The short- and long-term outcomes of pancreaticoduodenectomy for distal cholangiocarcinoma

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Background. The aim of the study was to calculate the short-term and long-term outcomes of curative-intent surgery in distal cholangiocarcinoma (DCC) patients to identify potential prognostic factors.
Patients and Methods. A retrospective cohort study of 32 consecutive DCC patients treated with pancreaticoduodenectomy between 2009–2017. The clinicopathological and histopathological data were evaluated for prognostic factors using the univariable Cox regression analysis. The Overall Survival (OS) was estimated using the Kaplan-Meier analysis.
Results. The study comprised a total of 32 patients, with a mean age of 65.8 (± 9.0) years at the time of surgery. R0 resection was achieved in 25 (86.2%) patients, 19 (65.5%) patients received adjuvant oncological therapy. The OS rates at 1, 3 and 5 years were 62.5%, 37.5% and 21.9%, respectively. The 90-day mortality was 3/32 (9.4%) accounting for one-fourth of the first-year mortality rate. The median OS was 28.5 months. The only statistically significant prognostic factor was vascular resection, which was associated with worse OS in the univariable analysis (HR: 3.644; 95%-CI: 1.179–11.216, *P*=0.025). An age less than 65 years, ASA grade I/II, hospital stay of fewer than 15 days, R0 resection, lymph node ratio less than 0.2 and adjuvant oncological therapy tended to be associated with better OS but without statistically significant relevance.
Conclusion. The main factor directly influencing the survival of DCC patients is surgical complications. Surgical mortality comprises a significant group of patients, who die in the first year following pancreaticoduodenectomy. Vascular resection is the most important negative prognostic factor for long-term survival.

Key words: cholangiocarcinoma, pancreaticoduodenectomy, long-term survival, prognostic factor

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INTRODUCTION

Distal cholangiocarcinoma (DCC) is a malignant disease which arises from the bile duct epithelium located in the distal part between the confluence of the cystic duct and above the Ampula of Vater and represents about 20–30% of all cholangiocarcinomas[1-3]. The incidence is 1.3 to 3.4 cases per 100,000 in Western countries[1]. According to the National Oncological Registry, the incidence is 3.9 cases per 100,000 and the mortality is 3 cases per 100,000 in the Czech Republic[4]. While the incidence and mortality have been decreasing slightly during the last 10 years, the DCC prognosis remains dismal and the total 5-year survival is 3.6–4.1% (ref.[5]). In a group of patients treated by curatively intended surgery, the OS is significantly higher with a 5-year survival rate of 18–54% (ref.[6,7]).

Symptoms of DCC include obstructive jaundice with/without weight loss[8]. The only potentially curative treatment modality is curatively intended surgery – pancreaticoduodenectomy (PD) with removal of the distal part of the bile duct and lymphadenectomy. Among cholangiocarcinomas, DCCs have the highest resectability rate. A specific feature of cholangiocarcinoma is submucosal and perineural spreading of tumour cells along the bile duct. The achievement of real negative resection margins seems very difficult in these cases and macroscopic margins do not correlate with microscopic histopathological spread[9]. R0 status (tumour-free resection margins) is the main goal of the procedure and the most important prognostic factors described previously in the literature are tumour-free resection margins and negative lymph node status[2,3]. In cases of venous infiltration, en bloc resection with portal vein resection might be necessary. There are some specific complications associated with this procedure, which modify the short-term outcome. Other previously described potential prognostic factors are: perineural invasion, venous invasion and postoperative complications[1].

Most published data analyse inhomogeneous patient groups according to the primary location of the biliary

tract carcinoma and type of surgical treatment[6,8,10,11]. The aim of this study was to calculate the short-term and long-term treatment outcomes of curative intent surgery in DCC patients and to identify potential prognostic factors.

MATERIALS AND METHODS

This is a retrospective cohort study using a single-centre database consisting in 32 consecutive DCC patients operated on with curative intent between 2009–2017. All the data were collected prospectively including sex, age, time of surgery, ASA, Intensive Care Unit (ICU) length of stay, hospital stay, in-hospital mortality, 30-day mortality, 90-day mortality, vascular resection and complications classified according to the Clavien-Dindo (CD) classification[12]. Pathological evaluation included radicality (resection margins), grading (low/moderate/high differentiation), T-stage, N-stage (lymph node status), number of lymph node metastases, number of lymph nodes removed, lymph node ratio (LNR), perineural invasion, vascular invasion and lymphatic invasion.

The surgical mortality (in-hospital mortality, 30-day, 90-day) was defined as the death of the patients during primary hospitalisation or during the first 30 and 90 days after the primary surgery.

Specific complications of pancreatic surgery, such as postoperative pancreatic fistula (POPF), delayed gastric emptying (DGE) and postpancreatectomy haemorrhage (PPH) are graded in accordance with the International Study Group of Pancreatic Surgery (ISGPS) definitions[13-15].

For histopathological evaluation, all the specimens were classified in accordance with the WHO classification of tumours of the digestive system and the results were verified by two independent pathologists. The TNM clinical classification (UICC 7th edition) was used for staging. The definition for R0 resection was ≥1 mm from the microscopic border of the tumour. An LNR cutoff of 0.20 was used. The impact of these parameters on the OS was evaluated. The OS was measured as the period between the date of surgery and the date of death.

The following criteria were used to assess the resectability of DCC: 1) absence of nodal metastases in the retropancreatic and paraceliac area or distant liver metastases, 2) absence of disseminated disease. PD with removal of the distal part of the bile duct en block with the head of the pancreas, gallbladder, duodenum and standard lymphadenectomy according to the International Study Group for Pancreatic Surgery recommendation (ISGPS) was the standard procedure[16]. The reconstruction was performed with a pancreatojejunostomy, hepaticojejunostomy and duodenojejunostomy performed on the same jejunal loop. In cases of a very soft pancreas with a tiny pancreatic duct, total pancreaticoduodenectomy was an option. Postoperative follow-up was performed every 3 months for two years and then every 6 months for up to five years postoperatively. The follow-up included clinical examination, level of carbohydrate antigen 19-9 (CA 19-9), abdominal computed tomography every 6 months or in cases of elevated CA 19-9.

For categorical values, absolute numbers and the distribution in percentages on available data are presented. The values of continuous variables are given as median and minimum-maximum range. Differences in survival were analysed from a cohort which excluded patients who died in the first 3 months following surgery, using a univariable Cox proportional hazards regression model. The hazard ratios (HRs) are presented with 95% confidence intervals (CI). The Kaplan-Meier analysis was used to estimate long-term survival. Statistical analysis was performed with IBM SPSS Statistics version 22.

This study was approved by the Ethics committee of the Faculty Hospital Olomouc.

RESULTS

Therapy outcomes

The study comprised a total of 32 patients, 26 (81.3%) men and 6 (18.7%) women, the age of the patients was between 36 and 76 years, with a mean of 65.8 (± 9.0) years at the time of surgery. The patients were mostly scored with a preoperative ASA score II (n=25/32; 78.1%), a few patients had ASA I (n=3/32; 9.4%) and ASA III (n=4/32; 12.5%), respectively (Table 1).

The most common postoperative complications were POPF, wound infection and pneumonia. According to the CD classification, 7 (21.9%) patients had a grade 0, 1 (3.1%) had a grade I, 14 (43.8%) grade II, 1 (3.1%) grade IIIa, 4 (12.5%) grade IIIb and 2 (6.3%) grade IVb complication. The median total hospital stay was 15 (11-83) days, the ICU stay was 5 (1-77) days. Three patients had to be rehospitalised due to complications. The 90-day mortality was 9.4% (n=3/32 patients). The OS rates at 1, 3 and 5 years were 62.5%, 37.5% and 21.9%, respectively (Fig. 1). The median survival was 28.5 months.

Prognostic factor evaluation

Clinically relevant factors such as sex, age and ASA status do not statistically associate with the OS of DCC patients in our study.

When staged in accordance with UICC 7th edition, 2 patients (6.9%) were stage I, 4 (13.8%) were stage IIa, 16 (55.2%) were stage IIb and 7 (24.1%) were stage III. The histopathological examination revealed lymph node involvement (pN1) in 15 patients (51.7%). The majority of the tumours were classified as low and moderately differentiated (grades 1 and 2) in 14 (48.3%) and in 10 (34.5%) cases, respectively (Table 2). None of these tumour histopathological characteristics was statistically significant as prognostic factors influencing the long-term therapy outcomes (Table 3).

R0 resection was achieved in 25 (86.2%) patients, 19 (65.5%) patients received adjuvant oncological therapy. Vascular resection was found to be significantly associated with worse OS in the univariable analysis (HR: 3.644; 95%-CI: 1.179–11.216, P=0.025) and the Kaplan-Meier analysis (P=0.016) (Fig. 2).

Concerning the surgery complications, none of them were statistically significantly verified as a prognostic

Table 1. Clinicopathological and perioperative data for patients with distal adenocarcinoma.

Variables	n=32	n (%), median (min–max)
Age (years)		67 (36–76)
Male sex		26 (81.3%)
Preoperative biliary drainage		
ERCP		28 (87.5%)
PTC		4 (12.5%)
ASA		
Score I		3 (9.4%)
Score II		25 (78.1%)
Score III		4 (12.5%)
Operative time (min)		291 (194–430)
Vascular resection		5 (15.6%)
Hospital stay (days)		15 (11–83)
ICU stay (days)		5 (1–77)
Rehospitalisation		3 (9.4%)
Mortality		
In-hospital		2 (6.3%)
30-day		1 (3.1%)
90-day		3 (9.4%)
POPF		
Grade B		3 (9.4%)
Grade C		3 (9.4%)
DGE		
Grade A		0 (0.0%)
Grade B		2 (6.3%)
Grade C		1 (3.1%)
PPH		
Grade A		0 (0.0%)
Grade B		2 (6.3%)
Grade C		3 (9.4%)
Wound infection		7 (21.9%)
Pneumonia		6 (18.8%)
Clavien-Dindo		
Grade 0		7 (21.9%)
Grade I		1 (3.1%)
Grade II		14 (43.8%)
Grade IIIa		1 (3.1%)
Grade IIIb		4 (12.5%)
Grade Iva		0 (0.0%)
Grade IVb		2 (6.3%)

n number of non-missing values. Qualitative data are expressed as n (%) and quantitative data as median (min-max)
ASA, American Society of Anesthesiologists; DGE, Delayed gastric emptying; ERCP, Endoscopic retrograde cholangiopancreatography; ICU, Intensive Care Unit; POPF, Postoperative pancreatic fistula; PPH, Postoperative pancreatic haemorrhage; PTC, Percutaneous transhepatic cholangiography.

factor in this study. However, the 90-day mortality was 9.4% (n=3/32) and accounts for one-fourth of the first-year mortality rate. It was caused only by specific surgical complications – POPF, PPH.

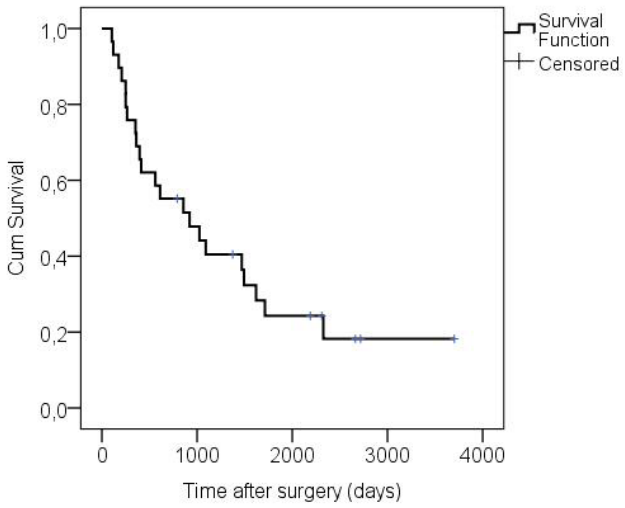

Fig. 1. Overall survival of all patients after resection for distal cholangiocarcinoma estimated using the Kaplan-Meier analysis.

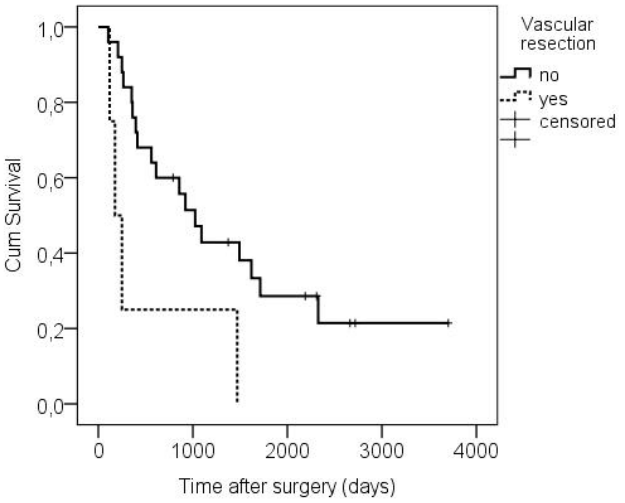

Fig. 2. Overall survival stratified by performing of vascular resection estimated using the Kaplan-Meier analysis (P=0.016).

DISCUSSION

Cholangiocarcinoma belongs to a group of aggressive cancers of pancreatobiliary origin with a dismal prognosis. Radical surgical resection of PD with lymphadenectomy is the standard therapy for early stage DCC and the only potentially curative therapy to date. In the present study, the median survival was 28.5 months and the 5-year survival was 21.9%. These results are comparable to data recently published by Zhou et al. in a systematic review of DCC survival, where 5-year survival ranged from 13-54% (ref.[2]). The reasons for this wide range in 5-year survival are unclear and variances in genetic factors, risk factors for DCC and patients' selection criteria for surgical treatment may play a crucial role, especially when confronting Asian[17-19] and European[20-24] studies.

The previously published prognostic factors for DCC patients who underwent primary surgical treatment were

Table 2. Histopathological data for patients with distal adenocarcinoma and long-term survival.

Variables	n=29	n (%), median (min-max)
T-stage		
Stage 1		2 (6.9%)
Stage 2		5 (17.2%)
Stage 3		21 (72.4%)
Stage 4		1 (3.5%)
N1 stage		15 (51.7%)
Number of lymph node metastases		1 (0–5)
Number of lymph nodes removed		7 (1–17)
LNR > 0.20		10(34.5%)
Grading		
G1		5 (17.2%)
G2		10 (34.4%)
G3		14 (48.8%)
R0 resection		25 (86.2%)
UICC stage		
Stage I		2 (6.9%)
Stage IIa		4 (13.8%)
Stage IIb		16 (55.2%)
Stage III		7 (24.1%)
Perineural invasion		19 (65.5%)
Vascular invasion		2 (6.9%)
Lymphatic invasion		9 (31.0%)

n number of non-missing values. Qualitative data are expressed as n (%) and quantitative data as median (min–max).
LNR, lymph node ratio; N1 stage, positive lymph node status; R0-resection, radical resection with ≥1 mm from microscopic border of the tumour.

pancreatic and duodenal invasion[25], surgical margin positivity[26,27], grades of tumour differentiation[23], depth of tumour invasion[28], vascular invasion[22,29], lymph node metastasis[18,27,30], perineural invasion[31,32] and postoperative adjuvant chemotherapy[33,34]. Only perineural invasion, lymph node metastasis, positive resection margin status and not-well-differentiated adenocarcinoma were associated with shorter survival in a large meta-analysis of the above-mentioned studies[35].

Concerning the tumour-related prognostic factors, we did not verify a statistically relevant association in our study, even though the R0 resection, three or fewer positive lymph nodes, LNR less than 0.2 and adjuvant oncological therapy tended to be associated with better OS but without statistically significant relevance. In our study, an R0 resection was achieved in 86.2% of the patients. The results of the OS show some tendency towards a worse OS for an R1 resection (HR: 2.205; 95%-CI: 0.723–6.724, *P*=0.165), but without statistical significance. Similar results have been published in some previous series with an R0 rate higher than 85% (ref.[1,25]). Other studies with a lower proportion of R0 resections confirmed R1 resections as a significant negative prognostic factor on the OS (ref.[35,36]) and meta-analysis showed a significant difference in the 5-year survival between those positive and negative for margin status. Therefore the primary endpoint of surgical resection should be an R0 resection. Preoperative cholangioscopy[37], frozen section examination of the resection line[38] and intraoperative cholangioscopy[39] are helpful in reaching this goal.

Various scale systems are used for the stratification of patients and their prognosis according to lymph node metastasis – lymph node status (N0/N1), number of lymph node metastases, number of lymph nodes removed and LNR (ref.[2,17,18,36,40-43]). We did not confirm lymph node status as a statistically significant risk factor for poor survival, contrary to some previous studies[17,18,41,43]. The newest TNM classification (8th edition) for DCC is setting up N2 status for patients with more than 4 positive lymph nodes. When comparing patients with 0 to 3 lymph node metastases and 4 lymph node metastases, we found an HR of 2.072 (95%-CI: 0.820–5.233, *P*=0.123) for this new N2 status. This tendency correlates with the results from Kiriyama et al.[18] and Beetz et al.[1] LNR can be used as a prognostic tool for gastric, colorectal and pancreatic ductal adenocarcinoma (PDAC) patients[44-47]. Several studies suggested LNR can be a prognostic factor for the survival of patients with DCC (ref.[48,49]). From our results' point of view, an LNR with a cutoff of 0.20 has indicated the best correlation with the OS among analysed lymph node parameters with an HR of 2.282 (95%-CI: 0.932–5.586, *P*=0.071) for an LNR greater than 0.20. The LNR results are on the bounds of statistical significance.

Table 3. Univariable analysis of clinicopathological and histopathological risk factors on overall survival of patients after resection for distal adenocarcinoma.

Variables	Hazard ratio	95% CI	*P*
ASA score III	2.134	0.700–6.505	0.183
Hospital stay ≥ 15 days	0.537	0.222–1.301	0.169
R1 resection	2.205	0.723–6.724	0.165
Lymph node metastases ≥ 4	2.072	0.820–5.233	0.123
LNR > 0.20	2.282	0.932–5.586	0.071
Adjuvant therapy	0.515	0.211–1.257	0.145

The differences in overall survival were analysed using a univariable Cox-regression model
ASA, American Society of Anesthesiologists; LNR, lymph node ratio; R1-resection, nonradical resection with <1 mm from microscopic border of the tumour.

Interestingly, the univariate analysis revealed a statistical significance of surgery-related prognostic factors such as vein resection, which had a statistically significant impact on the long-term survival and surgical complications on the short-term survival in the Kaplan-Meier analysis. This is in concordance with some previous studies, which described a worse prognosis for patients after portal vein resection[36,50,51], while other studies did not find statistically significant results[1,52]. A limitation for the evaluation of additional vein resection is the small number of patients who could be included, which in our study was only 15.6% of all patients. The benefit of portal vein resection therefore remains unclear and there is a need for an evaluation by large meta-analysis concerning all these potential factors, in particular the surgical complications.

One year of survival of the whole cohort is 62.5%. Surgical mortality is 9.4% in our cohort and in 25% of all patients who died in the first year following surgery. All cases of surgical mortality were caused only by specific surgical complications – POPF and PPH. Our surgical mortality rate is comparable to data presented by Petrova et al.[36] and Byrling et al.[52], where in-hospital mortality was 7.9% and 8.0%, respectively. On the other hand, when compared to our previously published study of PDAC patients[53], the mortality rate of PD in DCC patients seems significantly higher than in PDAC patients – 9.4% vs. 3.3%. This is probably due to obstruction and chronic inflammatory and fibrous parenchymal changes within the pancreatic tissue among PDAC patients. Contrarily, there is no obstruction nor parenchymal fibrotisation in the pancreas in DCC patients, and anastomotic complications are more frequent.

Because our study is retrospective with a limited number of patients, in addition to the fact that most of the previously published DCC analyses studied the prognostic DCC factors, large pooled data or a large multicentric trial should be used to assess the significance of surgical-related factors and their prognostic impact on DCC prognosis.

CONCLUSION

The prognosis of patients with DCC is dismal. The main factor directly influencing the survival of DCC patients is surgical complications. Surgical mortality comprises a significant group of patients, who die in the first year following PD. Vascular resection is the most important negative prognostic factor for long-term survival.

ABBREVIATIONS

ASA, American Society of Anesthesiologists; CA 19-9, Carbohydrate antigen 19-9; CD, Clavien-Dindo classification; CI, Confidence interval; DCC, Distal cholangiocarcinoma; DGE, Delayed gastric emptying; ERCP, Endoscopic retrograde cholangiopancreatography; HRs, Hazard ratios; ICU, Intensive care unit; ISGPS, International Study Group of Pancreatic Surgery; LNR, Lymph node ratio; OS, Overall Survival; PD, Pancreaticoduodenectomy; PDAC, Pancreatic ductal adenocarcinoma; POPF, Postoperative pancreatic fistula; PPH, Postoperative pancreatic haemorrhage; PTC, Percutaneous transhepatic cholangiography.

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