Distal Bile Duct Cancer: Radical (R0 > 1 mm) Resection Achieves Favorable Survival

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Objective: Evaluation of the outcome after resection for distal bile duct cancer (DBC) with focus on the impact of microscopic histopathological resection status R0 (>1 mm) versus R1 (≤1 mm) vs R1 (direct).

Summary Background Data: DBC is a rare disease for which oncologic resection offers the only chance of cure.

Methods: Prospectively collected data of consecutive patients undergoing pancreaticoduodenectomy for DBC were analyzed. Histopathological resection status was classified according to the Leeds protocol for pancreatic ductal adeno carcinoma (PDAC) (PDAC; R0 >1 mm margin clearance vs R1 ≤1 mm vs R1 direct margin involvement).

Results: A total of 196 patients underwent pancreaticoduodenectomy for DBC. Microscopic complete tumor clearance (R0 > 1 mm) was achieved in 113 patients (58%). Median overall survival (OS) of the entire cohort was 37 months (5- and 10-year OS rate: 40% and 31%, respectively). After R0 resection, median OS increased to 78 months with a 5-year OS rate of 52%. Negative prognostic factors were age > 70 years ($P < 0.0001$, hazard ratio (HR) 2.48), intraoperative blood loss > 1000 mL ($P = 0.0009$, HR 1.99), pN1 and pN2 status ($P = 0.0052$ and $P = 0.0006$, HR 2.14 and 2.62, respectively) and American Society of Anesthesiologists score > II ($P = 0.0259$, HR 1.61).

Conclusions: This is the largest European single-center study of surgical treatment for DBC and the first to investigate the prognostic impact of the revised PDAC resection status definition in DBC. The results show that this definition is valid in DBC and that "true" R0 resection (>1 mm) is a key factor for excellent survival. In contrast to PDAC, there was no survival difference between R1 (≤1 mm) and R1 (direct).

Keywords: distal cholangiocarcinoma, long-term survival, oncologic surgery, pancreatic resection, surgical outcomes

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Distal bile duct cancer (distal cholangiocarcinoma, DBC) is a relatively rare tumor entity with a considerably lower incidence in Western than in Asian countries (0.3–0.5 vs 1.5–3.3 per 100,000 inhabitants).[1–3] With regard to biological behavior, treatment options, and prognosis, DBC is distinct from intrahepatic and hilar bile duct cancers and from other periampullary malignancies. Irrespective of their histological and anatomical origin, the treatment of choice and sole curative treatment option for periampullary carcinomas is pancreaticoduodenectomy (PD). DBC accounts for only 3% to 24% of all periampullary tumors,[3–5] with upfront resection rates of around 30%[6,7] and 5-year survival rates ranging between 9% and 41%.[5,8–15] However, patient collectives are small (up to 50 patients) in previous studies – predominantly single-center studies from Europe.[4,10,11] In the recent literature, different prognostic factors for overall survival (OS) after DBC resection have been analyzed, including patient-related parameters (eg, sex and age), pathological results (eg, resection margin status, tumor grading, and lymph node status), and treatment-related factors (eg, preoperative biliary drainage, perioperative blood transfusion, and postoperative morbid-ity).[4,9–11,14,17–21] Evidence for the benefit of adjuvant chemotherapy after resection for DBC is sparse, and routine use remains controversial.[22,23] An unaddressed question is the issue of microscopic resection radicality, which has been shown to be of high relevance in pancreatic cancer [pancreatic ductal adeno carcinoma (PDAC)] resection, where a tumor-free margin of >1 mm has a strong prognostic impact.[8]

The aim of this study was to evaluate the oncological outcome after DBC surgery and identify prognostic factors for survival, with a special focus on microscopic resection radicality.

METHODS

Study Design and Patient Cohort

Data of all consecutive patients treated for DBC at the Department of Surgery, University of Heidelberg, Germany, between October 2001 and December 2017 were extracted from a prospec-tively maintained database. Surgical and oncological outcome parameters were assessed as described below. All patients included in this study gave their written informed consent. The study was approved by the local ethics committee (S-011/2015).

Data Collection and Outcome Parameters

The baseline data included patient's sex and age, body mass index, pre-existing diabetes mellitus, preoperative tumor-associated symptoms, preoperative biliary drainage, and the American Society of Anesthesiologists (ASA) score.

The surgical parameters included type of operative procedure, duration of operation, and intraoperative blood loss. Extended resection was defined as resection of major vessels and/or additional organs. Postoperative pancreas-specific complications (postpancreatectomy hemorrhage, postoperative pancreatic fistula, lymphatic fistula, delayed gastric emptying), as well as othercomplications, reoperation, mortality, histopathological findings (eg, tumor size, classification according to tumor, node and metastases, and resection margin status), and duration of hospital stay were analyzed. Postpancreatectomy hemorrhage, postoperative pancreatic fistula, delayed gastric emptying, and lymphatic fistula were defined according to the current International Study Group of Pancreatic Surgery definitions.[24–27] Tumor staging was based on the American Joint Committee on Cancer Staging Manual (8th edition).[28] As established for PDAC, a positive resection margin (R1) was defined as presence of cancer cells within 1 mm of the resection margin (R1 ≤1 mm) or direct invasion at the margin (R1 direct).[29] R0 resection was defined as tumor-free margin >1 mm.

Regular follow-up visits in the outpatient department for pancreatic diseases every 3 to 12 months were documented and analyzed. Each follow-up visit included physical examination, routine blood analysis, and cross-sectional imaging. Adjuvant treatment, the time and pattern of tumor recurrence, and the date of and reason for death were recorded. The date of the last follow-up was March 1, 2018.

Statistical Analysis

Data management and statistical analysis were carried out using SAS software, release 9.4 (SAS Institute, Cary, NC). The quantitative variables age, body mass index, serum levels of carbohydrate antigen (CA) 19–9, C-reactive protein (CRP), and albumin, tumor size, duration of operation, intraoperative blood loss, and length of hospital stay were presented as median and interquartile range, unless otherwise stated. For categorical parameters, absolute and relative frequencies were computed. OS was defined as the time from the date of primary pancreatic resection to either death from any cause or last follow-up. Disease-free survival (DFS) was defined as the time from the date of the operation to disease recurrence or last follow-up. Patients lost to follow-up were excluded from survival analyses. Survival was estimated using the Kaplan-Meier method. Patients alive at the last follow-up were censored and are marked in the figures (|). The 5- and 10-year survival rates are presented, if available. The log-rank test was used to compare survival curves. Univariable and multivariable proportional hazard regression (Cox model) analyses were performed to develop a final model that accurately predicted OS. Cases with missing values and patients lost to follow-up were excluded from the multivariable analyses. Known prognostic factors with a P value < 0.05 in univariable analyses were included in the multivariable analyses. Two-sided P values were computed, and a difference was considered statistically significant at P < 0.05.

RESULTS

Patient Characteristics and Preoperative Findings

During the study period, a total of 196 patients underwent PD for DBC (supplemental Table 1, http://links.lww.com/SLA/D210). The patients' age ranged from 38 to 87 years (median 70 years). One hundred forty-seven of the 196 patients (75%) were male. Six patients (3%) had an ASA score of I, while 90 (46%) and 95 (48%) were classified as ASA II and ASA III, respectively. Preoperative tumor-associated symptoms, relevant medical history, and preoperative laboratory parameters are shown in

supplemental Table 1, http://links.lww.com/SLA/D210. One hundred fifty-six of 177 patients (88%) displayed symptoms of jaundice, and 89 of 196 patients (45%) underwent preoperative biliary drainage. Other major symptoms included weight loss in 106 of 159 patients (67%) and abdominal pain in 72 of 160 patients (45%). An elevated CA 19–9 serum level (≥37 U/mL) was detected in 52% of the patients, while CRP was elevated (≥5 mg/L) in 110 of 171 patients (64%) and serum albumin was reduced below normal levels (<35 mg/L) in 15 of 177 patients (8%).

## Surgical Procedures and Perioperative Outcome Parameters

Overall, 178 of 196 patients (91%) received PD and 18 patients (9%) underwent total PD (supplemental Table 1, http://links.lww.com/SLA/D210). Pylorus preservation was possible in 180 of 196 patients (92%). The reasons for total pancreatectomy were preoperative endoscopic interventions with the intraoperative finding of pancreatitis in body and/or tail of the remnant pancreas (n = 7), the intraoperative estimation of a high-risk anastomosis due to extremely soft, fatty pancreatic tissue texture and duct size below 3 mm (n = 5), tumor extension to the left side of the portal vein axis (n = 5) and status after distal pancreatectomy in one patient who had undergone multivisceral gastrectomy for gastric cancer 10 years before. Extended resections were performed in 36 of 196 patients (18%), including vascular resections in 23 patients (12%). The mean intraoperative blood loss was 836 mL (range 50–4700 mL). The most common postoperative complications were DGE (44%) and surgical site infection (34%). Relaparotomy was required in 29 of 196 patients (15%), the most common indications being postoperative pancreatic fistula and post-pancreatectomy hemorrhage. Thirty- and Ninety-day mortalities were 3% and 8% (5/196 and 16/196 patients), respectively.

Histopathological Findings

Median tumor size was 20 mm (range 2–60 mm), and pT3 was the most common T stage (144/196, 74%). Seventy-two of 196 (37%) patients had no evidence of nodal involvement in histopathology (pN0), 66 (34%) patients were staged pN1, and 58 (30%) patients were staged pN2. Six (3%) patients had synchronous distant metastases: in 2 patients liver metastases were atypically resected; in 1 case only a liver biopsy was taken; 3 other patients were defined as pM1 for resected distant periaortic lymph node metastases. A negative resection margin status (R0) was achieved in 113 of 196 patients (58%). R1 ≤1 mm and R1 direct resections were found in 46 (23%) and 37 (19%) patients, respectively.

Overall and Disease-free survival

Long-term follow-up data were available from 173 of 196 patients (88%). Seven patients (4%) were lost to follow-up and 16 patients (8%) died within 90 days after surgery. After median follow-up of 48 months, 78 of 173 patients (45%) were still alive. The median OS was 36.8 months (95% CI 27.7–52.7), with 5- and 10-year survival rates of 40.3% (95% CI 32.0–48.5) and 30.5% (95% CI 21.8–39.6), respectively (Fig. 1A). Tumor recurrence was observed in 93 of 173 patients (54%) with metachronous distant metastases in 48 cases (52%), local tumor recurrence in 21 (23%), and concomitant local and distant tumor recurrence in 24 cases (25%). The median time to recurrence was 21 months. Twenty-five patients relapsed in the first year after resection, 44 patients in the second year, and 24 patients showed late recurrence more than 24 months after the initial resection. One hundred sixty-seven of 196 (85%) patients were included in DFS analysis, and 53 of these patients (32%) were disease-free. The median DFS was 21.4 months (95% CI 16.632.1), with
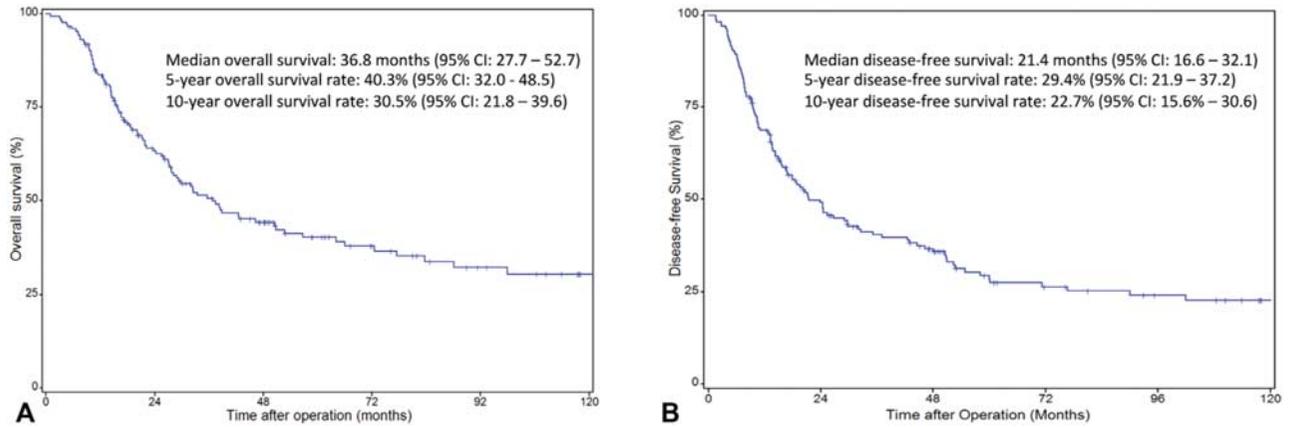
FIGURE 1. Survival after resection. A, Overall survival;B, disease-free survival. Patients alive at the last follow-up are censored (I).

5- and 10-year survival rates of 29.4% (95% CI 21.9–37.2) and 22.7% (95% CI 15.6–30.6), respectively (Fig. 1B).

After R0 resection median OS was 77.5 months (95% CI 38.2-n.a.), with a 5-year survival rate of 52.2% (95% CI 40.8– 62.4). In contrast, following R1 ≤ 1 mm and R1 direct resection median OS was 24.2months (95% CI 14.3-32.6), with a 5-year survival rate of 22.3% (95% CI 9.1–39.1) and 21.9 months (95% CI 15.2–37.5) with a 5-year survival rate of 21.8% (95% CI 7.3–41.2), respectively. The difference in OS between R0 and R1 status was statistically significant ($P < 0.0001$) (Fig. 2A).

Median DFS after R0 resection was 42.9 months (95% CI 23.9-58.1), with a 5-year survival rate of 39.2% (95% CI 28.6–49.5). After R1 ≤ 1 mm resection and R1 direct resection median DFS was 16.6 months (95% CI 7.7–24.5) with a 5-year survival rate of 14.9% (95% CI 5.0–29.8) and 13.7 months (95% CI 9.9–19.0) with a 5-year survival rate of 14.4% (95% CI 3.4-32.9), respectively. As for OS, these differences in DFS were statistically significant ($P = 0.0002$) (Fig. 2B).

Prognostic Factors for Overall Survival

Univariable analysis revealed that age ≥70 years, ASA III, preoperatively elevated serum CA 19-9 and CRP levels, and decreased serum albumin levels were significant negative prognostic factors for OS (supplemental Table 2, http://links.lww. com/SLA/D211). Gender, preoperative biliary drainage, and pre-existing diabetes mellitus had no statistically significant influence on survival. Surgery-related factors significantly associated with worse OS were vascular resection, operation time ≥300 minutes, and blood loss ≥1000 mL. Tumor-specific negative prognostic factors included pT3 and pT4 stage, positive lymph nodes, distant metastases, and positive resection margin, as well as microvascular, perineural, and lymphatic invasion (supplemental Table 2, http://links.lww.com/SLA/D211). Multivariable analysis identified age ≥70 years, ASA III, intraoperative blood loss ≥1000 mL, positive resection margin status, and positive lymph nodes as independent negative prognostic factors (Table 1).

Adjuvant Therapy

Information on adjuvant therapy was available for 172 of 196 (88%) patients. Of these, 77 patients (45%) received adjuvant chemotherapy or radiochemotherapy, mostly gemcitabine- based (88%). Radiotherapy was combined with chemotherapy in eight patients. The median OS for patients undergoing adjuvant
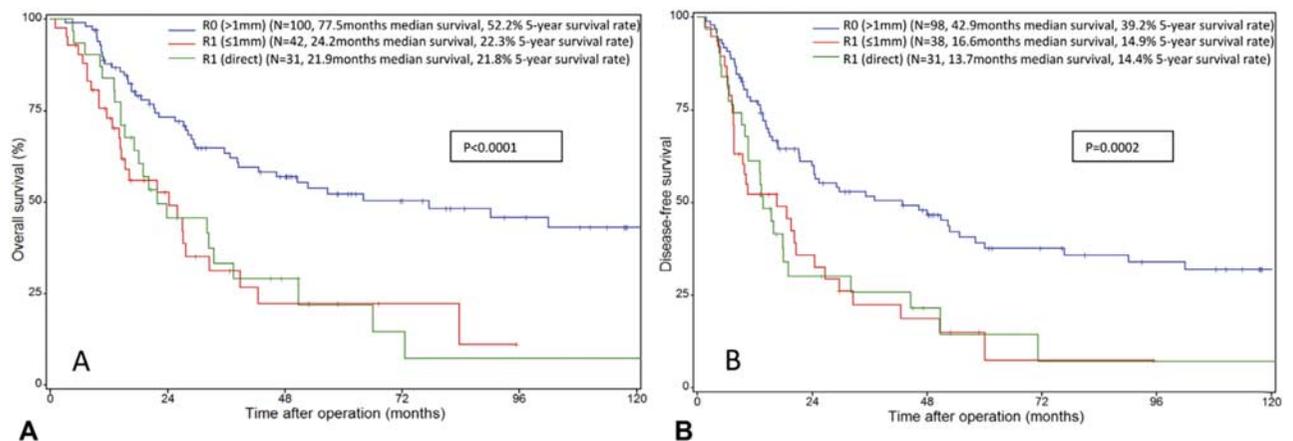
FIGURE 2. Survival after R0 > 1 mm, R1 ≤ 1 mm, and R1 direct resections. A, Overall survival;B, disease-free survival. Patients alive at the last follow-up are censored (I).

TABLE 1. Multivariable Survival Analysis

Multivariable analysis of the overall survival

| Variable	Category	HR	95% CI	*P*-value
(Likelihood Ratio: Chi^2 73.01, 6 DF, *P* < 0.0001)				
N-stage	N2 vs N0	2.62	1.51–4.54	0.0006
	N1 vs N0	2.14	1.26–3.64	0.0052
Age at operation	≥70 yr vs < 70 yr	2.48	1.63–3.77	< 0.0001
margin status	R0 > 1 mm vs R1	1.66	1.06–2.58	0.0254
	RRR1 ≤1 mm/R1			
Intraoperative blood loss	≥1000 mL vs < 1000 mL	1.99	1.33–3.01	0.0009
ASA classification	ASA III vs ASA I-II	1.61	1.06–2.45	0.0259
Not included:				
Perineural invasion	Yes vs no			0.9412
Lymphatic invasion	Yes vs no			0.7586
Operation time	≥300 min vs < 300 min			0.6926
M-stage	pM1 vs pM0			0.6564
T-stage	pT3 vs pT1/pT2			0.5078
Vessel resection	yes vs no			0.3399
Microvascular invasion	yes vs no			0.1527
Pre-operative CA 19–9	≥150 U/mL vs < 150 U/mL			0.2149
Preoperative albumin	< 35 g/L vs ≥35 g/L			0.6800
Pre-op C-reactive protein	≥10 mg/L vs < 10 mg/L			0.9777

CI indicates confidence interval; HR, hazard ratio.

therapy was similar to that for those not receiving adjuvant therapy (38.5 versus 36.8 months, *P* = 0.4708) (Fig. 3A). There was no statistically relevant difference in DFS with and without adjuvant therapy (Fig. 3B). Comparing predictors for the likelihood to receive adjuvant therapy, patients <70 years or ASA I/II were treated significantly more often with adjuvant chemotherapy compared to more elderly and co-morbid patients (≥70 years, ASA III). CA 19–9, albumin, and CRP were not statistically different between patients receiving adjuvant therapy and those who did not. In contrast, histopathologically more advanced findings (pN1, R1, perineural or lymphatic invasion) were associated with adjuvant chemotherapy compared to less advanced tumor findings (Table 2).

DISCUSSION

This is the largest European single-center study investigating the surgical and oncological outcomes of patients undergoing surgery for DBC. Despite the generally poor prognosis of DBC, a median OS of 36.8 months was achieved, with 5- and 10-year survival rates of 40.3% and 30.5%, respectively. In patients with "true" R0 resection and tumor-free margins > 1 mm, median OS was prolonged to 77.5 months, with a 5-year survival rate of 52.2%. In addition, prognostic factors were identified that can be used to identify patients and subgroups with exceptionally good survival.

Previous studies analyzing outcomes after DBC resection show heterogeneous median survival times ranging between 19 and 42 months.[9–16] Three European single-center collectives of 47 to 65 patients[9,10,14] and 2 multicenter collectives of around 200 patients[11,16] reported 5- year survival rates between 9% and 39%. A Japanese study of 370 patients with resected DBC from 24 centers found a median OS of 42 months and a 5-year survival rate of 41%.[15] A recent Dutch study compared survival after resection for DBC and for cholangiocarcinoma (CC) of other locations and found the worst survival times for DBC resection (29 months vs 37, 42, and 41 months for intrahepatic CC,
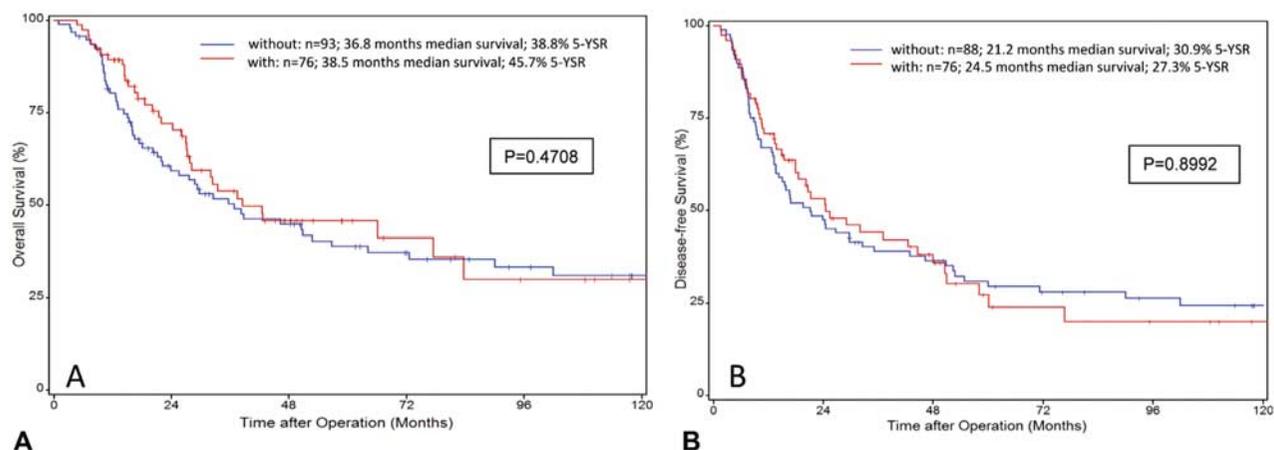
FIGURE 3. Survival after resection with and without adjuvant therapy. A, Overall survival; B, disease-free survival. Patients alive at the last follow-up are censored (I).

TABLE 2. Clinicopathological Findings Stratified for Application of Adjuvant Therapy (Data Available for 172 Patients)

Parameter	Category	No adjuvant therapy	Adjuvant therapy	*P* value
N total		95	77	
Age	<70 yr	37 (38.9%)	52 (67.5%)	0.0002
	≥70 yr	58 (61.1%)	25 (32.5%)	
ASA-score	1/2	43 (46.7%)	46 (61.3%)	0.0638
	3	49 (53.3%)	29 (38.7%)	
CA 19–9	<37 U/mL	45 (49.4%)	34 (48.6%)	0.4886
	37 to <150 U/mL	22 (24.2%)	22 (31.4%)	
	≥150 U/mL	24 (26.4%)	14 (20.0%)	
Albumin	< 35 g/L	6 (6.7%)	4 (5.6%)	1.0
	≥ 35 g/L	84 (93.3%)	67 (94.4%)	
C-reactive protein	< 5 mg/L	30 (34.9%)	30 (46.9%)	0.2761
	5to< 10 mg/L	22 (25.6%)	11 (17.2%)	
	≥10 mg/L	34 (39.5%)	23 (35.9%)	
pT stage	pT1/pT2	31 (32.6%)	16 (20.8%)	0.0887
	pT3	64 (67.4%)	61 (79.2%)	
pN stage	pN0	44 (46.3%)	20 (26.0%)	0.0070
	pN1	23 (24.2%)	34 (44.2%)	
	pN2	28 (29.5%)	23 (29.9%)	
Margin status	Negative (R0)	63 (66.3%)	37 (48.0%)	0.0209
	<1 mm (R1)	22 (23.2%)	21 (27.3%)	
	Positive (R1)	10 (10.5%)	19 (24.7%)	
Microvascular invasion	No	76 (80.0%)	62 (80.5%)	1.0
	Yes	19 (20.0%)	15 (19.5%)	
Perineural invasion	No	52 (54.7%)	28 (36.4%)	0.0210
	Yes	43 (45.3%)	49 (63.6%)	
Lymphatic invasion	No	74 (77.9%)	46 (59.7%)	0.0123
	Yes	21 (22.1%)	31 (40.3%)	

perihilar CC, and gallbladder cancer, respectively).[12] The largest single-center study to date, from the USA, included 317 DBC patients with a median OS of 23 months and 27% 5-year survival after resection.[5] Compared with the other tumor types in the overall collective of more than 2500 resected periampullary tumors in that series, the median survival for DBC was superior to that for PDAC (19 months), but clearly inferior to those for ampullary and duodenal cancer (47 and 54 months, respectively).[5] These data illustrate that DBC is the second most aggressive cancer among all periampullary tumor entities. The wide variation in survival times reported for resected DBC in the literature may be explained by relatively long study periods (up to 30 years) and the different times at which the studies were conducted, with considerable interstudy and intrastudy heterogeneity arising from changes in surgical and oncological treatment concepts over time.[7]

In the present study, adjuvant therapy (mainly chemotherapy with gemcitabine) was given in only 45% of cases and failed to prolong survival significantly, which is in line with a recent Japanese phase III study that did not show any significant advantage for adjuvant gemcitabine in patients with extrahepatic CC.[30] Similarly, the results from a French study investigating adjuvant gemcitabine plus oxaliplatin versus observation did not show a survival benefit in patients with resected DBC.[31] The British BILCAP trial demonstrated a survival benefit for adjuvant capecitabine in patients with resected CC in prespecified sensitivity and per-protocol analyses. The results of the intention-to-treat analysis, however, did not show a statistically significant prolongation of OS.[22] About one-third of the patients in the BILCAP trial had the diagnosis of DBC, and the hazard ratio in this subgroup (0.70) was superior to that of the entire cohort (0.81).[22] Based on these data, capecitabine is now recommended for adjuvant therapy in patients with resected DBC. Still, the findings of the present study might reflect current

clinical patterns of recommendation for adjuvant therapy after DBC resection: on one hand, younger patients who potentially tolerate chemotherapy better; on the other hand, patients with more advanced tumor stages who might benefit from a multimodal therapy regime were those who received the recommendation for – and finally underwent –adjuvant therapy.

Further prospective (ideally randomized) trials are needed to evaluate the benefit of multimodal treatment concepts in patients with DBC and to investigate whether more aggressive protocols might improve the patients' prognosis, as has been found to be the case in PDAC.[23,32]

The independent prognostic factors identified in the present study (i.e., pN+, age ≥70 years, positive resection margin status, intraoperative blood loss ≥1000 mL, and ASA stage > II) are in line with the recent literature identifying positive lymph node status as the most frequently observed negative prognostic factor.[3,4,9,10,14–17,19,20] A Japanese multicenter trial showed that not only the presence of positive lymph nodes, but also their number (pN1 vs. pN2), considerably impacts survival – an observation also recently made in PDAC.[15,33] Besides tumor-related and patient-related parameters, our study shows that surgical parameters significantly influence the oncological outcome. Firstly, a positive resection margin is an independent risk factor for worse survival, as already shown by previous studies.[3,17,11,14,16] The strong impact of a >1mm tumor clearance that was shown by transferring the Leeds protocol for histopathological PDAC workup to DBC underlines the importance of radical surgical approaches in order to achieve this goal.[32] Secondly, intraoperative blood loss showed an even more pronounced effect on OS and should therefore be minimized, especially when extended resections are performed. This is in line with the results of a recent study in the USA showing that the need for perioperative blood transfusion (> 1 unit of packed red blood cells) is associated with a 50% reduction in long-term

survival (15 vs 29 months)[21] and similar to the findings of a French multicenter study including 201 patients (HR 2.25).[11]

The 90-day mortality rates reported in the literature range between 3% and 8%,[5,9,11,12,14–16] which is comparable with our findings. Extended resections, with or without vascular resection, are certainly relevant risk factors for morbidity and mortality but may be necessary to achieve complete tumor removal.[34] In the light of the potentially considerable morbidity entailed by such procedures, the handling of complications is of utmost importance. Care must be taken not to turn morbidity into mortality ("failure to rescue").

The liver was the predominant site of tumor recurrence in this study, with half of the patients affected by metachronous liver metastases and another fourth by both liver metastases and local recurrence. The median time to tumor recurrence was 21 months in this study. Bergeat and colleagues also identified the liver as the most frequent site of tumor recurrence (39%), followed by local recurrence (28%), after a median DFS of 16 months.[18] Despite the observation that many recurrences occur within 24 months after surgery, 1 in every 4 patients shows late local recurrence. In this regard, a Japanese study on the timing of recurrence (≤12 months > 12 months in 61 patients after DBC resection) found that lymphatic invasion was an important independent predictive factor for late tumor recurrence.[20] Consequently, comparable with PDAC, structured oncological follow-up of resected DBC should be implemented to detect recurrence early; however, no evidence-based data on such protocols are yet available.[35,36]

The most striking finding of the present study is the observation that microscopic resection radicality with a resection margin clearance of > 1 mm (R0 CRM-) has a crucial impact on survival. The applied subdivision of margin clearance into R0 >1 mm (CRM-), R1 ≤ 1 mm (CRM+), and R1 direct was adopted from the Leeds protocol for PDAC. This classification has not specifically been used in DBC in the past, although – after long years of controversial discussion- it was included in the latest edition of the American Joint Committee on Cancer tumor, node and metastases staging system for PDAC due to its prognostic value in this tumor entity. In PDAC distinct prognostic differences among all 3 levels of radicality have been shown, but R0 >1 mm is the best prognostic group.[37] In contrast, in DBC we found only 2 tiers of prognostic relevance, namely R0 > 1 mm versus R1 ≤1 mm/R1 direct. Consequently, we suggest a revised staging of resection margin status for DBC, defined as R0 new (R0 >1 mm) and R1 new (including R1 ≤1 mm and R1 direct). To what extent the prognostic differences of resection margin status between PDAC and DBC can be explained by the use of adjuvant chemotherapy remains speculative. Adjuvant chemotherapy is very well standardized and is used in the majority of patients with PDAC. It may therefore contribute to compensate for "nonradical" resections in terms of prognosis. Contrarily, adjuvant chemotherapy is infrequently used in DBC, which may explain the dominant prognostic effect of truly radical surgery.

In conclusion, radical surgical treatment of DBC offers the chance of long-term survival to a considerable proportion of patients suffering from this rare but dismal tumor entity. For the first time in DBC surgery, we have shown that complete microscopic tumor removal with a resection margin clearance of > 1 mm is a key factor for an excellent prognosis. This must, therefore, be the primary goal of any surgical treatment strategy, including extended resections when required. The identified independent prognostic factors should be considered when stratifying patients to the available treatment options. Regarding the staging of DBC, only R0 >1 mm is prognos-tically relevant. In contrast to PDAC, for DBC there is no survival difference between R1 ≤1 mm and R1 direct.

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