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ORIGINAL ARTICLE

Pancreaticoduodenectomy for distal cholangiocarcinoma: surgical results, prognostic factors, and long-term follow-up

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Abstract
Purpose Prognostic indicators for distal cholangiocarcinoma have not been widely confirmed because of its rarity. Despite the early appearance of symptoms, it has a very poor prognosis. The aim of this study was to identify prognostic factors in patients undergoing pancreaticoduodenectomy (PD) for distal bile duct cancer (DBDC) in a high-volume center for pancreatic disease.
Methods From January 2000 to December 2013, 1490 PD were performed for periampullary disease. Data from all patients with histologically proven cholangiocarcinoma were reviewed. Preoperative data, post-operative complications, pathologic features, and survival were investigated.
Results Among 50 histologically proven DBDC (3.3 %), 4 patients who underwent CBD resection were excluded. Thus, the study population consisted of 46 patients. Overall surgical morbidity rate was 67.4 %; mortality was nil. Major complications were pancreatic fistula (47.8 %), abdominal collections (34.8 %), post-pancreatectomy hemorrhage (21.7 %), and delayed gastric emptying (10.9 %). The majority of resections were R0 (73.9 %). The presence of metastatic lymph nodes (N1) was identified in 76.1 % of cases. Among N1 cases, the most frequently involved lymph nodes were pancreaticoduodenal nodes (50 %), hepatoduodenal ligament nodes (21.7 %), superior mesenteric artery nodes (8.7 %), and anterior hepatic artery nodes (4.3 %). Overall, survival rates were 88.8, 40, and 18 % at 1, 3, and 5 years, respectively. Median survival was 31 months. By univariate analysis, only tumor grading and nodal metastasis were predictors of poor prognosis ($p<0.05$). These findings were not confirmed in multivariate analysis.
Conclusions This study shows that DBDC is a rare entity even if large surgical series are reviewed. Tumor differentiation and nodal status have been confirmed as important prognostic factors. Pancreaticoduodenectomy remains the procedure of choice in order to obtain free surgical margins and in order to harvest the correct number of lymph nodes for a correct staging.

Keywords Pancreaticoduodenectomy · Cholangiocarcinoma · Biliary tract cancer · Survival · Adjuvant therapy · Pancreatic fistula

Introduction

Malignant neoplasms of the bile duct are relatively uncommon, with an annual incidence in western countries of 1–2 cases per 100,000 [1]. The incidence of bile duct cancer is increasing with the increase of average age. Even in the presence of a small tumor, cholangiocarcinoma can infiltrate adjacent vessels becoming unresectable. Among biliary tract cancers, distal bile duct cholangiocarcinoma (DBDC) is the second most frequent [2], and it is considered part of the so-called periampullary cancers, together with pancreatic ductal adenocarcinoma (PDAC), ampullary cancer, and duodenal cancer [3]. As for the other periampullary lesions, pancreaticoduodenectomy (PD) represents the surgical procedure of choice for DBDC. In large surgical series, the rate of PD for DBDC ranged from 7 to 10 % [3, 4]. Because of its relative rarity, potential prognostic indicators have not been

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clearly elucidated. Here, we report data from a series of resected DBDC at a single high-volume center.

Methods

We retrospectively reviewed the records of all patients with histologically confirmed DBDC who underwent PD at the authors' institution from January 2000 to December 2013. Only the cases with a clear diagnosis of DBDC confirmed by a dedicated pathologist were included; all doubtful cases of malignant pancreaticobiliary histology were excluded. Demographics, clinical and surgical details, pathologic data, and follow-up information were captured and analyzed. PD was normally carried out with pylorus preservation (pylorus-preserving pancreaticoduodenectomy (PPPD)); the classic Whipple procedure (WPD) was considered when there was the suspect of cancer invasion over pyloric region or gastric antrum. Reconstruction consisted of pancreaticojejunostomy (either dunking or duct-to-mucosa) and a single layer hepaticojejunostomy 15 cm downstream. Frozen section of CBD margin and pancreatic stump margin was always performed, the resection being extended in case of neoplastic involvement of the neck margin. Lymph node dissection included peripancreatic nodes (anterior and posterior surface of the pancreatic head), as well as clearance of the hepatoduodenal ligament, of the anterior aspect of the common hepatic artery and of the right aspect of the superior mesenteric artery. We did not perform any palliative PD, and there were no R2 resections. Delayed gastric emptying, post-operative pancreatic fistula, and post-pancreatectomy hemorrhage were defined according to the International Study Group of Pancreatic Surgery [5–7]. Kaplan-Meier curves were plotted, and log-rank tests were used to compare survival in different groups of patients. Cox proportional hazard models were used to calculate hazard ratios for different variables (SPSS Statistics, Version 20 for Mac, IBM, SPSS Inc., Chicago, IL, USA).

Results

One thousand four hundred ninety PD were performed at our institution in the study period. Fifty patients (3.3 %) were found with DBDC. Four patients were excluded because they underwent CBD resection with regional lymphadenectomy. CBD resection was performed only in selected cases, when the risk of major morbidity after pancreatic head resection was considered too high. Thus, the study population consisted of 46 patients. Patients' characteristics are reported in Table 1. Patients were predominantly male (71.7 %). Age ranged from 42 to 82 years with a median of 68 years. Almost all patients (93.5 %) presented with jaundice as the first symptom, and preoperative jaundice treatment was the first approach to the disease, either with endoscopic stent placement (58.7 %) or percutaneous transhepatic biliary drainage (PTBD, 10.9 %). The majority of procedures were PPPD (89.1 %); no vascular resection was carried out. The mean operative time was 390 min.

Table 1 Demographics and preoperative and intra-operative data

Gender	Male	33 (71.7 %)
	Female	13 (28.3 %)
Age (median, min–max)		68 (42–82)
BMI (median, min–max)		23 (19–39)
Diabetics		11 (23.9 %)
Jaundice		43 (93.5 %)
Biliary drainage	Total	32 (69.5 %)
	PTBD	5 (10.9 %)
	ERCP	27 (58.7 %)
Type of operation	WPD	5 (10.9 %)
	PPPD	41 (89.1 %)
Operating time, min (mean, SD)		393 (±110)

Post-operative results are reported in Table 2. The overall complication rate was 76.1 %. Surgery-related morbidity was 67.4 %. The most common complication was post-operative pancreatic fistula (47.8 %) followed by infected abdominal collection (34.8 %), post-pancreatectomy hemorrhage (PPH, 21.7 %), delayed gastric emptying (DGE, 10.9 %), biliary fistula (6.5 %), and post-operative hyperamylasemia (8.7 %). Hospital mortality was nil. Only five patients (10.9 %) required re-laparotomy for major bleeding control or for post-operative pancreatic fistula (POPF)-related septic shock. Median length of hospital stay was 16 days, without index hospital readmission. Data on readmission to other hospitals were unavailable because the majority of patients come from

Table 2 Post-operative details

Overall morbidity	35 (76.1 %)
Surgical morbidity	31 (67.4 %)
Nonsurgical morbidity	19 (41.3 %)
Pancreatic fistula	22 (47.8 %)
Biliary fistula	3 (6.5 %)
Enteric fistula	3 (6.5 %)
Post-operative hyperamylasemia	4 (8.7 %)
Post-pancreatectomy hemorrhage	10 (21.7 %)
Intra-abdominal collection	16 (34.8 %)
Delayed gastric emptying	5 (10.9 %)
Pneumonia	11 (23.9 %)
Cardiac morbidity	3 (6.5 %)
Re-laparotomy	5 (10.9 %)
LHS, days (median, min–max)	16 (7–70)

outside the regional catchment area. For the same reason, it was not possible to obtain complete data on adjuvant therapy. Forty-two percent of patients were treated with adjuvant chemotherapy, most of them with gemcitabine-based protocols; only three patients received adjuvant chemoradiation. Pathological features are reported in Table 3. R1 resection rate was 23.9 %. The margin most frequently involved was the CBD, despite it being assessed intra-operatively. This phenomenon may be due to severe inflammatory changes in the CBD walls after preoperative biliary drainage (69.5 % of cases in the present series), which make it difficult to detect cancer cells on frozen section. The rate of R1 resections in the first study period was probably underestimated because more comprehensive protocols for specimen handling had not been published [8–10]. Most cases were moderately differentiated (G2, 56.5 %), T3 cholangiocarcinomas (78.3 %) with perineural invasion (76.1 %). Metastatic lymph nodes were found in 54.3 % of cases. Characteristics of nodal involvement are summarized in Table 4. The median number of harvested lymph nodes was 25 (range 3–65); the mean lymph node ratio was 0.08 (range 0–0.36). According to the Japan Pancreas Society (JPS) classification [11], the most frequently involved lymph nodes were pancreaticoduodenal nodes (station 13 and 17, 43.5 %), hepatoduodenal ligament nodes (station 12, 21.7 %), superior mesenteric artery nodes (station 14, 8.7 %), and anterior hepatic artery nodes (station 8a, 8.7 %).

The median follow-up of the study cohort was 21 months (range 2–163). The median overall survival was 31 months while 1, 3, and 5-year overall survival rates were 88.8, 40, and 18 %, respectively (Fig. 1). Twenty-one patients received adjuvant gemcitabine-based chemotherapy. Survival analysis is showed in Table 5. Factors associated with survival on univariate analysis were tumor grade (median survival of 32 months in G1 patients vs. 27 months in G2 patients vs. 19 months in G3 patients, p=0.04) and N status (median survival of 53 months in N0 patients vs. 27 months in N1 patients, p=0.02). Survival curves are shown in Fig. 2. There was no survival difference between R0 and R1 resections (p=0.983). Similarly, lymphatic invasion, vascular invasion, perineural invasion, T status, post-operative morbidity, and adjuvant therapy did not affect survival in the present study. When stratifying by nodal stations, only metastases to station 12 were associated with survival (median survival of 27 months in station 12+ patients vs. 48 months in station 12− patients, p=0.03). When the analysis was limited to N1 cases, there was no metastatic lymph node station significantly associated with a survival decrease. The Cox proportional hazard model failed to identify independent prognostic factors.

Table 3 Pathological features

R status	R0	34 (73.9 %)
	R1	11 (23.9 %)
R1 site	CBD	5 (10.9 %)
	Posterior pancreatic head surface	1 (2.2 %)
Grading	G1	4 (8.7 %)
	G2	26 (56.5 %)
	G3	12 (26.1 %)
Lymphatic invasion		18 (39.1 %)
Vascular invasion		30 (65.2 %)
Perineural invasion		35 (76.1 %)
T	T1	2 (4.3 %)
	T2	4 (8.7 %)
	T3	36 (78.3 %)
	T4	0
N1		25 (54.3 %)

Table 4 Lymph nodes involvement

Harvested lymph nodes (mean, min–max)	25 (3–65)
Lymph node ratio (mean, min–max)	0.08 (0–0.36)
Station 13 and 17, N+	20 (43.5 %)
Station 12, N+	10 (21.7 %)
Station 8a, N+	2 (4.3 %)
Station 14, N+	4 (8.7 %)

Discussion

Only few previously published papers analyzed the features of surgically resected DBDC [12–16]. Here, the 13-year experience with 46 DBDC resected at a single institution is reported. Considering the initial clinical suspect, nearly all cases (84 %) were considered DBDC at the preoperative assessment and

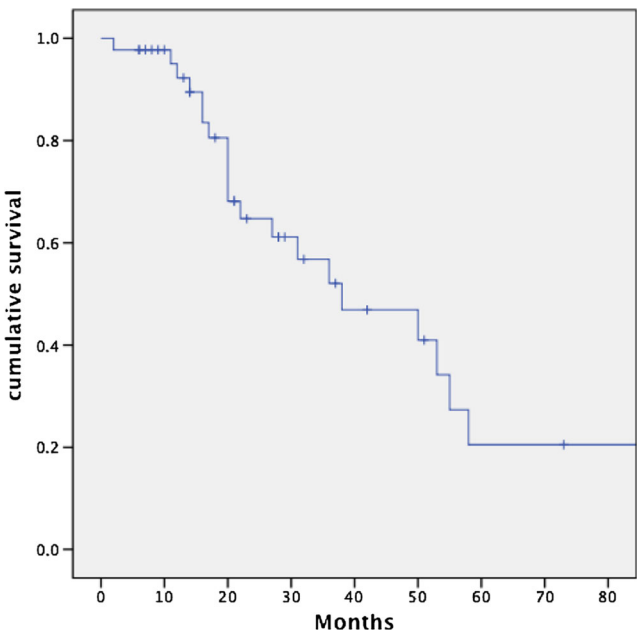

Fig. 1 Cumulative survival curve for DBDC

Table 5 Survival analysis

		N of patients	Median survival (months)	Univariate	Risk ratio (CI)	Multivariate
Age	<70	32	23	0.06	1 (reference)	0.1
	>70	18	25		3.7 (1.3–10.4)	
Gender	M	33	23	0.34	1 (reference)	0.1
	F	13	25		5.9 (0.7–48.8)	
T status	T1	2	50	0.46	1 (reference)	0.9
	T2	4	57		0.005 (0.001–54.7)	
	T3	36	29		8.7 (0.001–129.1)	
N status	N0	21	53	0.02	1 (reference)	0.09
	N1	25	27		1.2 (0.62–1.6)	
R status	R0	34	25	0.99	1 (reference)	0.9
	R1	11	21		0.93 (0.29–2.91)	
Lymphatic invasion	Yes	18	16	0.99	1 (reference)	0.82
	No	28	24		1.06 (0.61–1.8)	
Perineural invasion	Yes	35	27	0.26	1 (reference)	0.27
	No	11	34		0.45 (0.1–1.8)	
Vascular invasion	Yes	30	22	0.46	1 (reference)	0.6
	No	16	30		1.26 (0.44–3.5)	
Grading	G1	4	32	0.04	1 (reference)	0.94
	G2	26	27		0.01 (0.001–131.2)	
	G3	12	19		13 (0.1–97.3)	
Post-operative morbidity	Yes	31	27	0.3	1 (reference)	0.5
	No	15	32		0.5 (0.18–1.4)	
Adjuvant therapy	Yes	21	23	0.46	1 (reference)	0.3
	No	25	21		0.55 (0.17–1.7)	
Metastatic nodes in station 12	Yes	10	27	0.03	1 (reference)	0.9
	No	36	48		0.9 (0.09–10.5)	

then confirmed with histological examination. Considering the entire series of 1490 patients, only 43 % of cases considered DBDC at the preoperative assessment were confirmed as cholangiocarcinoma at the final histologic analysis; in fact, the majority of them were diagnosed with PDAC.

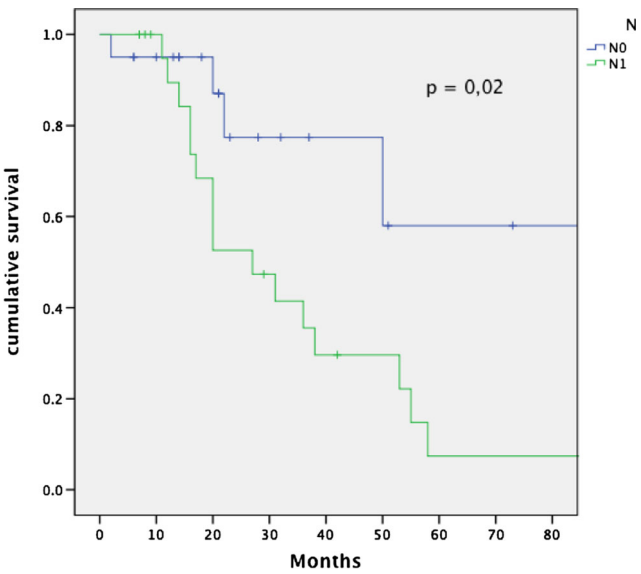

Fig. 2 Cumulative survival curve for N1 vs. N0

The first noteworthy evidence is that the incidence of DBDC is actually much lower than the expected, considering that only 3.3 % of the cases received a diagnosis of DBDC in a large surgical series. Histologic confirmation of DBDC was obtained only from pathological records; no independent review of surgical samples was performed. All the doubtful cases of malignant pancreaticobiliary histology were excluded. Data regarding bile duct dysplasia were not available, and in most cases, the biliary epithelium showed inflammatory changes due to the presence of biliary drainage or stents. Due to the relative rarity of DBDC, it is difficult to identify each prognostic factor. Negative margin status is a widely recognized and demonstrated predictor of long-term survival also in DBDC [14, 17] even if this evidence was not confirmed in the present series. The use of intra-operative frozen section of CBD resection margin is mandatory to attempt an R0 resection that is related to a long-term survival when compared with R1 resection [16, 17]. CBD resection margin is not the only margin to be considered in PD for DBDC but also the entire pancreatic head circumferential margin must be evaluated [10]. DBDC shares its pancreaticobiliary origin with PDAC and often presents the same biological aggressiveness, as reflected by the poor prognosis [2], and should be analyzed relying on similar principles. The prognostic role of surgical

margin status after PD for PDAC is not fully clear, so further studies would investigate the role of the microscopic residual tumor on different margins, not only on CBD margin, after PD for DBDC.

High-volume centers reported an overall 3-year survival that ranges from 33 to 63 %, whereas 5-year survival ranges from 16 to 52 % [12, 13, 16, 17]. The present series is consistent with this evidence reporting 3 and 5-year survival rates of 40 and 18 %, respectively. We reported a R0 resection rate of 73.9 %, but as reported in other studies [8, 9], it has been probably overestimated if we consider only 18 % of a 5-year survival rate. Data on patterns of disease recurrence were available only for 12 patients who underwent radical R0 resection: 11 patients recurred with distant metastasis; only one of them developed local recurrence. It has been reported that the frequency of lymph node metastases in distal cholangiocarcinoma ranges from 22 to 58 %, and the absence of lymph node metastases represents a useful predictor of favorable outcome in DBDC [15]. We reported a 54.3 % rate of nodal involvement, and patients with N1 disease showed a markedly worse prognosis if compared with node-negative cases (p=0.02).

The metastatic nodal spread in DBDC is different to that reported for PDAC on the basis of the results of the present study. Station 14 nodes, according to JPS classification [11], are less frequently involved in DBDC (about 8 % of cases) than in PDAC (about 28 % of cases) [18]. This probably reflects a different disease spread that proceeds from nodal station 13 and 17 to nodal station 12. The presence of metastatic nodes in station 12 represents another prognostic factor for the present series (median survival 27 vs. 48 months; p= 0.03), although it was not confirmed, evaluating only N1 cases. Other studies had shown that nodal metastases at the level of the common hepatic artery [19] and at the level of the para-aortic region [20] are negative prognostic factors. Although the role of lymphadenectomy in periampullary cancers is not completely defined [21, 22], the evidence of an early locoregional spread, expressed by nodal involvement and microvascular, perineural, and lymphatic invasiveness, would seem to justify an aggressive surgical approach like PD.

In case of PD, for PDAC, at least 13 to 15 lymph nodes must be collected to obtain a correct staging as recently proposed by ISGPS [23]. Only PD allows obtaining a high rate of R0 resection with optimal lymph nodes retrieval (25 nodes harvested in the present study as a median value). Bile duct resection alone cannot reach the appropriate lymph node collection and should be reserved for highly selected cases because only few patients obtain curative resection margins at the final pathology [12, 24, 25], and disease staging is less accurate. Considering 4 cases of CBD resection for DBDC, excluded from the presented series, we never achieved a number of lymph nodes greater than 11. All the four patients treated with common bile duct resection alone died within 18 months, most of them with locoregional recurrence. Due to the smallness of the sample of CBD resection for DBDC. we did not perform any survival analysis comparing this group to patients that underwent major pancreatic resections.

Compared with PD for PDAC, PD for DBDC is associated with a different distribution of post-operative morbidity. Usually, in case of PDAC, PD has a relatively low incidence of POPF [26]. There are a lot of studies that explored this aspect. Generally, overall morbidity reaches 50 %, where POPF accounts for around 15 %, DGE for 13 %, intra-abdominal collections for 16 %, biliary fistula for 5 %, and PPH for 7 % [27, 28]. Considering our experience of PD for PDAC, POPF accounts for 17 %, PPH for 8 %, and mortality for 1 % (complete data not reported). The present series of resected DBDC shows an overall morbidity rate of 74 % with POPF rate of 48 %, DGE 10 %, intra-abdominal collections 34 %, biliary fistula 8 %, and PPH at 20 %. Post-operative morbidity was relatively high in the present series that, however, includes also cases of the early 2000s. If we consider only surgical morbidity, the incidence reaches 66 % of cases. We can argue that the higher incidence of PPH, biliary fistula, and intra-abdominal collections was directly related to the higher incidence of POPF. Almost all cases of PPH were late bleeding that is often caused by pancreatic fistula. All five re-laparotomy were necessary for bleeding control. The other five cases of PPH were managed with interventional procedures. Post-operative pancreatic fistula is often related to certain factors like intra-operative blood loss, pancreatic remnant texture, pancreatic duct diameter, and histology of the primitive tumor [26]. With the exception of intra-operative blood loss, all the other three factors share the possible presence of chronic obstructive pancreatitis that leads to a high suture holding capacity and to a reduced risk of POPF [29]. However, full details about pancreatic remnant texture and main pancreatic duct diameter are not available for the study cohort. Thanks to early symptoms like jaundice; DBDC is often diagnosed in an early stage, and often, main pancreatic duct is not involved by the cancer, so pancreatic parenchyma rarely develops the morphological changes of obstructive pancreatitis that produces a hard stump texture. At the end, we can speculate that the higher incidence of POPF is related to the higher incidence of soft pancreatic parenchyma in case of DBDC.

Conclusions

Only few series of radically resected DBDC have been reported in the literature. This study confirms that DBDC is a rare entity even if large surgical series are reviewed. Distal cholangiocarcinoma still remains a disease with a poor prognosis due to local recurrence and distant metastatic spread. Tumor differentiation and nodal status have been confirmed as important prognostic factors in univariate analysis as already

investigated in previous studies [14, 19, 24, 30, 31]. Metastatic spread to locoregional lymph nodes is a major negative prognostic factor, but the correct staging requires harvesting a number of lymph nodes that cannot be obtained with a simple bile duct resection alone. In case of DBDC, gold standard surgical treatment is represented by pancreaticoduodenectomy with the achievement of an R0 resection, also through the intra-operative assessment of surgical margins.

Conflicts of interest None.

Compliance with ethical standards The research was designed as a retrospective study approved by the Ethical Committee of the University of Verona Hospital Trust and did not require economic funding.

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