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The prognostic role of lymphovascular invasion and lymph node metastasis in perihilar and intrahepatic cholangiocarcinoma

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ABSTRACT

Introduction: Cholangiocellular carcinoma (CCA) is an aggressive malignancy with a dismal prognosis. Among curative treatment options for CCA, radical surgical resection with extrahepatic bile duct resection, hepatectomy and en-bloc lymphadenectomy are considered the mainstay of curative therapy. Here, we aimed to identify prognostic markers of clinical outcome in CCA-patients who underwent surgical resection in curative intent.

Material and methods: Between 2011 and 2016, 162 patients with CCA (perihilar CCA (pCCA): n = 91, intrahepatic CCA (iCCA): n = 71) underwent surgery in curative intent at our institution. Preoperative characteristics, perioperative data and oncological follow-up were obtained from a prospectively managed institutional database. The associations of overall- (OS) and disease-free-survival (DFS) with clinico-pathological characteristics were assessed using univariate and multivariable cox regression analyses.

Results: The median OS and DFS were 38 and 36 months for pCCA and 25 and 13 months for iCCA, respectively. Lymphovascular invasion (LVI) and lymph node metastasis as well as surgical complications as assessed by the comprehensive complication index (CCI) and tumor grading were independently associated with OS for the pCCA (LVI; RR = 2.36, p = 0.028; CCI; RR = 1.04, p < 0.001) and iCCA cohorts (N-category; RR = 3.21, p = 0.040; tumor grading; RR = 3.75, p = 0.013; CCI, RR = 4.49, p = 0.010), respectively. No other clinical variable including R0-status and Bismuth classification was associated with OS.

Conclusion: Major liver resections for CCA are feasible and safe in experienced high-volume centers. Lymph node metastasis and LVI are associated with adverse clinical outcome, supporting the role of systematic lymphadenectomy. The assessment of LVI may be useful in identifying high-risk patients for adjuvant treatment strategies.

1. Introduction

Cholangiocellular carcinoma (CCA) is the second most common primary liver cancer and presumed to originate from the biliary tract epithelium and is typically diagnosed at advanced disease stages. CCAs are often difficult to diagnose, their pathogenesis is poorly understood, and their dismal prognosis has resulted in an

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Abreviations

ALPPS	Associating liver partition and portal vein ligation for staged hepatectomy
ALT	Alanine aminotransferase
AP	Alkaline phosphatase
ASA	American society of anesthesiologists
AST	Aspartate aminotransferase
BMI	Body mass index
CA 19-9	Carbohydrate antigen 19-9
CCA	Cholangiocellular carcinoma
CCI	Comprehensive complication index
CI	Confidence interval
CRLM	Colorectal liver metastases
CRP	C reactive protein
CT	Computed tomography
CUSA	Cavitron Ultrasonic Surgical Aspirator
dCCA	Distal cholangiocellular carcinoma
DFS	Disease-free survival
EBP	Endoscopic biliary drainage
ERCP	Endoscopic retrograde cholangiopancreatography
FFP	Fresh frozen plasma
FLR	Future liver remnant
GGT	Gamma glutamyltransferase
iCCA	Intrahepatic cholangiocarcinoma
INR	International normalized ratio
LiMAx	Maximum liver function capacity
MRCP	Magnetic resonance cholangiopancreatography
MRI	Magnetic resonance imaging
OS	Overall Survival
PBD	Percutaneous biliary drainage
PET-CT	Positron emission tomography–computed tomography
pCCA	Perihilar cholangiocarcinoma
PSC	Primary sclerosing cholangitis
RWTH	Rheinisch-Westfälische Technische Hochschule
UICC	Union for international cancer control

overall nihilistic approach to their management [1,2]. With the advent of new surgical techniques, major liver resections with vascular resections and radical lymphadenectomy – a procedure coined hilar en-bloc resection – have evolved as the mainstay of treatment for patients with CCA [3–5].

Chronic inflammation with the release of inflammatory cytokines as well as structural changes of the liver parenchyma (fibrosis or cirrhosis) promote CCA tumorigenesis. In the context of chronic inflammation in primary sclerosing cholangitis (PSC), the cumulative incidence of CCA among PSC patients is markedly elevated, being higher than 10% [6]. While PSC is especially associated with pCCA, viral hepatitis in combination with liver cirrhosis is recognized to be a significant risk factor for the development of iCCA [7,8]. Cholangiocellular carcinomas are classified based on their anatomic location within the biliary tree, as follows: (1) intrahepatic CCA (iCCA) (10%), (2) perihilar CCA (pCCA) (50%), or (3) distal CCA (dCCA) (40%) and radical surgical resections in combination with extended lymphadenectomy are typically necessary to achieve complete tumor clearance. As these surgical procedures are also associated with significant perioperative morbidity and mortality, careful patient selection is of utmost clinical importance. As such, Nagino et al. have recently reported that tumor differentiation, R0 status and lymph node status are important prognostic factors to predict adverse clinical outcome in pCCA [9]. Other authors identified serum albumin or perioperative blood transfusion as factors impacting survival after surgery in curative intent [10,11]. In iCCA, tumor differentiation, R0 status and lymph node metastases are also associated with impaired survival as well as multinodular disease [12–14].

While nodal status is of major predictive value in numerous gastrointestinal malignancies including esophageal and rectal cancer, little is known about the role of lymphovascular invasion (LVI) in CCA [15,16]. Therefore, we aimed to investigate clinical determinants of oncological outcome in a large Western European cohort of pCCA and iCCA patients undergoing surgical resection in curative intent.

Material and Methods

Patients

Between 2011 and 2016, all consecutive patients with localized pCCA and iCCA with no signs of systemic disease who were treated with surgical resection at the University Hospital RWTH Aachen (UH-RWTH), were included in this study. Clinical staging was performed according to the International Union Against Cancer (UICC). The study was conducted at the UH-RWTH in accordance with the requirements of the Institutional Review Board of the RWTH-Aachen University (EK 252/15), the current version of the Declaration of Helsinki, and the good clinical practice guidelines (ICH-GCP). All clinical data were prospectively collected and entered in an institutional hepatobiliary database.

Staging and surgical technique

All patients who were referred for surgical treatment of iCCA or pCCA to our institution underwent a detailed clinical work-up. None of the patients underwent neoadjuvant chemotherapy. DCCA were not included in this analysis due to the markedly different surgical treatment. The preoperative work-up included the availability of at least one suitable cross-sectional imaging e.g. contrast-material enhanced multiphase computed tomography (CT) to rule out the presence of distant metastases and CT or dynamic magnetic resonance imaging (MRI) of the liver to visualize the invasion of major vessels in the liver hilum and an endoscopic retrograde cholangiopancreatography (ERCP) or magnetic resonance cholangiopancreatography (MRCP) to assess the tumor anatomy in case of pCCA or iCCA extending to the liver hilum. Even though PET-CTs are not part of our routine preoperative work-up, patients with suspected extrahepatic disease on conventional cross-sectional imaging underwent PET-CT in selected cases. Patients with extrahepatic disease on conventional and/or PET-CT imaging were excluded from further analysis.

In addition, the preoperative work-up included unilateral stenting to relieve the future liver remnant (FLR) from cholestasis if present. This was preferably achieved by endoscopic biliary drainage (EBD) and if technically not feasible by percutaneous biliary drainage (PBD) or both. Bilateral stenting was performed on occasions where complications of the contralateral biliary system, such as persisting cholangitis, increased the perioperative risk of the patient.

The assessment of the patients' perioperative risk was based on the American society of anesthesiologists- (ASA) and the Eastern Cooperative Oncology Group (ECOG)-performance status, the analysis of the quantitative and functional parenchymal liver

function as assessed by laboratory parameters, the LiMAx (maximum liver function capacity) test and CT or MRI-based 3D-calculation of the FLR [16]. The decision for surgery as primary treatment and the specific surgical procedure was made by an experienced hepatobiliary surgeon and approved by the local interdisciplinary tumor board in all cases.

Surgical resection was carried out in accordance with common clinical standards. After laparotomy, an intraoperative ultrasound was performed to visualize the local tumor extent and other suspicious lesions. Parenchymal transection was carried out using the Cavitron Ultrasonic Surgical Aspirator (CUSA) with low central venous pressure and intermittent Pringle maneuvers if necessary. Lymphadenectomy comprising the pericholedochal, the periportal, the common hepatic lymph nodes, the posterior pancreaticoduodenal and the celiac lymph nodes was routinely performed. All surgical specimens underwent routine histopathological work-up according to current national guidelines, WHO– and UICC-classifications. Tumor type, histopathological grading and staging, loco-regional lymph node metastasis, resection margins, and vessel invasion was evaluated by an experienced board-certified staff pathologist.

The surgical procedure for CCA was carried out as previously described by Neuhaus et al. [3,5,17]. Briefly, a “no-touch” hilar en-bloc resection approach, as defined by extended liver resection with portal vein resection and reconstruction, was carried out in all cases of pCCA. Additional arterial resection and reconstruction was necessary in selected cases (6). For iCCA, anatomic resections - as defined by resection of the related portal vein branch - and non-anatomic atypical wedge resections with an adequate resection margin were carried out based on the surgeon's preference. Non-anatomic wedge resections were generally preferred for small peripherally located iCCAs. Portal vein resection and reconstruction was not necessary in all reported cases of iCCA.

Follow-up

Patients with high risk for tumor recurrence (e.g. positive nodal status or R1 resection) were subjected to adjuvant chemotherapy. Each patient was assessed regularly by the referring oncologist or the local outpatient clinic. The follow-up included clinical examinations, standard blood tests with follow-up tumor markers (CA 19–9) and radiologic cross-sectional imaging. If a tumor recurrence was suspected, an additional imaging and/or biopsy was performed to confirm the diagnosis. The referring oncologists and the local outpatient clinic provided all analyzed follow-up data.

Statistical analysis

The primary endpoint in this study was overall survival (OS), which was measured from the date of resection to the date of death from any cause or the last contact if the patient was alive. The secondary endpoint was disease-free survival (DFS), which was defined as the period from surgery to the date of first recurrence. Patients without tumor recurrence were censored at the time of death or at the last follow-up. Perioperative Mortality is reported as inhouse mortality. Categorical data are presented in the form of numbers and percentages and were compared using the chi-squared test, fisher's exact test or linear-by-linear association according to scale and number count. Data derived from continuous variables were presented as mean and standard deviation and comparisons between different groups were conducted by Mann-Whitney-U-Test. The associations of OS and DFS with clinico-pathological characteristics were assessed using univariate and multivariable cox regression analyses. Survival curves were generated by the Kaplan-Meier method and compared with the log-rank test. Median follow up was accessed with the reverse Kaplan-Meier method. All survival analyses were carried out excluding cases with perioperative mortality. The level of significance was set to $p < 0.05$ and p-values are given for two-sided testing. Analyses were performed using SPSS Statistics 24 (IBM Corp., Armonk, NY, USA)).

Results

Patient cohort and perioperative data

Between 2011 and 2016, 162 consecutive patients, consisting of 92 men (56.8%) and 70 women (43.2%) with a mean age of 65 years (standard deviation 11 years), were evaluated within this study. The median follow-up was 2.7 years. After excluding perioperative mortality and patients with no information regarding disease recurrence, tumor recurrence occurred in 72 out of 144 (50%) patients. The median DFS was 2.7 years (95% confidence interval (CI): 1.2–3.3). The median OS for the cohort was 2.6 years (95% CI: 1.5–3.7) with 85 out of 162 (52%) patients having died at the time of analysis.

The majority of the patients underwent an extended hepatectomy or trisectionectomy (53.7%, 87/162) with another 6.8% (11/162) that underwent associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) and 4.9% (8/162) that underwent hepatoduodenoectomy. Portal vein resection and reconstruction was carried out in all cases of pCCA (91/91, 100%), while arterial resection and reconstruction was required in 6 patients with pCCA (6/91, 6.6%). The overall mortality rate (Clavien-Dindo, CD5) constituted 11.1% (18/162) and the rate of major complications (>CD3b) was 22.0% (33/162). Histopathological examination of the specimens revealed LVI in 22.4% (32/143) and clear resection margins (R0) in 85.2% (138/162) of cases. The majority of patients were staged stadium IV according to the union for international cancer control (UICC) classification (44%, 65/148). A detailed synopsis regarding patients' characteristics for the overall cohort as well as the two anatomical sub-cohorts is presented in Table 1.

Survival analysis in pCCA

The median DFS and OS were 3.0 years (95% CI: 2.1–3.9) and 3.2 years (95% CI: 2.2–4.2), respectively (Fig. 1A and B). Hemoglobin (DFS: $p < 0.001$; OS: $p = 0.027$), intraoperative blood transfusions (DFS: $p = 0.023$, OS: $p = 0.021$), LVI (DFS: $p = 0.007$; OS: $p = 0.010$), tumor grading (DFS: $p = 0.033$; OS: $p = 0.002$), and pN-category (DFS: $p = 0.040$, OS: $p = 0.009$) were significantly associated with both DFS and OS, whereas serum albumin ($p = 0.047$) and adjuvant therapy ($p = 0.022$) were associated with DFS only. UICC tumor stage ($p = 0.048$), ICU time ($p = 0.020$) and comprehensive complication index (CCI) ($p < 0.001$) were associated with OS. There were no significant associations between other demographic, clinical or histo-pathological characteristics and DFS or OS (Table 2). All variables with statistical significance from univariable analysis were included in a multivariable cox regression model. In this model, LVI ($p = 0.003$) and tumor grading ($p = 0.003$) were independently associated with DFS (Table 3), whereas LVI ($p = 0.028$) and CCI ($p < 0.001$) were independently associated with OS (Table 3). A Kaplan-Meier analysis with respect to LVI showed a median OS of 3.4 years (95% CI: 2.7–4.2) in patients without LVI compared to 1.0 years (95% CI: 0.6–1.4) in patients with LVI ($p = 0.013$ log rank, Fig. 1C).

Table 1
Patients' characteristics.

Demographics	pCCA + iCCA (n = 162)	pCCA (n = 91)	iCCA (n = 71)
Gender, m/f (%)	92 (56.8)/70 (43.2)	58 (63.7)/33 (36.3)	34 (47.9)/37 (52.1)
Age (years)	65 ± 11	66 ± 11	65 ± 12
BMI (kg/m^2)	25 ± 5	26 ± 5	25 ± 4
Portal vein embolization, n (%)	49 (30.2)	41 (45.1)	8 (11.3)
ASA, n (%)			
I	6 (3.8)	4 (4.6)	2 (2.9)
II	67 (42.7)	41 (47.1)	26 (37.1)
III	78 (49.7)	40 (46.0)	38 (54.3)
IV	6 (3.8)	2 (2.3)	4 (5.7)
V		0	0
Bismuth classification, n (%)			
I	n.a.	4 (4.4)	n.a.
II	n.a.	7 (7.7)	n.a.
IIIa	n.a.	28 (30.8)	n.a.
IIIb	n.a.	23 (25.3)	n.a.
IV	n.a.	29 (31.9)	n.a.
Preoperative PBD	23 (14.3)	22 (24.4)	1 (1.4)
Preoperative EBD	88 (54.3)	70 (76.9)	18 (25.4)
Preoperative Chemotherapy	0	0	0
Clinical chemistry			
Albumin (g/dl)	39 ± 7	38 ± 7	41 ± 5
AST (U/l)	82 ± 237	102 ± 303	56 ± 100
ALT (U/l)	98 ± 185	139 ± 238	51 ± 70
GGT (U/l)	264 ± 223	566 ± 521	269 ± 383
Total bilirubin (mg/dl)	1.9 ± 3.9	2.2 ± 2.8	1.5 ± 5.0
Platelet count (/nl)	294 ± 118	323 ± 128	257 ± 92
Alkaline Phosphatase (U/l)	264 ± 223	310 ± 231	207 ± 200
Prothrombin time (%)	96 ± 17	93 ± 19	99 ± 15
INR	1.04 ± 0.17	1.06 ± 0.19	1.02 ± 0.13
Hemoglobin (g/dl)	12.5 ± 1.7	12.2 ± 1.7	13.0 ± 1.7
CRP (mg/l)	33 ± 45	32 ± 42	27 ± 49
Operative Data			
Operative time (minutes)	364 ± 115	416 ± 87	299 ± 113
Operative procedure, n (%)			
Atypical	6 (3.7)	0	6 (8.5)
Bisegmentectomy	6 (3.7)	0	6 (8.5)
Hemihepatectomy	38 (23.5)	16 (17.6)	22 (31.0)
Extended hepatectomy	51 (31.5)	40 (44.0)	11 (15.5)
Trisectionectomy	36 (22.2)	24 (26.4)	12 (17.0)
Hepatoduodenoectomy	8 (4.9)	8 (8.8)	0
ALPPS	11 (6.8)	2 (2.2)	9 (12.7)
other	6 (3.7)	1 (1.1)	5 (7.0)
Intraoperative blood transfusion	1 ± 2	1 ± 2	1 ± 3
Intraoperative FFP	3 ± 4	3 ± 3	2 ± 4
Pathological examination			
R1 resection, n (%)	24 (14.8)	15 (16.5)	9 (13.9)
pT category			
1	27 (17.9)	7 (7.7)	20 (33.3)
2	77 (51.0)	54 (59.4)	23 (38.3)
3	34 (22.5)	23 (25.3)	11 (18.3)
4	13 (8.6)	7 (7.7)	6 (10.0)
Multifocal disease, n (%)	20 (11.6)	0	20 (28.2.)
pN category			
N0	89 (59.3)	53 (58.9)	36 (60.0)
N1	61 (40.7)	37 (41.1)	24 (40.0)
Tumor grading, n (%)			
G1	3 (2.1)	3 (3.5)	0
G2	106 (73.6)	62 (72.1)	44 (74.6)
G3	34 (23.6)	20 (23.3)	14 (23.7)
G4	1 (0.7)	1 (1.2)	0
MVI, n (%)	36 (24.8)	18 (20.9)	18 (30.5)
LVI, n (%)	32 (22.4)	19 (22.6)	13 (18.3)
Tumor stage UICC, n (%)			
I	19 (12.9)	6 (6.6)	13 (22.8)
II	26 (17.6)	22 (24.2)	4 (7.0)
III	38 (25.7)	32 (35.2)	6 (10.5)
IV	65 (44.0)	31 (34.1)	34 (58.4)
Postoperative Data			
Intensive care, days	2 ± 2	3 ± 5	2 ± 7
Hospitalization, days	23 ± 17	26 ± 18	18 ± 14
Postoperative complications, n (%)			

(*continued on next page*)

Table 1 (*continued*)

Demographics	pCCA + iCCA (n = 162)	pCCA (n = 91)	iCCA (n = 71)
No complications	36 (22.2)	11 (12.1)	25 (35.2)
Clavien-Dindo I	6 (3.7)	5 (5.5)	1 (1.4)
Clavien-Dindo II	36 (22.2)	19 (20.9)	17 (23.9)
Clavien-Dindo IIIa	27 (16.7)	16 (17.6)	11 (15.5)
Clavien-Dindo IIIb	24 (14.8)	19 (20.9)	5 (7.0)
Clavien-Dindo IVa	12 (7.4)	6 (6.6)	6 (8.5)
Clavien-Dindo IVb	3 (1.9)	3 (3.3)	0
Clavien-Dindo V	18 (11.1)	12 (13.2)	6 (8.5)
CCI	38 ± 32	45 ± 32	29 ± 30
Oncologic Data*			
Adjuvant chemotherapy	71 (43.8)	37 (40.7)	34 (47.9)
Recurrence, n (%)	72 (50.0)	35 (44.3)	37 (60.7)
Median DFS, months (95% CI)	27 (14–40)	36 (25–47)	13 (6–20)
Median OS, months (95% CI)	31 (18–44)	38 (26–50)	25 (4–46)

Data presented as mean and standard deviation if not noted otherwise. ALT, alanine aminotransferase; ASA, American society of anesthesiologists classification; AST, aspartate aminotransferase; BMI, body mass index; CCI, comprehensive complication index; DFS, disease free survival; OS, overall survival; EBD, endoscopic biliary drainage; FFP, fresh frozen plasma; pCCA, perihilar cholangiocarcinoma; GGT, gamma glutamyltransferase; iCCA; intrahepatic cholangiocarcinoma; INR, international normalized ratio; LVI, lympho-vascular invasion; MVI, microvascular invasion; PBD, percutaneous biliary drainage; UICC, Union for international cancer control. *Oncologic data with exclusion of perioperative mortality.

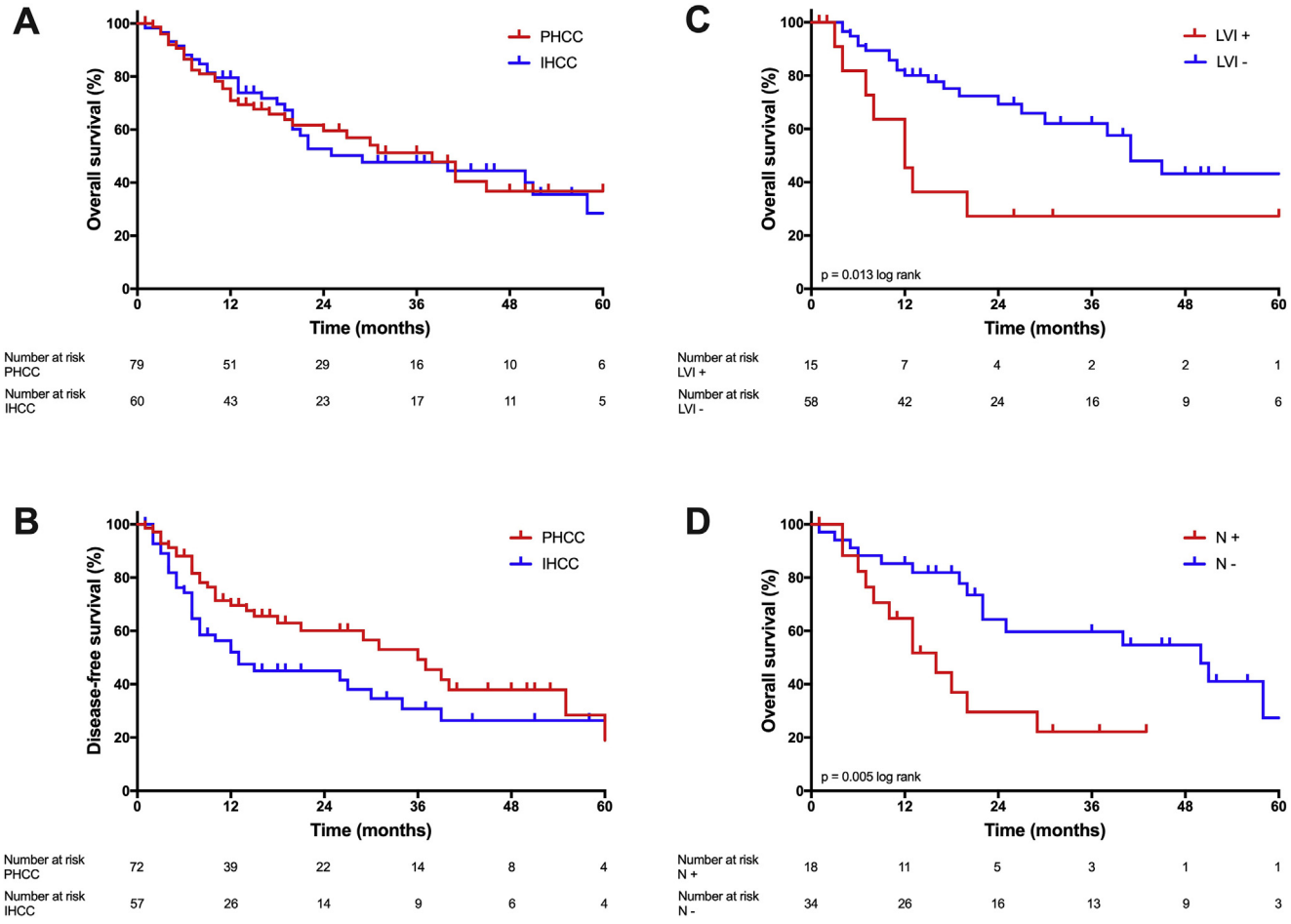

Fig. 1. Oncological survival in cholangiocarcinoma. **A: Overall survival in perihilar and intrahepatic cholangiocarcinoma**. The median OS for pCCA and iCCA was 3.2 years (95% CI: 2.2–4.2) and 2.1 years (95% CI: 0.3–3.8), respectively. **B: Disease-free survival in perihilar and intrahepatic cholangiocarcinoma**. The median DFS for pCCA and iCCA was 3.0 years (95% CI: 2.1–3.9) and 1.1 years (95% CI: 0.5–1.7), respectively. **C: Overall survival in perihilar cholangiocarcinoma stratified by lymph-vascular invasion**. The Kaplan-Meier analysis with respect to LVI showed a median OS of 3.4 years (95% CI: 2.7–4.2) in patients without LVI compared to 1.0 years (95% CI: 0.6–1.4) in patients with LVI ($p = 0.013$ log rank). **D: Overall survival in intrahepatic cholangiocarcinoma stratified by pN-category.** The Kaplan-Meier analysis with respect to pN-category showed a median OS of 4.2 years (95% CI: 1.7–6.7) in patients without lymph node metastases compared to 1.1 years (95% CI: 0.5–1.7) in patients with lymph node metastases ($p = 0.005$ log rank).
CI, confidence interval; DFS, disease-free survival; iCCA, intrahepatic cholangiocarcinoma; LVI, lympho-vascular invasion; OS, overall survival; pCCA, perihilar cholangiocarcinoma.

Table 2
Univariable analysis of disease-free and overall survival in perihilar cholangiocarcinoma.

	n	*Disease-free survival (DFS)*			*Overall survival (OS)*		
		Median DFS, m (95% CI)	Relative risk (95% CI)	*P* value	Median OS, m (95% CI)	Relative risk (95% CI)	*P* value
Sex				0.996			0.363
Male	58	36 (18–54)			38 (14–62)		
Female	33	29 (0–62)			20 (4–36)		
Age, years				0.887			0.562
≤ 65	38	39 (33–45)			24 (0–50)		
> 65	53	29 (14–44)			27 (8–46)		
BMI, kg/m²				0.583			0.664
≤ 25	47	37 (18–56)			24 (4–44)		
> 25	44	31 (11–51)			30 (17–43)		
ASA#				0.493			0.913
I/II	45	39 (13–65)			41 (0–83)		
III/IV	42	31 (10–52)			30 (21–39)		
PVE				0.871			0.422
No	50	36 (8–64)			41 (17–65)		
Yes	41	36 (25–48)			20 (5–35)		
EBD*				0.381			0.975
No	21	21 (1–41)			35 (22–48)		
Yes	70	37 (27–47)			34 (26–42)		
PBD				0.262			0.611
No	68	39 (34–44)			20 (4–36)		
Yes	22	29 (4–54)			38 (20–56)		
Albumin, g/l#				0.047			0.343
≤ 35	22	23 (11–35)	1		12 (7–17)		
> 35	45	42 (31–53)	0.416 (0.176–0.987)		41 (9–73)		
AST, U/l				0.363			0.639
≤ 40	37	37 (25–49)			19 (0–38)		
> 40	54	31 (4–58)			27 (2–52)		
ALT, U/l				0.753			0.514
≤ 40	14	29 (8–50)			30 (0–71)		
> 40	42	37 (14–60)			15 (0–34)		
GGT, U/l				0.927			0.129
≤ 100	23	40 (4–76)			20 (0–40)		
> 100	61	31 (13–49)			31 (8–54)		
Bilirubin, mg/dl				0.051			0.217
≤ 1	43	40 (25–55)			31 (13–49)		
> 1	48	21 (0–48)			13 (0–30)		
Alkaline phosphatase, U/l				0.995			0.988
≤ 100	29	40 (4–76)			20 (1–39)		
> 100	54	31 (13–49)			30 (14–46)		
Platelet count, 1/nl#				0.187			0.985
≤ 200	31	47 (30–64)			30 (0–71)		
> 200	59	32 (4–39)			27 (14–42)		
INR#				0.224			0.072
≤ 1	35	41 (30–52)			45 (0–94)		
> 1	55	32 (22–42)			15 (0–32)		
Hemoglobin*, g/dl				<0.001			0.027
≤ 12	36	14 (4–24)	1		23 (15–30)	1	
> 12	54	55 (34–76)	0.285 (0.138–0.591)		43 (33–53)	0.513 (0.284–0.927)	
CRP, mg/l				0.167			0.183
≤ 10	35	61 (31–91)			41 (17–65)		
> 10	51	29 (15–43)			30 (8–52)		
Operative time, min				0.266			0.232
≤ 360	26	37 (17–57)			38 (20–56)		
> 360	63	36 (17–55)			24 (7–41)		
Blood transfusions*				0.023			0.021
No	46	55 (33–77)	1		45 (34–57)	1	
Yes	45	21 (0–43)	2.342 (1.123–4.886)		25 (17–31)	2.071 (1.118–3.838)	
FFP*#				0.105			0.092
No	30	42 (28–55)			42 (28–55)		
Yes	61	32 (23–41)			31 (22–39)		
R1 resection				0.205			0.481
Yes	15	37 (23–51)			12 (4–20)		
No	76	36 (0–88)			30 (16–44)		
MVI				0.446			0.928
No	67	39 (28–50)			30 (10–50)		
Yes	18	37 (0–76)			31 (0–71)		
LVI				0.007			0.010
No	65	39 (33–45)	1		41 (26–56)	1	
Yes	19	7 (0–21)	3.482 (1.416–8.558)		8 (2–14)	2.467 (1.243–4.899)	
Tumor grading				0.033			0.002
G1/G2	65	36 (23–49)	1		38 (27–49)	1	
G3/G4	21	7 (4–10)	2.381 (1.075–5.277)		8 (3–14)	2.684 (1.436–5.016)	
Tumor stage UICC*				0.344			0.048
I/II	28	31 (26–36)			46 (32–60)	1	

(*continued on next page*)

Table 2 (*continued*)

	n	*Disease-free survival (DFS)*			*Overall survival (OS)*		
		Median DFS, m (95% CI)	Relative risk (95% CI)	*P* value	Median OS, m (95% CI)	Relative risk (95% CI)	*P* value
III	32	36 (8–64)			30 (20–41)	2.118 (0.920–4.872)	
IV	31	40 (0–92)			27 (15–39)	2.711 (1.192–6.166)	
pT category				0.650			0.090
pT1-2	61	36 (26–46)			31 (16–46)		
pT3-4	30	40 (0–83)			12 (5–19)		
pN category				0.040			0.009
N0	53	39 (23–55)	1		38 (26–50)	1	
N1	37	15 (0–41)	2.094 (1.035–4.237)		10 (3–17)	2.167 (1.211–3.879)	
ICU time, days				0.938			0.020
≤ 1	62	36 (26–46)			38 (20–56)	1	
> 1	29	40 (0–96)			12 (9–15)	2.008 (1.117–3.608)	
Hospitalization, days				0.654			0.187
≤ 14	27	39 (27–51)			45 (13–67)		
> 14	62	36 (9–63)			20 (4–36)		
CCI*				0.502			< 0.001
≤ 40	47	39 (12–66)			50 (40–60)	1	
> 40	44	31 (9–53)			20 (13–28)	3.847 (2.019–7.330)	
Adjuvant therapy				0.022			0.866
No	54	55 (4–106)	1		30 (0–62)		
Yes	37	31 (4–58)	2.401 (1.136–5.074)		27 (13–41)		
Tumor recurrence							0.509
No	53	n.a.			45 (11–79)		
Yes	36	n.a.			20 (4–36)		

Various parameters are associated with overall or disease-free survival. ALT, alanine aminotransferase; ASA, American society of anesthesiologists classification; AST, aspartate aminotransferase; BMI, body mass index; CCI, comprehensive complication index; CRP, c-reactive protein; DFS, disease-free survival; EBD, endoscopic biliary drainage; FFP, fresh frozen plasma; GGT, gamma glutamyltransferase; ICU, intensive care unit; INR, international normalized ratio; LVI, lympho-vascular invasion; OS, overall survival; MVI, microvascular invasion; PBD, percutaneous biliary drainage; PVE, portal vein embolization; UICC, Union for international cancer control. * Mean OS. #Mean DFS.

Table 3
Multivariable analysis of overall and disease-free survival in perihilar cholangiocarcinoma.

	Disease-free survival (DFS)			Overall survival (OS)		
	Relative risk	95% CI	*P* value	Relative risk	95% CI	*P* value
LVI	4.75	1.18, 13.41	0.003	2.36	1.10, 5.07	0.028
CCI				1.04	1.03, 1.05	< 0.001
Tumorgrading	3.74	1.58, 8.86	0.003			

Only significant parameters are shown. The following parameters were included in the multivariable analysis for OS: Hemoglobin, blood transfusions, LVI, tumor grading, tumor stage UICC, pN-category, ICU time and CCI. The following parameters were included in the multivariable analysis for DFS: Albumin, Hemoglobin, blood transfusions, LVI, tumor grading, DFS, disease-free survival; pN-category and adjuvant therapy. CCI, comprehensive complication index; ICU, intensive care unit; LVI, lympho-vascular invasion; OS, overall survival; UICC, Union for international cancer control.

Survival analysis in iCCA

The median DFS and OS were 1.1 years (95% CI: 0.5–1.7) and 2.1 years (95% CI: 0.3–3.8), respectively (Fig. 1A and B). Serum c-reactive protein (CRP) (DFS: $p = 0.026$; OS: $p = 0.011$), UICC tumor stage (DFS: $p = 0.047$, OS: $p = 0.002$), multifocal disease (DFS: $p = 0.002$, OS: $p = 0.015$) and hospitalization (DFS: $p = 0.045$, OS: $p = 0.006$) were significantly associated with both DFS and OS, whereas adjuvant therapy ($p < 0.001$) was associated with DFS only. Serum albumin ($p = 0.049$), hemoglobin ($p = 0.050$), operative time ($p = 0.048$), intraoperative application of fresh frozen plasma (FFP) ($p = 0.026$), LVI ($p = 0.003$), tumor grading ($p = 0.001$), pN-category ($p = 0.001$), ICU time ($p = 0.036$) and CCI ($p = 0.003$) were associated with OS. There were no significant associations between other demographic, clinical or histopathological characteristics and DFS or OS (Table 4). All variables with statistical significance from univariable analysis were included in a multivariable cox regression model. In this model, adjuvant therapy ($p < 0.001$) was independently associated with DFS (Table 5), whereas tumor grading ($p = 0.013$), pN-category ($p = 0.040$) and CCI ($p = 0.010$) were independently associated with OS (Table 5). A Kaplan-Meier analysis with respect to pN-category showed a median OS of 4.2 years (95% CI: 1.7–6.7) in patients without lymph node metastases compared to 1.1 years (95% CI: 0.5–1.7) in patients with lymph node metastases ($p = 0.005$ log rank, Fig. 1D).

Discussion and conclusion

Among the different treatment options for CCA, radical surgical resection with extrahepatic bile duct resection, hepatectomy and en-bloc lymphadenectomy have evolved as the mainstay of curative therapy. While progress has been made in the detection, screening and treatment of patients with CCA, tumor recurrence after curative resection continues to impose a significant problem in these patients [18,19]. In this context, balancing the risks and benefits of the surgical procedure for the patient are of utmost clinical importance. Therefore, we aimed to investigate clinical outcome (DFS and OS) in pCCA and iCCA patients undergoing radical surgical resection in curative intent. Our multivariable model identified LVI and tumor grading as well as adjuvant therapy as independent prognostic markers for tumor recurrence in pCCA and in iCCA, respectively. Also, LVI and CCI were significantly associated with impaired OS in pCCA, while pN-category, tumor grading and CCI were associated with impaired OS in iCCA, respectively.

Table 4
Univariable analysis of disease-free and overall survival in intrahepatic cholangiocarcinoma.

	n	*Disease-free survival (DFS)*			*Overall survival (OS)*		
		Median DFS, m (95% CI)	Relative risk (95% CI)	*P* value	Median OS, m (95% CI)	Relative risk (95% CI)	*P* value
Sex				0.798			0.085
Male	32	12 (2–22)			18 (7–29)		
Female	37	13 (0–33)			40 (5–75)		
Age, years				0.113			0.417
≤ 65	37	10 (5–15)			20 (11–29)		
> 65	32	19 (1–77)			22 (13–31)		
BMI, kg/m²				0.342			0.417
≤ 25	39	13 (0–30)			25 (8–42)		
> 25	29	8 (1–15)			19 (15–23)		
ASA				0.849			0.318
I/II	27	15 (0–31)			40 (7–73)		
III/IV	41	10 (5–15)			20 (17–23)		
PVE#				0.430			0.311
No	61	42 (25–58)			5 (12–32)		
Yes	8	22 (11–34)			13 (0–28)		
EBD				0.628			0.285
No	52	12 (5–19)			25 (4–46)		
Yes	17	26 (2–50)			6 (2–24)		
PBD				n.a.			n.a.
No	68	13 (6–20)			22 (14–30)		
Yes	1	n.a.			n.a.		
Albumin*, g/l				0.737			0.049
≤ 42	25	8 (0–17)			25 (14–37)	1	
> 42	12	13 (8–18)			29 (5–53)	0.287 (0.083–0.993)	
AST, U/l				0.489			0.758
≤ 40	44	13 (8–18)			22 (16–28)		
> 40	25	10 (5–15)			20 (0–41)		
ALT#, U/l				0.089			0.937
≤ 40	34	66 (39–92)			22 (0–45)		
> 40	14	17 (8–25)			20 (15–25)		
GGT, U/l				0.384			0.357
≤ 100	40	13 (8–18)			22 (16–28)		
> 100	24	12 (3–21)			19 (12–26)		
Bilirubin, mg/dl				0.814			0.536
≤ 1	54	13 (5–21)			21 (15–27)		
> 1	13	12 (0–38)			20 (2–38)		0.229
Alkaline phosphatase, U/l				0.212			
≤ 100	42	13 (8–18)			22 (16–28)		
> 100	22	8 (1–15)			13 (2–24)		
Platelet count, 1/nl				0.423			0.335
≤ 200	39	12 (7–17)			20 (17–23)		
> 200	28	27 (5–49)			29 (0–65)		
INR				0.588			0.624
≤ 1	33	13 (8–18)			21 (18–24)		
> 1	33	12 (0–31)			22 (1–43)		
Hemoglobin, g/dl				0.161			0.050
≤ 12	19	8 (0–20)			13 (0–31)	1	
> 12	48	15 (0–35)			22 (11–33)	0.513 (0.263–1.001)	
CRP*, mg/l				0.026			0.011
≤ 10	33	13 (0–38)	1		43 (30–56)	1	
> 10	27	8 (2–14)	2.309 (1.105–4.821)		21 (12–31)	2.534 (1.236–5.193)	
Operative time, min							0.048
≤ 300	54	13 (0–30)		0.190	25 (5–45)	1	
> 300	15	8 (5–11)			18 (0–35)	2.097 (1.006–4.371)	
Blood transfusions				0.55			0.336
No	46	15 (0–32)			22 (16–28)		
Yes	23	7 (0–16)			16 (0–33)		
FFP				0.342			0.026
No	38	13 (7–20)			29 (6–52)	1	
Yes	31	12 (3–21)			13 (3–23)	2.080 (1.092–3.962)	
R1 resection#				0.522			0.178
Yes	7	12 (3–21)			22 (10–34)		
No	55	46 (28–65)			9 (1–17)		
MVI				0.122			0.849
No	39	23 (0–59)			20 (7–33)		
Yes	18	10 (4–16)			22 (7–37)		
LVI				0.244			0.003
No	45	13 (0–38)			40 (15–65)	1	
Yes	13	10 (0–25)			4 (0–7)	3.037 (1.452–6.352)	
Tumor grading				0.365			
G1/G2	45	15 (0–37)			50 (20–80)	1	0.001
G3/G4	13	7 (0–14)			9 (0–18)	3.699 (1.698–8.058)	
Tumor stage UICC*				0.047			0.002
I/II	17	39 (27–51)	1		67 (46–87)	1	

(*continued on next page*)

Table 4 (*continued*)

	n	*Disease-free survival (DFS)*			*Overall survival (OS)*		
		Median DFS, m (95% CI)	Relative risk (95% CI)	*P* value	Median OS, m (95% CI)	Relative risk (95% CI)	*P* value
III	12	8 (0–16)	3.272 (1.144–9.357)		33 (21–44)	2.428 (0.708–8.325)	
IV	27	8 (2–14)	2.903 (1.079–7.815)		15 (9–2)	5.652 (1.872–17.065)	
pT category				0.737			0.092
pT1-2	43	12 (7–17)			29 (9–49)		
pT3-4	16	13 (0–27)			9 (1–17)		
Multifocal disease				0.002			0.015
No	20	27 (9–45)	1		40 (3–77)	1	
yes	51	7 (4–10)	3.046 (1.494–6.208)		16 (1–31)	2.418 (1.186–4.929)	
N category				0.213			0.001
pN0	36	26 (5–47)			50 (20–80)	1	
pN1	23	8 (2–14)			13 (6–20)	3.292 (1.575–6.880)	
ICU time, days				0.213			0.036
≤ 1	59	13 (7–19)			25 (5–45)	1	
> 1	9	7 (2–12)			7 (1–13)	2.453 (1.060–5.677)	
Hospitalization*, days				0.045			0.006
≤ 14	38	39 (8–70)	1		68 (45–91)	1	
> 14	30	8 (5–11)	1.998 (1.017–3.924)		23 (14–32)	2.526 (1.301–4.905)	
CCI							0.003
≤ 40	50	13 (0–30)		0.114	29 (1–57)	1	
> 40	19	8 (5–11)			7 (0–19)	2.705 (1.397–5.236)	
Adjuvant therapy#				<0.001			0.249
No	36	78 (51–105)	1		20 (0–60)		
Yes	33	9 (5–13)	7.767 (3.288–18.346)		22 (13–27)		
Tumor recurrence							0.518
No	30	n.a.			58 (0–145)		
Yes	37	n.a.	.		21 (18–24)		

Various parameters are associated with overall or disease-free survival. ALT, alanine aminotransferase; ASA, American society of anesthesiologists classification; AST, aspartate aminotransferase; BMI, body mass index; CCI, comprehensive complication index; CRP, c-reactive protein; EBD, endoscopic biliary drainage; DFS, disease-free survival; FFP, fresh frozen plasma; GGT, gamma glutamyltransferase; ICU, intensive care unit; INR, international normalized ratio; LVI, lympho-vascular invasion; MVI, microvascular invasion; OS, overall survival; PBD, percutaneous biliary drainage; PVE, portal vein embolization; UICC, Union for international cancer control. * Mean OS. #Mean DFS.

Table 5
Multivariable analysis of overall and disease-free survival in intrahepatic cholangiocarcinoma.

	Disease-free survival (DFS)			Overall survival (OS)		
	Relative risk	95% CI	*P* value	Relative risk	95% CI	*P* value
Tumor grading				3.75	1.32, 10.64	0.013
pN-category				3.21	1.05, 9.77	0.040
CCI				4.49	1.43, 14.13	0.010
Adjuvant therapy	8.14	2.73, 24.26	< 0.001			

Only significant parameters are shown. The following parameters were included in the multivariable analysis for OS: Albumin, hemoglobin, CRP, operative time, FFP, LVI, tumor grading, tumor stage UICC, multifocal disease, pN-category, ICU time, hospitalization and CCI. The following parameters were included in the multivariable analysis for DFS: CRP, tumor stage UICC, multifocal disease, hospitalization and adjuvant therapy. CCI, comprehensive complication index; ICU, intensive care unit. CRP, c-reactive protein; DFS, disease-free survival; FFP, fresh frozen plasma; ICU, intensive care unit; LVI, lympho-vascular invasion; OS, overall survival; UICC, union for international cancer control.

Lymphangiogenesis, the formation of lymphatic vessels from pre-existing lymphatic vessels is considered the hallmark feature of early tumor cell dissemination [20]. While lymphovascular invasion of tumor cells, as defined by tumor cells present within a definite endothelial-lined space surrounding invasive carcinoma, has been identified as an important prognostic factor in patients with breast, esophageal and rectal cancer [15,16], the prognostic value of LVI in patients with iCCA and pCCA is controversial [21–23]. Interestingly, Kim et al. reported that LVI has no impact on survival in dCCA [21], whereas another study found that LVI might have an adverse effect on survival in patients with iCCA [22]. It has to be noted, however, that in this study by Fischer et al. the authors did not differentiate between LVI and perineural infiltration. Even though another study highlights the prognostic value of LVI in Bismuth type IV tumors, the role of LVI in pCCA remains to be investigated [23]. To the best of our knowledge, this is one of the first reported CCA cohorts to include all Bismuth type tumors, suggesting that LVI has a distinct adverse effect on both OS and DFS in pCCA. Of note, LVI and peritumoral lymph vessel density are associated with nodal metastases in iCCA, suggesting LVI-dependent tumor cell dissemination through the lymphatic system in CCA [24]. In our iCCA cohort, lymph node metastases, rather than LVI, were associated with OS, suggesting that these patients might suffer from a biologically more advanced tumor stage than patients with pCCA. In this context, it may be speculated that the observed difference between pCCA and iCCA is likely due to a distinct genetic profile of two separate tumor entities.

Lymph node involvement (N-category) was independently associated with an impaired OS in our cohort and constitutes a known prognostic factor for adverse clinical outcome in iCCA [25]. As CCA lymph node metastases are detectible preoperatively by Positron Emission Tomography–Computed Tomography (PET-CT) [26], lymph node involvement may be a suitable parameter for preoperative patient stratification and patient selection for alternative treatment options, such as suitable chemotherapy regimens. While chemotherapy alone shows poor results in CCA patients [27], the role of neoadjuvant therapy for iCCA has recently been discussed in a multinational analysis of retrospective survival data [28]. This mirrors the recent developments in treatment strategies of other gastrointestinal malignancies such as esophageal and rectal cancer [29,30].

Importantly, R1 status was not associated with impaired outcome in neither the pCCA- nor the iCCA-cohort. Even though R0 resection is traditionally considered the main goal in oncologic surgery for CCA and other gastrointestinal malignancies, this paradigm has recently been challenged in patients with colorectal liver metastases (CRLM) and other malignancies. As such, several groups demonstrated that patients with R1 resections for CRLM showed similar oncologic outcomes compared to patients with conventional R0 resections [31,32]. While Andreou et al. demonstrated that R0 resection might be dispensable if the resected metastases exhibit pathological response to preoperative chemotherapy, Margonis et al. showed that a R0 margin only provides a survival benefit in patients with KRAS wild type tumors, indicating that the tumor biology rather than the surgical technique determines the prognosis in patients with CRLM [31–33]. Even though a recent meta-analysis of 22 studies on oncologic outcome of pCCA identified tumor resection margin as an important prognostic parameter [34], other studies indicate that R0 resection may be less important than traditionally propagated [35]. As such, Ebata et al. recently published their experience with Bismuth type IV tumors comprising 332 patients. While the authors did not find R0-resection to be associated with OS in univariate and multivariable analysis, they have identified lymph-node involvement as assessed by N-category to be significantly associated with OS [35]. Interestingly, postoperative adjuvant chemotherapy with gemcitabine or S-1 was administered in all patients with nodal metastasis and/or a positive surgical margin for at least 6 months after surgery in this study [35]. In patients with positive resection margins after surgical resection for CCA, postoperative adjuvant chemotherapy is standard of care also in our center, while patients with R0 resections undergo regular watch and wait follow-up. In the era of modern multimodal targeted treatment strategies, it remains debatable whether the oncologic disadvantage of a R1 resection might be compensated by the application of adjuvant chemotherapy, suggesting that tumor biology may be more important than the status of the surgical margin.

In this context, the preliminary results of the BILCAP trial, a prospective multicenter randomized controlled trial on 447 adjuvant CCA-patients receiving adjuvant capecitabine, showed a survival benefit for patients undergoing postoperative chemotherapy [36]. Based on these findings, many centers have nowadays adopted adjuvant chemotherapy after surgery for CCA irrespective of the surgical resection margin. During the study period, patients with a high risk for tumor recurrence (e.g. positive nodal status or R1 resection) were subjected to adjuvant chemotherapy [13,37]. Nowadays, in the light of the recent results of the BILCAP trial, our institution recommends capecitabine-based adjuvant therapy in every patient with acceptable performance status [36]. Patients willing to participate in clinical trials are referred to the currently recruiting ACCTICA trial (Adjuvant Chemotherapy With Gemcitabine and Cisplatin Compared to Standard of Care After Curative Intent Resection of Biliary Tract Cancer, NCT02170090), which randomizes patients between gemcitabine plus cisplatin and capecitabine and observation [38].

As with all clinical outcome studies, our analysis has potential limitations. All patients included in this study were treated at a single institution reflecting the authors' individual clinical approach and the study is based on data that were not obtained during a prospective clinical trial. Moreover, as reflected in the clinical characteristics (Table 1) as well as in the extensive surgeries required in most cases, our cohort was characterized by an extensive tumor burden, representing considerably more advanced cases compared to prior surgical studies. While this fact well explains the relatively poor survival data, it was certainly "enriched" for LVI and lymph node metastasis, enabling us to derive such clear data on the prognostic value of these histological features from a single-center analysis. The fraction of patients with LVI or lymph node involvement might be considerably lower in surgical cohorts with earlier disease states. Thirdly, we also recognize that the observed associations and patterns require confirmation within an independent dataset.

Notwithstanding the aforementioned limitations, we have identified LVI and lymph node metastasis as important independent prognostic markers in CCA. Also, no preoperatively available tumor or patient characteristics were associated with clinical outcome, highlighting the importance of surgical treatment for patients with localized CCA. Lymph node metastasis and LVI are associated with adverse clinical outcome, supporting the role of systematic lymphadenectomy. In addition, the assessment of LVI may be useful in the identification of high-risk patients for adjuvant treatments. Larger, prospective and biomarker embedded clinical trials are however needed to confirm and validate our findings.

Disclosure

All contributing authors have no conflicts of interest to declare.

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