Long-term Survival after resection for perihilar cholangiocarcinoma: Impact of UICC staging and surgical procedure

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ABSTRACT

Background/Aims: Perihilar cholangiocarcinoma is a rare disease with unfavorable prognosis resulting in low survival rates. This study aims to retrospectively assess the beneficial histopathological features and surgical procedures in long-term survivors (i.e., patients surviving perihilar cholangiocarcinoma for at least 2 y).

Material and Methods: In total, 322 patients with perihilar cholangiocarcinoma underwent surgery at our center. The follow-up ended in 2017; 76 patients survived for >2 y. The type of resection, UICC stage, and histopathological features were compared between three survival groups (>2-3, >3-5, and >5 y).

Results: The >5-year-survival rate in our selected study cohort was 43.4% (>3-5 y,31.6% and >2-3 y, 25.0%), and 14.5% of the patients survived for >10 y after surgery. Patients with non-regional lymph node positive tumors and/or distant metastasis (i.e., UICC stage IVb; p=0.0112), R2 status (p=0.0288), and exploratory laparotomy only (p=0.0157) showed the poorest survival rates. Perineural invasion had no significant impact on the overall survival. However, 29.0% patients surviving for >5 y displayed the lowest perineural infiltration prevalence. Interestingly, Bismuth-Corlette stage IIIa (p=0.0467), especially caudate lobectomy (p=0.0034), was associated with disease-specific overall survival of >5y.

Conclusion: Complete/extended tumor resection with additional caudate lobe resection is strongly associated with long-term survival. Perineural infiltration as a negative prognostic marker for prolonged survival needs to be evaluated in larger study cohorts.

Keywords: Klatskin tumor, long-term survival, caudate lobectomy, Bismuth-Corlette classification, perineural invasion

INTRODUCTION

Perihilar cholangiocarcinoma is a rare disease with unfavorable prognosis. A complete margin-free resection of the tumor is the only curative treatment for this condition (1). Palliative combination chemotherapy with gemcitabine and cisplatin is the standard treatment for advanced perihilar cholangiocarcinoma if the tumor cannot be resected (2). Extrahepatic bile duct resection, hepatic resection, vascular resection, and lymph node dissection comprise the surgical procedures for resectable disease. These operations are associated with up to 19% patient mortality and a perioperative morbidity ranging from 14% to 76% (3). The 5-year-survival rates for patients undergoing surgical resection for perihilar cholangiocarcinoma range from 10% to 30% depending on resection margins (4). Further, the UICC classification aims to reflect the outcome of patients with perihilar cholangiocarcinoma. For the first time, the seventh edition published in 2009 separates extrahepatic cholangiocarcinoma into two groups of either perihilar (proximal) or distal localization, and thus allows a more specific pathological staging and prediction of survival for this tumor (5). Precise tumor staging, potential infiltration in adjacent structures, lymph node involvement, and the detection of metastases are important to decide if a curative tumor resection can be performed. Therefore, preoperative tumor staging might be improved by the use of dual modality positron emission tomographycomputed tomography (6).

The long-term survival of patients with this morbid disease is low and corresponding studies are scarce; the relevant prognostic factors remain uncertain. We and other au-

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thors have reported that caudate lobe resection in combination with extended liver resection is associated with prolonged disease-specific overall survival (7-11). Consistent with this observation, microscopic tumor infiltration of the caudate lobe can be found in many patients with perihilar cholangiocarcinoma (12). Currently, caudate lobe resection is highly recommended for tumors classified as Bismuth Type II and higher (13). A multivariate analysis identified R1 resection, lymph node metastases, T stage of three or higher, and perineural invasion as independent prognostic factors for poor overall survival (14). These histopathological findings and surgical approaches have been frequently discussed. Given this background, in the present follow-up study (9), we compared the histopathological parameters and surgical procedures between mid- and long-term surviving patients with perihilar cholangiocarcinoma who underwent surgery at the University Hospital of Essen, to identify potential prognostic factors and recommendations for surgery.

MATERIAL AND METHODS

Patients

This study was approved by the ethics committee of the medical faculty of the University Hospital of Essen, Germany. A total of 322 patients with perihilar cholangiocarcinoma were surgically treated at our center. Out of these patients, 76 had an overall survival of 2, 3, or >5 y. The remaining 246 were excluded from the study. A routine histopathological workup was conducted for all resected tumors or biopsies by the Institute of Pathology at the University Hospital of Essen. Of the 76 patients in the study population, 28 were females (36.8%) and 48 were males (63,2%) with a mean age of 59.0±11.6 y. Patients were subdivided into the following three groups: group A, B and C corresponding to >2-3, >3-5, and >5 y of survival, respectively. The routine follow-up ended in 2017 to ensure that at least a 5-year-follow-up for every patient was possible. The histopathological characteristics according to the seventh UICC classification and surgical procedures between the groups were compared and correlated with patients' survival, respectively.

Statistical analysis

Data are displayed as mean±standard deviation and percentage of total (%) unless stated otherwise. Categorical variables were analyzed using the χ^2 test and continuous variables using one-way ANOVA with the Bonferroni post-test. The overall survival was defined as the time from surgery to the tumor-specific death or date of last follow-up. Kaplan-Meier survival plots were generated and analyzed using the log-rank test. All parameters that revealed significance in the univariate Kaplan-Meier analysis were additionally analyzed using the multivariate cox proportional hazards regression survival analysis. A confidence interval of 95% was used and p value of <0.05 was considered statistically significant.

RESULTS

In the present study cohort of 76 patients with perihilar cholangiocarcinoma for >2 y, the >5-year-survival rate was 43.4% (>2-3 and >3-5-year-survival rate was 25.0% and 31.6%, respectively), with 14.5% of the patients surviving for >10 y after the surgery (Figure 1). After compar-

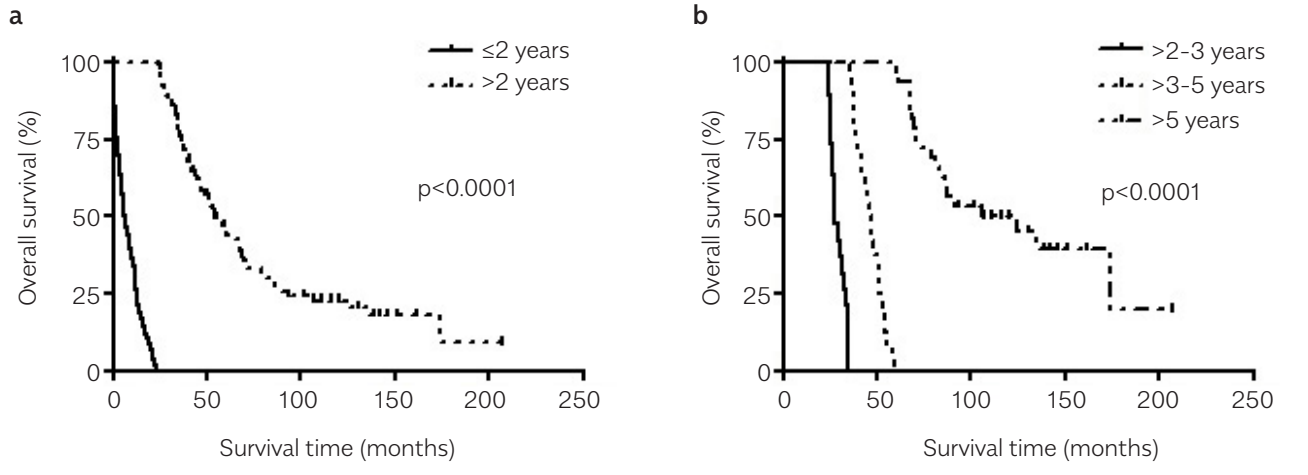

Figure 1. a, b. Kaplan-Meier survival curves comparing survival among the three study groups (N=76)

Table 1. UICC tumor stages and histopathological differences among the survival groups

	Overall (%) N=76 (100%)	Group A (>2-3 year survival) N=19 (25.0%)	Group B (>3-5 year survival) N=24 (31.6%)	Group C (>5 year survival) N=33 (43.4%)	p
UICC 0 (Tis)	2 (2.6%)	1 (5.3%)	1 (4.2%)	0 (0%)	0.2240
UICC I	5 (6.6%)	0 (0%)	0 (0%)	5 (15.2%)	0.0193
UICC II	35 (46.1%)	6 (31.6%)	12 (50.0%)	17 (51.5%)	0.1939
UICC IIIa	9 (11.8%)	3 (15.8%)	2 (8.3%)	4 (12.1%)	0.7721
UICC IIIb	14 (18.4%)	2 (10.5%)	6 (25.0%)	6 (18.2%)	0.6021
UICC IVa	3 (3.9%)	2 (10.5%)	1 (4.2%)	0 (0%)	0.0622
UICC IVb	8 (10.5%)	5 (26.3%)	2 (8.3%)	1 (3.0%)	0.0112
G1	6 (8.5%)	0 (0%)	4 (16.7%)	2 (6.5%)	0.6369
G2	54 (76.1%)	14 (87.5%)	15 (62.5%)	25 (80.6%)	0.7413
G3	11 (15.5%)	2 (12.5%)	5 (20.8%)	4 (12.9%)	0.9915
R0	44 (68.8%)	6 (50.0%)	15 (68.2%)	23 (79.3%)	0.0641
R1	16 (25.4%)	4 (33.3%)	6 (27.3%)	6 (20.7%)	0.3776
R2	3 (4.8%)	2 (16.7%)	1 (4.5%)	0 (0%)	0.0288
Perineural* invasion	24 (34.8%)	6 (40.0%)	9 (39.1%)	9 (29.0%)	0.4075

UICC: International Union Against Cancer; Tis: tumor in situ; N: nodus; G: grading; R: residual tumor classification; %: percentage related to groups

ing the three survival groups, the following differences in histopathological features and surgical procedures were observed (Tables 1 and 2): in group A, patients significantly displayed more often a UICC stage IVb disease (i.e., non-regional lymph node positive tumors and/or distant metastasis; 26.3% vs. 8.3% and 3.0% for group B and C, respectively; p=0.0112), whereas UICC stage I (T1 tumors without positive lymph nodes or metastasis) was associated with group C (>5-year-survival; 15.2% vs. 0% in group A and B, p=0.0193; Table 1, Figure 2A). Group A was also associated with the highest rate of R2 resections (16.7%, p=0,0288) compared to groups B and C (4.5% and 0%, respectively; Table 1, Figure 2B). Perineural invasion had no significant impact on the overall survival. However, 29.0% patients surviving for >5 y displayed the lowest perineural infiltration prevalence (vs. 40% and 39.1% in group A and B, respectively; Table 1, Figure 2C). No significant differences were observed in tumor grading (G1-3) between the groups. Additional information is shown in Table 1.

Further, no significant differences in age or gender were observed among the three groups (Table 2). With regard to the Bismuth-Corlette classification, patients with stage IIIa surprisingly displayed a prolonged disease-specific overall survival (>5- vs. >3-5- vs. >2-3-year- survival rate, 30.3%, 8.3%, and 10.5%, respectively; p=0.0467; Table 2, Figure 2D).

Patients undergoing only exploratory laparotomy due to an unresectable disease displayed poor overall survival in this selected study cohort as expected (>2-3- vs. >3-5- vs. >5-year- survival rate, 36.8%, 12.5%, and 9.1%, respectively; p=0.0157; Table 2, Figure 2E). Regarding the different types of tumor resection (only bile duct resection or right/left hemihepatectomy; exploratory laparotomy due to unresectable disease excluded), no significant differences in survival were observed among the three groups. However, there was a tendency (p=0.1207) of right hemihepatectomy to be associated with prolonged survival (>5- vs. >3-5- vs. >2-3-year-survival rate, 39.4%, 20.8%, and 21.1%, respectively; Table 2). Interestingly, caudate lobectomy, which in some cases was independently performed of the above-listed surgical procedures, was frequently applied in groups B and C and associated

Table 2. Patient demographics, Bismuth-Corlette classification, and surgical procedure

	Overall (%) N=76 (100%)	Group A (>2-3 year survival) N=19 (25.0%)	Group B (>3-5 year survival) N=24 (31.6%)	Group C (>5 year survival) N=33 (43.4%)	p
Age, y	59.03 ±11.63	58.68±15.22	58.88±10.08	59.33±15.66	0.9790
Female	28 (36.8%)	5 (26.3%)	8 (33.3%)	15 (45.5%)	0.1533
Male	48 (63.2%)	14 (73.7%)	16 (66.7%)	18 (54.5%)	
Bismuth I	4 (5.3%)	1 (5.3%)	3 (12.5%)	0 (0%)	0.2685
Bismuth II	3 (3.9%)	0 (0%)	2 (8.3%)	1 (3.0%)	0.7438
Bismuth IIIa	14 (18.4%)	2 (10.5%)	2 (8.3%)	10 (30.3%)	0.0467
Bismuth IIIb	11 (14.5%)	3 (15.8%)	1 (4.2%)	7 (21.2%)	0.4249
Bismuth IV	44 (57.9%)	13 (68.4%)	16 (66.7%)	15 (45.5%)	0.0786
Exploratory laparotomy	13 (17.1%)	7 (36.8%)	3 (12.5%)	3 (9.1%)	0.0157
Bile duct resection alone	18 (23.7%)	5 (26.3%)	7 (29.2%)	6 (18.2%)	0.4384
Right hemihepatectomy	22 (28.9%)	4 (21.1%)	5 (20.8%)	13 (39.4%)	0.1207
Left hemihepatectomy	23 (30.3%)	3 (15.8%)	9 (37.5%)	11 (33.3%)	0.2439
Caudate lobectomy	24 (31.6%)	2 (10.5%)	6 (25.0%)	16 (48.5%)	0.0034

%: percentage related to groups

with a very significant survival benefit (>5- vs. >3-5- vs. >2-3-year-survival rate, 48.5%, 25.0%, and 10.5%, respectively; p=0.0034; Table 2, Figure 2F).

Additionally, the Kaplan-Meier survival analyses revealed a significant association between the following clinicopathological parameters and improved overall survival rates (Figure 2A-F): UICC stages I-IVa [hazard ratio (HR), 0.3506; 95% confidence interval (CI), 0.0557-0.5659; p=0.0035; Figure 2A], R0 status (HR, 0.4908; 95% CI, 0.2058-0.8157; p=0.0111; Figure 2B), Bismuth-Corlette stage IIIb (HR, 0.5198; 95% CI, 0.3106-0.9899; p=0.0461; Figure 2D), tumor resection (HR, 0.3937; 95% CI, 0.1002-0.6059; p=0.0023; Figure 2E), and segment I resection (HR, 0.3612; 95% CI, 0.2375-0.6587; p=0.0004; Figure 2F). Kaplan-Meier survival analysis was also performed for perineural invasion, which did not show significant differences (HR of no perineural invasion, 0.8243; 95% CI, 0.4642-1.441; p=0.4862; Figure 2C).

Finally, in the present study cohort, multivariate cox proportional hazards regression survival analysis identified additional resection of liver segment I (i.e., caudate lobectomy) as the only independent prognostic parameter for prolonged overall survival (p=0.0013).

DISCUSSION

In the present follow-up study, we compared long- and mid-term survivors after surgery for patients with perihilar cholangiocarcinoma to identify the prognostic factors for prolonged disease-specific overall survival, including >5-year-survival. Our observations indicate that patients with metastatic perihilar cholangiocarcinoma and/or additional non-regional tumor cell positive lymph nodes (i.e., UICC IVb), R2 status, and (as expected) exploratory laparotomy only display dismal survival rates. Perineural tumor invasion did not differ significantly among the three survival groups, but the highest invasion rates were observed in the lower survival groups (groups A and B). Interestingly, Bismuth-Corlette stage IIIa and particularly caudate lobectomy were associated with improved overall survival. These findings are discussed in greater detail below.

Previous studies, similarly employing the seventh TNM classification, also demonstrated that patients with an UICC stage IVb disease have the poorest prognosis (5, 9, 15). Within the seventh UICC classification, tumor cell positive lymph nodes have been redefined regarding their tumor distance (i.e., non-regional lymph nodes in UICC stage IVb) emphasizing more on this prognostic param-

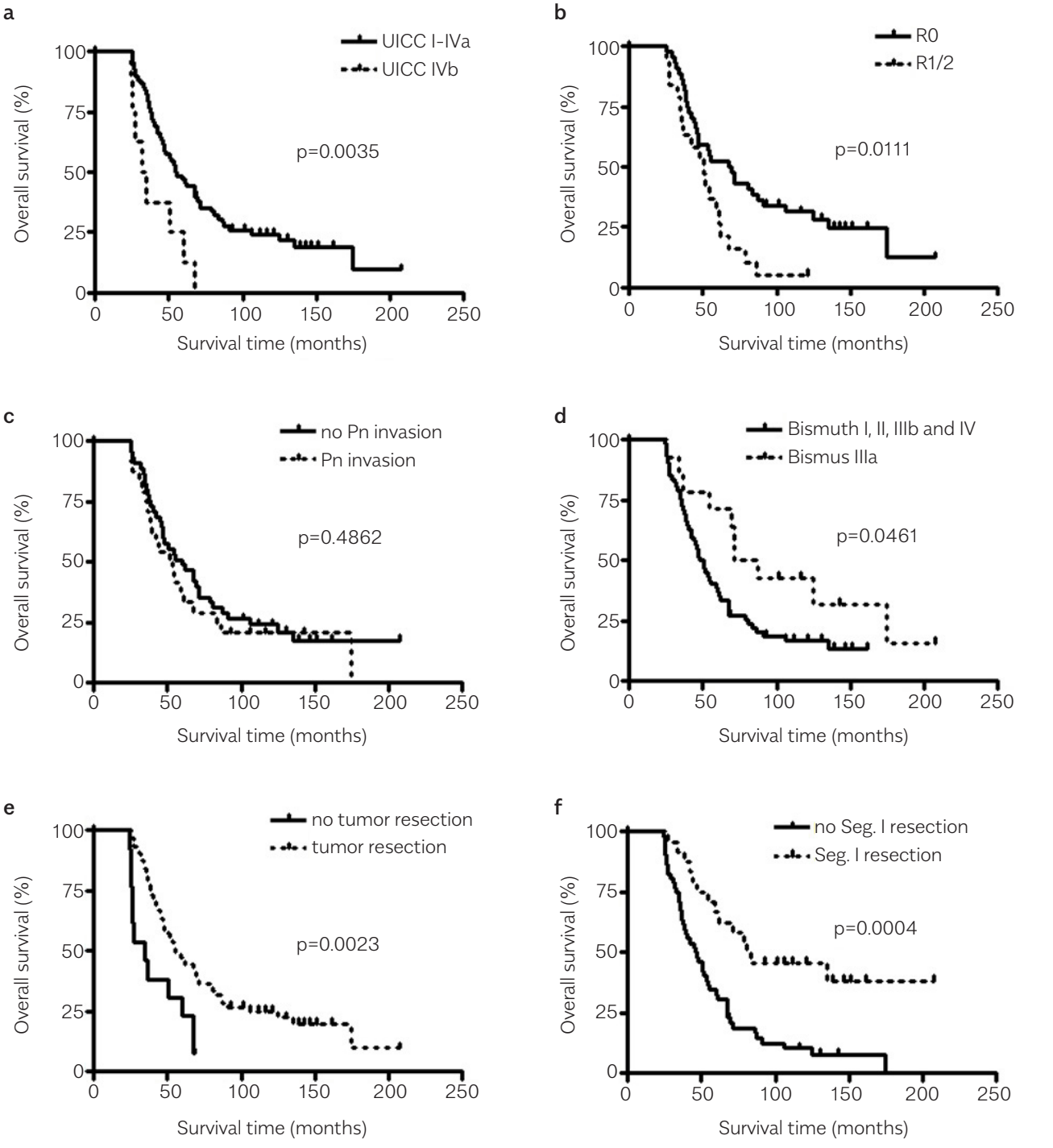

Figure 2. a-f. Kaplan-Meier survival curves (n=76) comparing different clinicopathological parameters. (a) UICC stage I-IVa vs. UICC stage IVb tumors. (b) R0-status vs R1/R2-status. (c) No perineural invasion (Pn) vs Pn invasion. (d) Bismuth-Corlette stage I, II, IIIb, and IV vs Bismuth-Corlette stage IIIa. (e) No tumor resection (exploratory laparotomy only) vs tumor resection. (f) No segment I (Seg. I) resection vs Seg. I resection (i.e., caudate lobectomy). Survival differences (p values) were assessed employing the log-rank test
UICC: International Union Against Cancer; R: residual tumor classification

eter (15). Patients with such an advanced tumor stage unfortunately display overall survival rates <1 y despite systemic chemotherapy (2). The benefit of adjuvant chemotherapy following curative resection of hilar cholangiocellular carcinoma remains inconclusive. Studies are currently going on to evaluate the efficacy of gemcitabine, 5-FU, and cisplatin (13). There is a tendency of a potential benefit regarding radiotherapy or radiochemotherapy in patients with resection margin positive tumors or even with unresectable tumors (16-18).

Histopathological parameters, such as perineural invasion, could help identify patients that might benefit from adjuvant chemotherapies. As perineural invasion is frequently discussed as a prognostic marker for patient survival (14), we also assessed this parameter in the present study. The highest rates of perineural invasion (up to 40.0%) were observed in those groups with impaired survival. Conversely, <29.0% of the long-term survivors (>5 y) displayed perineural invasion. These findings are in line with a study of Tabata and coworkers who reported an association of perineural infiltration with higher T and UICC tumor stages, respectively (19). However, this parameter did not reach statistical significance in the present study, and thus should be investigated in larger patient cohorts.

Regarding the R status, R1/2 resections were associated with poor survival (Figure 2B). This finding is in line with previous studies reporting that a low R status is required to improve patient survival, particularly when radiotherapy has been used (13, 18). Histopathological grading in the present study had no impact on survival, which is in contrast to data from Vern-Gross and coworkers, who reported that moderately (G2) and poorly differentiated tumors (G3) negatively influence the patient outcome (20). However, in this study, 1491 patients were included within a 30-year-period, probably explaining the statistical difference in tumor grading. Interestingly, patients with Bismuth-Corlette stage IIIa also displayed improved survival rates in the present study. One explanation might be that complete tumor resection is more likely to be achieved with right hemihepatectomy. Consistently, patients who underwent this surgical procedure also displayed prolonged survival rates (although this parameter barely missed significance).

Regarding surgical procedures, the present data strongly suggest that caudate lobe resection is associated with improved long-term survival, which is in line with a pilot study of the present and previous reports (8-11). As previously mentioned, tumor infiltration into the caudate lobe is a common phenomenon in perihilar cholangiocarcinoma (12). Thus, it seems that caudate lobectomy should be performed whenever feasible to achieve long-term survival in patients suffering from this morbid disease.

In conclusion, patients with perihilar cholangiocarcinoma should undergo complete/extended tumor resection with additional caudate lobe resection (if possible) to achieve long-term survival. Perineural infiltration seems to have a negative impact on disease-specific overall survival. However, this prognostic parameter needs to be evaluated in larger study cohorts.

Ethics Committee Approval: This study was conducted in accordance with the Helsinki Declaration of 1975 and approved by the Ethics Committee of the University Hospital of Essen, Germany (License Number: 14-6101-BO).

Informed Consent: Written informed consent was obtained from the patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - B.J.; Design - G.M.K.; Supervision - A.P. and C.D.F.; Materials - H.R.; Data Collection and/or Processing - S.K., H.R. and S.G.; Analysis and/or Interpretation - G.M.K., C.D.F.; Literature Review - B.J.; Writing Manuscript - B.J., C.D.F.; Critical Review - G.M.K., A.C.

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Conflict of Interest: The authors have no conflicts of interest to declare.

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