23 (12.5)	2 (9.1)	6 (15.8)	15 (12.1)	0.730	0.462
BMI (mean ± SD)	22 (6/3/13)	25.6 ± 3.9	25.3 ± 3.6	25.7 ± 3.3	25.6 ± 4.1	0.961	0.744
Presenting symptoms	0						
- Jaundice	0	168 (91.3)	20 (90.9)	33 (86.8)	115 (92.7)	0.527	0.636
- Abdominal pain	0	57 (31.0)	6 (27.3)	13 (34.2)	38 (30.6)	0.846	0.578
- Weight loss	0	124 (67.4)	12 (60)	22 (57.9)	90 (72.6)	0.094	0.801
- Cholangitis	0	24 (13.0)	3 (13.6)	5 (13.2)	16 (12.9)	0.995	0.958
Preoperative biliary drainage (yes)	0	163 (88.6)	18 (81.8)	33 (86.8)	112 (90.3)	0.477	0.599
Highest preoperative bilirubin (median, IQR)	68 (6/13/49)	206 (122-302)	201 (97-299)	180 (123-272)	225 (124-334)	0.709	0.968
Last preoperative bilirubin (median, IQR)	92 (13/19/60)	20 (13-37)	27 (15-39)	17 (11-49)	21 (12-37)	0.779	0.595
Preoperative diagnosis of malignancy confirmed by pathology	0	85 (46.2)	9 (40.9)	19 (50.0)	57 (46.0)	0.790	0.496
Adjuvant chemotherapy	0	8 (4.3)	1 (4,5)	0	7 (5.6)	0.328	0.367

Abbreviations: ASA, American Society of Anesthesiologists; BMI, body mass index; DC, distal cholangiocarcinoma; LR, local resection; PD-mid, pancreatoduodenectomy for mid-bile duct carcinoma; PD-distal, pancreatoduodenectomy for distal cholangiocarcinoma.

Table 2
Operative details and postoperative complications.

	Missing N (group A/B/C)	Total N = 184%)	Group A LR N = 22 (%)	Group B PD-mid N = 38 (%)	Group C PD-distal N = 124 (%)	p-value	p-value LR vs PD (A vs B + C)
Operative time (mean, SD)	13 (1/5/7)	342 ± 105	310 ± 97.5	378 ± 98.7	340 ± 105	0.052	0.018
Vascular resection (yes)	0	20 (10.9)	2 (9.1)	6 (15.8)	12 (9.7)	0.548	0.449
- RHA, segmental resection with e-e anastomosis		2	1	1	0		
- RHA, segmental resection with venous reconstruction		3	1	1	1		
- PV, wedge resection with primary closure		13	0	3	10		
- PV, segmental resection with e-e reconstruction		1	0	1	0		
- SMV, segmental resection with e-e reconstruction		1	0	0	1		
Overall morbidity	0	126 (68.5)	13 (59.1)	31 (81.6)	82 (66.1)	0.120	0.058
Severe morbidity (Clavien-Dindo ≥3)	0	69 (37.3)	5 (22.7)	19 (50.0)	46 (37.1)	0.103	0.038
Highest Clavien-Dindo:	0					0.525	0.170
- 0		58 (31.5)	9 (40.9)	7 (18.4)	42 (33.9)		
- 1		9 (4.9)	1 (4.5)	1 (2.6)	7 (5.6)		
- 2		48 (26.1)	7 (31.8)	11 (28.9)	30 (24.4)		
- 3		44 (23.9)	5 (22.7)	6 (15.8)	28 (22.6)		
- 4		19 (10.3)	0	2 (5.3)	13 (10.5)		
- 5 (90-day mortality)	0	6 (3.2)	0	2 (5.3)	4 (3.2)	0.542	0.349
Relaparotomy	0	11 (6.0)	0	3 (7.9)	8 (6.5)	0.428	0.207
Bile leakage (yes)	0	16 (8.6)	4 (18.2)	4 (10.5)	8 (6.5)	0.179	0.106
- Grade A		2	1	1	0		
- Grade B		13	3	3	7		
- Grade C		1	0	0	1		
Hemorrhage	0	18 (9.8)	0	8 (21.1)	10 (8.1)	0.016	0.010
- Grade B		10	0	4	6		
- Grade C		8	0	4	4		
POPF	0	53 (28.8)	0	16 (42.1)	37 (29.8)	0.002	<0.001
- Grade A		3	0	0	3		
- Grade B		42	0	14	28		
- Grade C		9	0	3	6		
Intra-abdominal abscess	0	40 (21.7)	5 (22.7)	9 (23.7)	26 (21.0)	0.932	0.905
Chyle leakage	0	16 (8.7)	0	4 (10.5)	12 (9.7)	0.117	0.123
Delayed gastric emptying	0	64 (34.8)	4 (18.2)	17 (44.7)	43 (34.7)	0.101	0.038
- Grade A		13	1	5	7		
- Grade B		25	1	7	17		
- Grade C		26	2	5	19		
Pneumonia	0	16 (8.7)	1 (4.5)	3 (7.9)	12 (9.7)	0.719	0.462
Surgical site infection	0	27 (14.7)	1 (4.5)	4 (10.5)	22 (17.7)	0.196	0.152
Length of stay (days)	0	12 (9-22)	11 (7-15)	14 (11-22)	12 (9-25)	0.049	0.050

The definitions of the International Study Group of Pancreatic Surgery were used for hemorrhage and POPF, and the definitions of the International Study Group of Liver Surgery were used for bile leakage. Abbreviations: DC, distal cholangiocarcinoma; LR, local resection; mid-BDC, mid-bile duct carcinoma; PD, pancreatoduodenectomy; POPF, postoperative pancreatic fistula; PV, portal vein; RHA, right hepatic artery; SMV, superior mesenteric vein.

but higher for PD-distal (83/124, 66.9%; $p < 0.001$). When comparing only patients who underwent PD, PD-distal still had a significantly higher proportion of pN1 patients ($p < 0.001$). The median number of resected lymph nodes between the two groups undergoing PD was comparable ($p = 0.178$).

Differentiation grade and resection margin status were comparable between groups. Of patients undergoing LR, tumor-positive resection margins were present in 9/22 patients (40.9%). In two patients, the distal bile duct transection margin was tumor-positive although peroperative frozen section was considered tumor-free. In one patient, the proximal bile duct resection margin was tumor-positive on frozen section; because of a suspicious lesion in the liver no additional resection was performed. However, on final pathology of the liver lesion, there was no liver metastasis. One patient had involvement of the hepatic artery. In the remaining 5 patients, the tumor invaded the circumferential resection margin.

Oncological outcomes

Median OS was 28 months (95% CI 21–35 months) and did not differ between groups: 46 months (95%CI 10–82) for LR, 19 months. (95%CI 11–27) for PD-mid, and 29 months (95%CI 23–35) for PD-distal, $p = 0.394$, see Table 4 and Fig. 1. Median follow-up time of censored patients for OS was 67 months (IQR 23–106 months).

Ninety-two patients (50.3%) developed a recurrence during follow-up. The majority of patients had local tumor recurrence (60/184, 66.7%). There were no significant differences between groups regarding tumor recurrence or site of recurrence. Median DFS was 26 months (95% CI 19–33 months) and also did not differ between groups: 30 months (95%CI 11–50 months) for LR, 13 months. (95%CI 1–52) for PD-mid, and 24 months (95%CI 18–31) for PD-distal, $p = 0.968$ (LR versus PD-mid, $p = 0.839$). Median follow-up time of censored patients for DFS was 16 months (IQR 8–45 months)

On univariate Cox regression, the number of lymph nodes resected showed no correlation with OS (HR 1.006, 95%CI 0.976–1.038, $p = 0.682$). For DFS, HR for the number of resected lymph nodes was 1.045 (95%CI 1.014–1.077, $p = 0.004$). When considering only N0 patients, the HR for OS for number of lymph nodes resected was 0.913 (95%CI 0.850–0.981, $p = 0.013$. When considering only lymph node positive patients, the number of lymph nodes resected showed no correlation with OS (HR 1.006, 95%CI 0.971–1.041, $p = 0.754$).

An R1 resection was associated with worse OS (HR 1.782, 95%CI 1.237–2.565, $p = 0.002$) and worse DFS (HR 2.067, 95%CI 1.360–3.141, $p = 0.001$).

Table 3
Pathological findings.

	Missing N (group A/B/C)	Total N = 184	Group A LR N = 22 (%)	Group B PD-mid N = 38 (%)	Group C PD-distal N = 124 (%)	p-value	P value LR vs PD-mid (A vs B)
Tumor size (mm, median (IQR))	20 (2/5/13)	20 (15-26)	20 (15-25)	20 (15-25)	21 (15-27)	0.708	0.932
Differentiation grade	4 (3/0/1)					0.492	0.193
- Well		13 (7.2)	2 (10.5)	1 (2.6)	10 (8.1)		
- Moderate		96 (52.2)	12 (63.2)	19 (50.0)	65 (52.8)		
- Poor		71 (39.4)	5 (26.3)	18 (47.4)	48 (39.0)		
Perineural invasion	42 (5/4/33)	132 (93.0)	17 (100)	33 (100)	82 (89.7)	0.082	>0.999
Lymphangio-invasion	77 (15/17/40)	68 (63.6)	4 (57.1)	9 (42.9)	55 (69.6)	0.078	0.431
T stage	1 (1/0/0)					0.008	0.434
- pT1		16 (8.7)	3 (14.3)	3 (7.9)	10 (8.1)		
- pT2		41 (22.4)	5 (23.8)	16 (42.1)	20 (16.1)		
- pT3		113 (61.4)	11 (52.4)	14 (36.8)	88 (71.0)		
- pT4		13 (7.1)	2 (9.5)	5 (13.2)	6 (4.8)		
N stage	0					<0.001	0.578
- pN0		82 (44.6)	16 (72.7)	25 (65.8)	41 (33.1)		
- pN1		102 (55.4)	6 (27.3)	13 (34.2)	83 (66.9)		
M stage							
- M0	0	184 (100)	22 (100)	32 (100)	130 (100)	>0.999	>0.999
Lymph nodes resected, median (IQR)	2 (0/0/2)	11 (7-15)	5 (3-7)	9 (7-14)	12 (8-16)	<0.001	<0.001
Tumorpositive lympnodes	1 (0/0/1)	1 (0-3)	0 (0-1)	0 (0-1)	1 (0-4)	<0.001	0.490
Margin status	0					0.830	0.928
- R0		116 (63.0)	13 (59.1)	22 (57.9)	81 (65.3)		
- R1		67 (36.4)	9 (40.9)	16 (42.1)	42 (33.9)		
- R2		1 (0.5)	0 (0)	0 (0)	1 (0.8)		
Place of irradicality:	0						
- Proximal bile duct transection margin		10 (5.4)	1 (4.5)	2 (5.3)	5 (4.0)	0.187	0.346
- Distal bile duct transection margin		2	2 (9.1)	–	–	–	
- Circumferential bile duct margin		18 (9.8)	5 (22.7)	12 31.6)	1 (0.8)	<0.001	0.560
- Anterior margin		14	–	3 (7.9)	11 (8.9)	–	
- Posterior (retroperitoneal) margin		24	–	6 (15.8)	18 (14.5)	–	
- SMV/PV margin		16 (8.7)	0	3 (7.9)	13 (10.5)	0.269	0.292
- SMA/HA margin		24 (13.0)	1 (4.5)	3 (7.9)	20 (16.1)	0.189	>0.999
- Pancreatic neck margin		3	–	0	3 (2.4)	–	

Abbreviations: HA, hepatic artery; LR, local resection; PD-distal, pancreatoduodenectomy for distal cholangiocarcinoma; PD-mid, pancreatoduodenectomy for mid-bile duct carcinoma; PV, portal vein; SMA, superior mesenteric artery; SMV, superior mesenteric vein.

Table 4
Oncological outcomes.

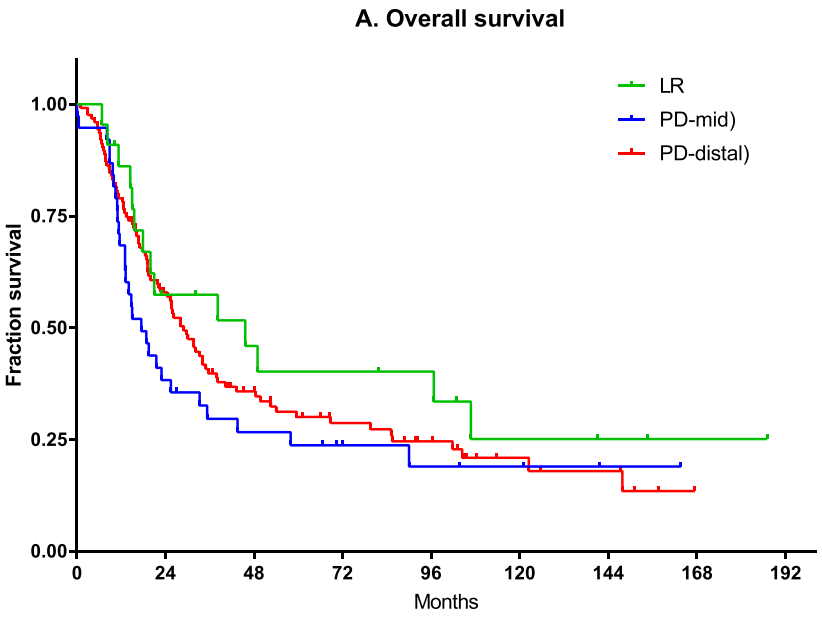
	Missing N (group A/B/C)	Total N = 184%)	Group A LR N = 22 (%)	Group B PD-mid N = 38 (%)	Group C PD-distal N = 124 (%)	p-value	p-value LR vs PD-mid (A vs B)
Median OS in months (95%CI)[a]	0	28 (21-35)	46 (10-82)	19 (11-27)	29 (23-35)	0.394	0.201
1-year OS		80%	86%	72%	80%		
3-year OS		41%	57%	31%	41%		
5-year OS		31%	40%	25%	31%		
Recurrence during follow-up	1 (0/1/0)	92 (50.3)	15 (68.2)	17 (48.6)	59 (49.2)	0.243	0.228
Site of recurrence:							
- Local		60 (66.7)	11 (73.3)	13 (81.3)	36 (61.0)	0.262	0.598
- Liver metastasis		31 (34.4)	4 (26.7)	7 (43.8)	20 (33.9)	0.600	0.320
- Lung metastasis		10 (11.1)	0 (0)	3 (18.8)	7 (11.9)	0.240	0.226
- Peritoneal metastasis		11 (12.2)	2 (13.3)	4 (25.0)	5 (8.5)	0.199	0.411
Median DFS in months (95%CI)[a]	1 (0/1/0)	26 (19-33)	30 (11-50)	13 (1-52)	24 (18-31)	0.968	0.839
1-year DFS		70%	68%	59%	74%		
3-year DFS		40%	41%	47%	38%		
5-year DFS		33%	33%	39%	32%		

Abbreviations: DFS, disease-free survival; LR, local resection; OS, overall survival; PD-distal, pancreatoduodenectomy for distal cholangiocarcinoma; PD-mid, pancreatoduodenectomy for mid-bile duct carcinoma.
[a] Excluding patients who deceased within 90 days of surgery.

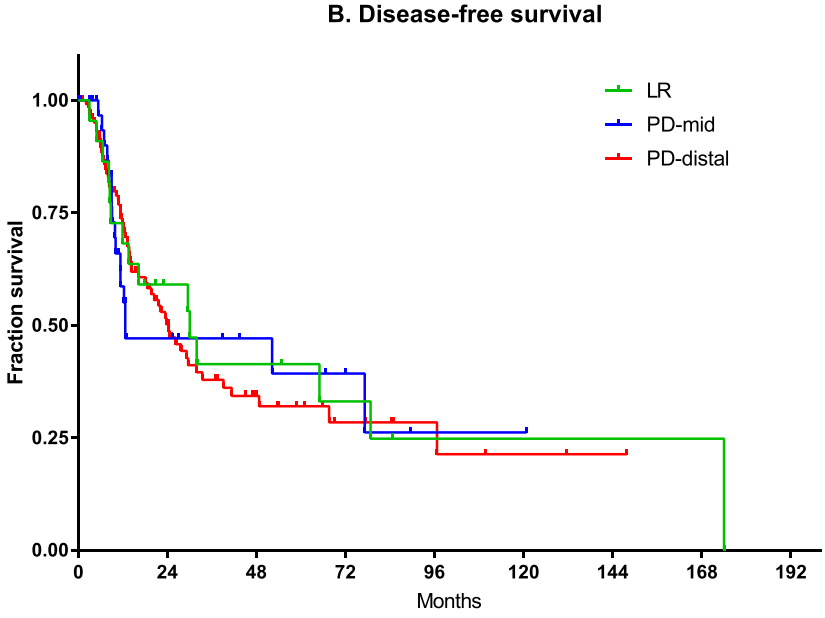
Discussion

Tumors along the biliary tract show high similarity in biological behavior and have comparable oncological outcomes. However, surgical approach depends on anatomical localization along the biliary tree [16,17].[*Strijker* et al., *submitted]* Therefore, from a surgical point of view mid-BDC could be considered as a separate entity. In this retrospective study undertaken in a tertiary referral center, patients undergoing LR for mid-BDC showed lower incidence of major complications, but similar OS and DFS when compared to patients undergoing PD for mid-BDC and PD for DC.

Few studies have evaluated outcomes of LR for mid-BDC. In a study comparing 45 patients after LR with 149 patients after PD, Lee et al. found no difference in OS [4]. Similarly, Kwon et al. found that if an R0 resection could be achieved, LR and PD showed similar survival in an analysis comparing 43 and 90 patients, respectively.



Number at risk									
Group A	22	11	8	7	6	3	3	2	1
Group B	36	14	9	6	4	3	1		
Group C	120	61	33	21	15	7	5		



Number at risk									
Group A	22	10	6	4	1	1	1	1	
Group B	35	11	6	4	1	1			
Group C	120	36	16	7	3	2	1		

Fig. 1. Survival according to type of resection (Kaplan-meier) **a)** Overall survival; **b)** Disease-free survival.
Abbreviations: LR, local resection; PD-mid, pancreatoduodenectomy for mid-bile duct carcinoma; PD-distal, pancreatoduodenectomy for distal cholangiocarcinoma.

Several smaller studies also concluded that LR of mid-BDC is a sufficient treatment [3,18].

It is obvious that LR leads to harvesting of fewer number of lymph nodes compared to PD, as was also the case in this study. This may lead to 'understaging', and thus less adequate estimation of the prognosis of a patient [5]. Several studies have demonstrated a negative correlation between the number of tumor positive lymph nodes and survival in patients with DC [19–21]. Positive lymph node status has also shown a negative correlation with survival [6,22]. However, some studies claimed that resection margin status is a stronger predictor for survival than lymph node status [6,7]. Lymph node ratio (LNR) has proven to be a strong

predictor for survival in patients with distal cholangiocarcinoma [23,24]. However, the low number of lymph nodes resected with LR most probably hampers adequate assessment of LNR or pN1 status in patients with mid-BDC, and was therefore not assessed in this study.

It remains unclear whether the number of resected lymph nodes only allows for a better estimation of prognosis, or whether the extent of lymphadenectomy actually influences survival in patients with extrahepatic cholangiocarcinoma. Extended lymphadenectomy in addition to PD has not shown beneficial for survival of adenocarcinoma of the pancreas [10]. In our present study, patients undergoing LR did not show worse survival rates, despite a significantly lower number of resected lymph nodes.

In this study, lymph node status in patients who underwent PD for a mid-BDC was significantly more often 'pN0' compared to patients who underwent PD for a DC (66% versus 33%) despite a comparable number of resected lymph nodes as these patients all underwent the same procedure. A possible explanation could be that lymphatic drainage of tumors arising from the middle part of the bile duct may go directly towards the liver as the absence of valves in the lymphatic ducts surrounding the CBD allows for a 'two-way flow' [25].

Although patients with a DC (who would be confined to a PD regardless of tumor size) in this study showed a higher proportion of pT3/T4 tumors, T-stage between group A and group B did not differ. Furthermore, median tumor size did not differ between groups. We therefore believe that the impact of tumor size or stage as a confounder in this study was minimal. The exact localization of the tumor may have influenced the choice for LR or a PD, however, it is unlikely that this localization influenced survival [6,7,26].

LR for mid-BDC was associated with lower severe morbidity, which is in accordance with previous publications [4]. Also, we observed a lower operative mortality in patients undergoing LR, although significance could not be demonstrated presumably due to the small sample size. Specific major complications, including hemorrhage, DGE and POPF, were less frequent or even completely absent in patients undergoing LR. These complications are known to have a major impact on patient recovery [27,28].

A limitation to this study and other studies assessing the correlation between lymph node status, LNR, or number of tumor positive lymph nodes and survival, is the fact that during pathological assessment, lymph nodes may either be missed or counted double [29]. Likewise, the assessment of residual disease may be influenced by the lack of a standardized description of all relevant resection planes.*[Roos* et al.*, submitted]* Furthermore, the retrospective nature of the study renders it prone to bias. Especially assessing DFS in a retrospective manner is subject to uncertainty due to loss to follow-up and the lack of a standardized follow-up scheme. OS can be considered more reliable, especially as in this study, survival was checked using the Dutch municipal registry.

As mid-BDC is relatively rare, this group was somewhat underrepresented in the total study population. This compromised the statistical power of the study. Nevertheless, a number of significant differences in perioperative outcomes were found. The single-center aspect of this study can be considered a limitation and at the same time a strength, as this also led to a standardized preoperative evaluation and work-up, improving comparability of patients within the study. Obviously, these tumors need to and will be treated in specialized centers anyway. During the study period, no major changes were made in surgical technique or in the postoperative treatment protocol. Furthermore, rates of local resection were spread evenly across the years. We therefore consider the risk of treatment evolution bias to be low.

In the Bismuth-Corlette classification for PHC, Bismuth type I is classified as tumors not invading the biliary confluence, above the level of the insertion of the cystic duct in the CBD [30]. However, the insertion of the cystic duct is known to vary across individuals [31]. Therefore, we propose to consider all tumors below the level of the confluence and above the upper pancreatic border as mid-BDC.

In this study, we chose to classify patients based on perioperative findings of tumor location. This implies that, in clinical practice, the surgical strategy may be changed during the course of an operation. Frozen section should be routinely performed in order to verify margin status. Furthermore, it is important to consider possibilities for extended resections preoperatively. PD, liver resection, or in highly selected cases even a hepatopancreatoduodenectomy may be required in order to achieve negative resection margins [32]. Comorbidity and clinical condition of the patient should be considered in making the decision for an extended resection, for example by the use of preoperative prediction models. Our data, along with others, supports intraoperative decision on surgical management based on intraoperative findings and frozen section of resection margins. LR is preferred considering the lower postoperative morbidity, if negative resection margins can be obtained, especially in patients with high operative risk.

In conclusion, for selected patients with mid-BDC, local resection of the extrahepatic bile ducts is an acceptable treatment strategy with lower rates of severe morbidity, shorter operative time and length of stay, and comparable overall and disease-free survival, regardless of a lower number of resected lymph nodes.

Conflicts of interest

None.

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