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ORIGINAL SCIENTIFIC REPORT

Clinicopathological Characteristics and Surgical Outcomes of Primary Cystic Duct Carcinoma: A Multi-institutional Study

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Abstract

Background The role of surgery in the management of primary cystic duct carcinoma (CDC) remains unclear especially in advanced disease. This study aimed to evaluate long-term outcomes in patients undergoing surgery for primary CDC.

Methods From a multi-institutional database, we identified 41 patients who underwent surgery for primary CDC, defined as a part of gallbladder carcinoma with the tumor centre located in the cystic duct.

Results Of the 41 patients, 31 (75.6%) underwent preoperative biliary drainage for jaundice. Twenty-eight (68.3%) patients underwent extensive resection including major hepatectomy (n = 21), pancreaticoduodenectomy (n = 4), or both procedures (n = 3). Thirty-four (82.9%) patients had ≥ pT3 tumor, while 31 (75.6%) patients had involvement of contiguous organs/structures. Nodal and distant metastasis was found in 26 (63.4%) and 7 (17.1%) patients, respectively. Most patients (90.2%) had perineural invasion. Median overall survival was 23.7 months in all 41 patients. Factors independently associated with both overall and disease-specific survival were pN (P = 0.003 and P = 0.007, respectively) and pM (P = 0.003 and P = 0.013, respectively) classification. Median survival was 75.3, 17.7, and 5.2 months for patients with pN0M0 (n = 14), pN1/2pM0 or pN0pM1 (n = 21), and pN1/2pM1 (n = 6) disease, respectively (P < 0.001).

Conclusions Primary CDC is characterized by locally advanced disease with aggressive histopathological characteristics at surgery, leading to extensive resection during treatment. Surgery provides potential benefits for patients with pN0pM0 disease, whereas pN1/2 and/or pM1 status appear to have strong adverse effects on survival.

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Introduction

Since Farrar proposed "strict" diagnostic criteria for primary cystic duct carcinoma (CDC) in 1951 [1], the criteria have been the mainstay for diagnosis of this rare condition. These criteria are, briefly, growth restricted to the cystic duct, absolutely no neoplastic process in the gallbladder, hepatic, or common bile ducts, and histological confirmation of the presence of carcinoma cells. Farrar's criteria allow for accurate diagnosis of "early-stage" primary CDC but can be problematic in the diagnosis of "advanced-stage" primary CDC, where the tumor centre is located in the cystic duct but it has invaded adjacent organs/structures. Several studies have recently sought to address this issue and a new definition has been proposed based on the location of the tumor centre, which is presumed to serve as a clinically rational definition [2–6].

Surgery offers the best chance of long-term survival in patients with primary CDC as well as in those with other biliary tract carcinomas [3–6]. However, few clinical studies have been conducted to evaluate the benefits of surgery for primary CDC (defined as tumor centred in the cystic duct) in terms of long-term outcomes. Also, no clinical studies have investigated the independent prognostic factors associated with survival after surgery for primary CDC by using multivariate analysis. These are clinically important issues because after the new criteria are adopted, we will more frequently encounter this type of tumor in clinical practice than has previously been reported [2, 4, 6].

This study aimed to clarify the clinicopathological characteristics of patients undergoing surgery for primary CDC and to evaluate the long-term outcomes of these patients. Specifically, we sought to define the role of surgery in the management of CDC and to identify potential candidates for this approach using a multi-institutional cohort.

Methods

Patients

Patients who underwent radical resection involving surgical resection of both the primary tumor and regional lymph nodes for primary CDC from January 1991 to June 2016 were identified from a multi-institutional database of gallbladder carcinoma patients (n = 662). This study was approved by the institutional review board of each participating institution.

Definition of Primary CDC

Primary CDC was defined based on previously described criteria [2–6] as a part of gallbladder carcinoma with the centre of the tumor located in the cystic duct. The final diagnosis was made based on histopathological examination of the resected specimen, but most diagnoses were made from the findings of preoperative imaging [7–10].

Surgical Resection Procedure

The choice of surgical resection procedure for each patient was made based on the extent of tumor spread and the patient's condition (Table 1). Indications for major hepatectomy, defined as right hepatectomy or more extended hepatectomy, included massive hepatic involvement, involvement of the right hepatic pedicle, and/or extensive ductal involvement [7, 8]. Indications for pancreaticoduodenectomy included evident peripancreatic nodal disease, direct invasion of the pancreas or duodenum, and/or extensive ductal involvement [8, 9]. For some cases of early-stage disease, resection of the extrahepatic bile duct, cholecystectomy with or without resection of the gallbladder bed, and regional lymphadenectomy (extended cholecystectomy) were indicated [10, 11]. No patients received neoadjuvant chemotherapy.

In most patients undergoing radical resection, the cystic duct, common bile duct (pericholedochal), posterosuperior pancreaticoduodenal, retroportal, right celiac, and hepatic artery group of nodes were dissected en bloc [10, 11]. In patients undergoing pancreaticoduodenectomy, the right portion of the superior mesenteric nodes was also dissected together with the above-mentioned lymph nodes [10, 11]. In this study, 13 patients underwent sampling or dissection of the para-aortic lymph nodes.

Histopathological Examination

Histopathological findings were described according to the AJCC Cancer Staging Manual, 8th edition [12]. The extent of the primary tumor was determined by examining multiple sections of the entire lesion in each resected specimen. A 3-μm thick representative section was cut from each lymph node taken from resected specimens. Histological grade was determined based on the areas of the tumor having the highest grade [12].

Statistical Analysis

Deaths from other causes were treated as uncensored observations in overall survival (OS) analysis but were treated as censored observations in disease-specific survival (DSS) analysis. The Kaplan–Meier method was used

to calculate the cumulative incidences of events, and variations in these events were assessed using the log-rank test. A Cox proportional hazards regression model was used to identify independent factors. All statistical analyses were performed using IBM SPSS Statistics 24 (IBM Japan, Inc., Tokyo, Japan). All tests were two-sided, and P values of < 0.05 were regarded as statistically significant.

Results

Clinical Characteristics

A total of 41 patients (29 men and 12 women, median age 70 [range, 53–86] years) who underwent radical resection for primary CDC were included in the study cohort. The preoperative diagnosis of the 41 patients with confirmed primary CDC was primary CDC in 19 patients, gallbladder cancer in 10, perihilar cholangiocarcinoma in 8, and distal cholangiocarcinoma in 4. Of these 41 patients, 31 (75.6%) underwent preoperative biliary drainage for jaundice. Surgical resection procedures included extended cholecystectomy (n = 13 [31.7%]) and more extensive resection (n = 28 [68.3%]) (Table 1). More extensive resection included major hepatectomy (n = 21), pancreaticoduodenectomy (n = 4), and both procedures (n = 3). In this series, 11 patients underwent combined resection of contiguous tissues comprising the portal vein (n = 9), duodenum (n = 2), hepatic artery (n = 1), stomach (n = 1), transverse colon (n = 1), and inferior vena cava (n = 1).

Of the 41 patients, 24 (58.5%) had Clavien-Dindo grade IIIa or greater complications [13] (Table 2). Three patients died during hospitalization, giving an in-hospital mortality rate of 7.3%. Surgical procedures for these 3 patients were extended right hepatectomy plus pancreaticoduodenectomy with resection of the portal vein and inferior vena cava (n = 1) and extended right hepatectomy plus extrahepatic bile duct resection with portal vein resection (n = 2). Adjuvant chemotherapy was administered in 3 (7.3%) of the 41 patients at the discretion of the attending surgeon.

Histopathological Characteristics

Median tumor size was 35 (range, 10–95) mm. The primary tumor was pT1 in 2 patients, pT2 in 5, pT3 in 24, and pT4 in 10; 31 (75.6%) patients had involvement of contiguous organs or structures (median, 1; range, 1–5 organs or structures). Sites of contiguous involvement were the extrahepatic bile ducts (n = 30), liver (n = 10), portal vein (n = 8), pancreas (n = 5), hepatic artery (n = 4), duodenum (n = 2), transverse colon (n = 1), inferior vena cava (n = 1), and omentum (n = 1). Adenocarcinoma was identified in 39 patients, adenosquamous carcinoma in 1, and adenosquamous plus undifferentiated carcinoma in 1. Histological grade was G1 in 9 patients, G2 in 20, G3 in 11, and G4 in 1. Lymphatic, venous, and perineural invasion was observed in 24 (58.5%), 19 (46.3%), and 37 (90.2%) patients, respectively.

The number of lymph nodes dissected per patient ranged from 3 to 47 (median, 15). A total of 87 positive nodes (median, 2 nodes; range, 1–22 nodes) were found in 26 (63.4%) patients. The para-aortic nodes were positive in 4 of 13 patients who underwent sampling or dissection of these nodes. Liver metastases were found histologically in 2 patients. In this series, pathologically confirmed sites of distant metastasis included distant lymph nodes (n = 5), liver (n = 1), and distant lymph nodes plus the liver (n = 1).

Overall, 26 patients had no residual tumor, while microscopic residual tumor was found in 13 patients and macroscopic residual tumor in 2. Microscopic residual tumor was found in the intrahepatic ductal stump (5

Table 1 Surgical procedures for 41 patients with primary cystic duct carcinoma

Procedures	No. of patients
Extended cholecystectomy (n = 13)	
Cholecystectomy with wedge resection of the gallbladder bed and extrahepatic bile duct resection	2
Cholecystectomy* with extrahepatic bile duct resection	11
More extensive resection (n = 28)	
Major hepatectomy† with extrahepatic bile duct resection	21
Pancreaticoduodenectomy*‡	4
Major hepatectomy† with pancreaticoduodenectomy‡	3

*Cholecystectomy with full-thickness dissection

†Major hepatectomy included extended right hepatectomy (right hepatectomy extended to the inferior portion of Couinaud segment IV) and right hepatectomy

‡Pancreaticoduodenectomy included Whipple, pylorus-preserving, and subtotal stomach-preserving procedures

patients), around the preserved portal vein (3 patients), around the preserved hepatic arteries (3 patients), around the superior mesenteric artery (1 patient), and around both preserved hepatic arteries and the intrahepatic ductal stump (1 patient). Macroscopic residual tumor was observed in the liver (1 patient) and in the para-aortic lymph nodes (1 patient).

Factors Influencing DSS After Resection

The median follow-up period was 123 (range, 34–343) months. DSS after resection was 29.8% at 5 years with median DSS of 27.0 months (Fig. 1a). Univariate analysis revealed that preoperative jaundice ($P = 0.024$), pN classification ($P = 0.001$), pM classification ($P < 0.001$), histological type ($P = 0.002$), venous invasion ($P = 0.003$), perineural invasion ($P = 0.015$), and residual tumor status ($P = 0.006$) were significantly associated with DSS (Table 2). Multivariate analysis identified pM classification (hazard ratio [HR] 3.783; $P = 0.013$) and pN classification (HR 3.594; $P = 0.007$) as independent significant variables associated with DSS (Table 3).

Table 2 Postoperative complications in 41 patients with primary cystic duct carcinoma

	No. of patients
Clavien-Dindo grade IIIa or greater complications	24
In-hospital mortality	3
All complications (n = 35)	
Intraabdominal abscess	13
Biliary fistula	7
Pleural effusion	6
Pancreatic fistula	5
Chylous ascites	5
Methicillin-resistant Staphylococcus aureus or pseudomembranous enterocolitis	4
Liver failure	3
Intraabdominal bleeding	3
Gastrointestinal bleeding	3
Delayed gastric emptying	3
Anastomotic leakage	2
Disseminated intravascular coagulation	2
Incisional dehiscence	2
Wound infection	2
Biliary bleeding	2
Acute respiratory distress syndrome	1
Pneumonia	1
Pulmonary embolism	1
Renal failure	1
Gastrointestinal perforation	1
Thoracic empyema	1
Catheter-associated infection	1
Cholangitis	1

Factors Influencing OS After Resection

OS after resection was 23.6% at 5 years with median OS of 23.7 months (Fig. 1b). Univariate analysis revealed that preoperative jaundice ($P = 0.015$), portal vein resection ($P = 0.006$), pN classification ($P < 0.001$), pM classification ($P < 0.001$), histological type ($P = 0.019$), lymphatic vessel invasion ($P = 0.009$), venous invasion ($P = 0.002$), perineural invasion ($P = 0.0028$), and residual tumor status ($P = 0.017$) were significantly associated with OS (Table 3). Multivariate analysis identified pM classification (HR 4.240; $P = 0.003$), pN classification (HR 3.681; $P = 0.003$), and portal vein resection (HR 2.479; $P = 0.042$) as independent significant variables associated with OS (Table 4).

Impact of pN and pM Classification on OS After Resection

pN and pM classification were independently associated with both DSS and OS. OS after resection was significantly worse in 26 patients with pN1/2 disease (median OS, 16.8 months) than in 15 patients with pN0 disease (median OS, 75.3 months; $P < 0.001$) (Fig. 2a). Of 26 patients with pN1/2 disease, 24 (92.3%) had pT3/4 tumor and only 2 (7.7%) had pT2 tumor. OS after resection was significantly worse in 7 patients with pM1 disease (median OS, 5.4 months) than in 34 patients with pM0 disease (median OS, 29.3 months; $P < 0.001$) (Fig. 2b). When examining the cumulative effect of pN and pM classification, patients were stratified three groups as follows: pN0pM0 ($n = 14$), pN1/2pM0 or pN0pM1 ($n = 21$), and pN1/2pM1 ($n = 6$). Median OS for patients with pN0pM0, pN1/2pM0 or pN0pM1, and pN1/2pM1 disease was 75.3, 17.7, and 5.2 months, respectively. OS after resection was significantly different among these groups ($P < 0.001$) (Fig. 2c).

Discussion

This study revealed that primary CDC is characterized by locally advanced disease with aggressive histopathological characteristics at the time of surgery and thus extensive resection is often required when treating this disease. It also demonstrated that pN and pM classification were independent prognostic factors associated with both OS and DSS for patients with primary CDC, indicating that radical resection provides potential benefits for patients

with pN0pM0 disease, whereas pN1/2 and/or pM1 status appear to have strong adverse effects on survival.

Applying the strict diagnostic criteria for primary CDC proposed by Farrar could lead to accurate diagnosis [1], but the criteria are apparently impractical in terms of not facilitating the diagnosis of advanced disease [2–6]. In 1994, Ohtani et al. proposed a definition for the sites of primary extrahepatic cholangiocarcinoma as the geometric centre of the tumor, the centre of which is the longitudinal diameter of the gross tumor in surgical specimens [2]. Subsequently, several authors have shown the clinical efficacy of this definition for the diagnosis of primary CDC [3–6]. We think that this definition based on the location of the tumor centre is relatively simple, practicable, and clinically rational, allowing for consistent diagnosis of primary CDC from the early to advanced stage.

The clinicopathological characteristics and surgical outcomes of primary CDC reported in recent studies are shown in Table 5. Primary CDC is usually at an advanced stage when radical resection is performed, with a reported frequency of invasion to adjacent organs/structures ranging from 60.0 to 100% [4–6]. Also, most patients with primary CDC have preoperative jaundice and thus undergo preoperative biliary drainage [3–6]. As a reflection of the extent of disease at surgery, a higher rate of extensive resection including major hepatectomy and/or pancreaticoduodenectomy, ranging from 66.7 to 84.1%, has been reported for treatment of this disease [4–6]. Histopathologically, a high frequency of perineural invasion, which is an indicator of tumor aggressiveness, has been observed, ranging from 73.3 to 95.7% [4–6]. This study showed similar results and the frequency of invasion to adjacent organs/structures was 75.6%, leading to extensive resection in 68.3% of the patients; most patients (90.2%) had perineural invasion. The above observations indicate that primary CDC is characterized by locally advanced disease with aggressive histopathological characteristics at surgery, leading to extensive resection during treatment.

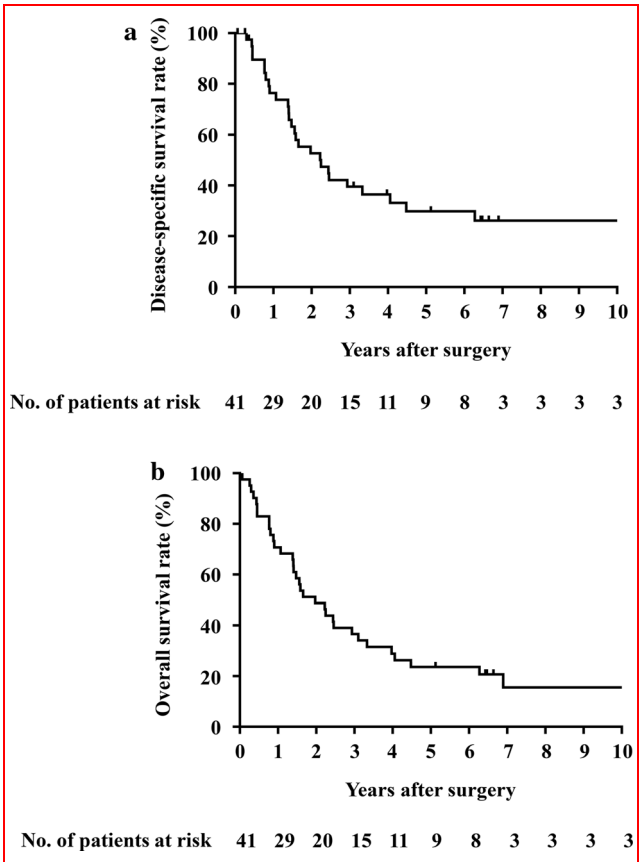


Fig. 1 Kaplan–Meier survival estimates in all 41 patients who underwent radical resection for primary cystic duct carcinoma. **a** Disease-specific survival (median disease-specific survival 27.0 months; 5-year disease-specific survival, 29.8%). **b** Overall survival (median overall survival 23.7 months; 5-year overall survival, 23.6%)

Despite this aggressive operative approach, surgical outcomes after resection in patients with primary CDC remain unsatisfactory, with a reported median OS after resection ranging from 15.7 to 28.8 months [4–6]. Consistent with these data, findings from our study revealed that median OS after resection for primary CDC was 23.7 months. These poor outcomes of primary CDC could be attributed to the high frequency of locally advanced disease at surgery described thus far. Relatively high postoperative morbidity, which is known to negatively affect survival, with a low frequency of administering neoadjuvant and adjuvant chemotherapy partly explains the poor outcomes [3, 5].

The prognosis of patients with primary CDC was not homogenous but varied according to several prognostic factors. In this study, the two independent prognostic factors identified as adversely affecting both OS and DSS were pN and pM classification. Examining the cumulative effect of these two factors on OS revealed that patients who had none of these factors (pN0pM0) had median OS of 75.3 months compared with 17.7 months for patients with one (pN1/2pM0 or pN0pM1) and 5.2 months for patients with two risk factors (pN1/2pM1). These findings indicate that radical resection offers potential benefit for patients with pN0pM0 disease. In contrast, the poor OS seen in the other patients should be considered in deciding whether to proceed with surgical management. Although surgery may benefit some patients, neoadjuvant approaches would be a wiser option allowing for clearer manifestation of the tumor biology preoperatively. Current practice in our department is that administration of neoadjuvant chemotherapy is considered for patients with cN1/2 and/or cM1 disease, although preoperative diagnosis of primary CDC is not always possible.

Table 3 Univariate and multivariate analysis for disease-specific survival after radical resection in 41 patients with primary cystic duct carcinoma

Variables	Categories	No. of patients	Univariate analysis		Multivariate analysis	
			5-year survival (%)	*P* value	HR (95% CI)	*P* value
Age (years)	≤70	21	37.5	0.263		
	>70	20	20.9			
Gender	Male	29	26.9	0.865		
	Female	12	33.3			
Preoperative jaundice	Absent	10	60.0	0.024		
	Present	31	18.8			
Timing of radical resection	Initial radical resection	39	31.5	0.386		
	Radical second resection	2	0			
Surgical procedure	Extended cholecystectomy	13	23.1	0.519		
	More extensive resection	28	32.5			
Portal vein resection	Absent	32	30.7	0.346		
	Present	9	33.3			
Postoperative morbidity	<CD grade IIIa	17	26.5	0.879		
	≥CD grade IIIa	24	32.7			
Adjuvant chemotherapy	Absent	38	30.2	0.487		
	Present	3	33.3			
Size of the primary tumor (mm)	≤35	23	22.9	0.199		
	>35	18	38.6			
pT classification	pT1 plus pT2	7	57.1	0.162		
	pT3 plus pT4	34	24.0			
pN classification	pN0	15	56.6	0.001	1.000	
	pN1 plus pN2	26	13.1		3.594 (1.430–9.032)	0.007
pM classification	pM0	34	34.3	<0.001	1.000	
	pM1	7	0		3.783 (1.325–10.800)	0.013
Histological type	Adenocarcinoma	39	31.5	0.002		
	Adenosquamous carcinoma	2	0			
Histological grade	G1	9	62.5	0.149		
	G2 plus G3	32	21.2			
Lymphatic vessel invasion	Absent	17	46.3	0.055		
	Present	24	15.9			
Venous invasion	Absent	22	45.4	0.003		
	Present	19	11.8			
Perineural invasion	Absent	4	100.0	0.015		
	Present	37	21.6			
Residual tumor status	R0	26	48.8	0.006		
	R1 plus R2	15	0			

HR hazard ratio, *CI* confidence interval, *CD* Clavien-Dindo classification, *pT classification* pathological primary tumor classification, *pN classification* pathological regional lymph nodes classification, *pM classification* pathological distant metastasis classification, *G1* well differentiated, *G2* moderately differentiated, *G3* poorly differentiated, *R0* no residual tumor, *R1* microscopic residual tumor, *R2* macroscopic residual tumor

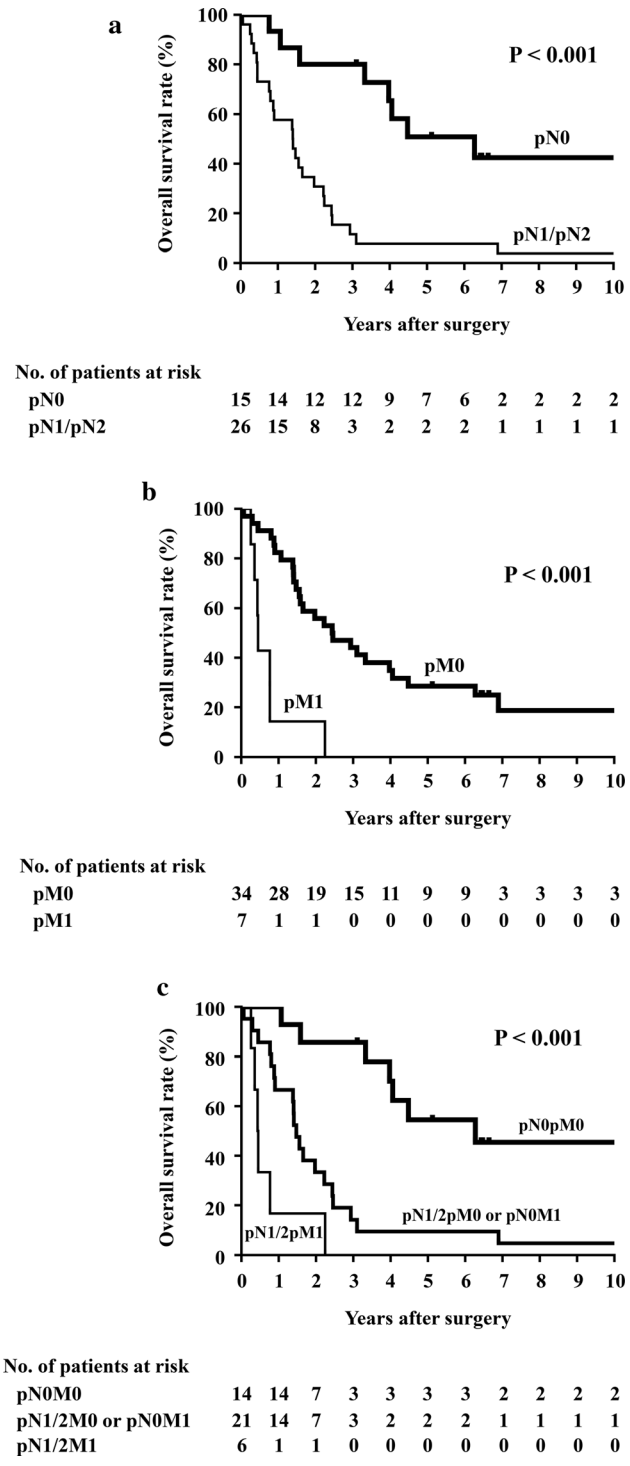
Since 1982, we have routinely performed regional lymphadenectomy for T2 or higher gallbladder carcinoma and shown that this procedure is effective for selected patients with nodal disease [10, 11, 14]. In this study, however, surgical outcomes for patients with pN1/2 disease (median OS, 16.8 months) were poor, despite

Table 4 Univariate and multivariate analysis for overall survival after radical resection in 41 patients with primary cystic duct carcinoma

Variables	Categories	No. of patients	Univariate analysis 5-year survival (%)	*P* value	Multivariate analysis HR (95% CI)	*P* value
Age (years)	≤70	21	31.7	0.125		
	>70	20	15.0			
Gender	Male	29	19.2	0.529		
	Female	12	33.3			
Preoperative jaundice	Absent	10	60.0	0.015		
	Present	31	12.9			
Timing of radical resection	Initial radical resection	39	24.9	0.501		
	Radical second resection	2	0			
Surgical procedure	Extended cholecystectomy	13	23.1	0.744		
	More extensive resection	28	23.6			
Portal vein resection	Absent	32	28.1	0.006	1.000	
	Present	9	11.1		2.479 (1.035–5.940)	0.042
Postoperative morbidity	<CD grade IIIa	17	22.1	0.820		
	≥CD grade IIIa	24	25.0			
Adjuvant chemotherapy	Absent	38	25.5	0.225		
	Present	3	0			
Size of the primary tumor (mm)	≤35	23	20.9	0.274		
	>35	18	27.8			
pT classification	pT1 plus pT2	7	57.1	0.083		
	pT3 plus pT4	34	17.6			
pN classification	pN0	15	50.9	<0.001	1.000	
	pN1 plus pN2	26	7.7		3.681 (1.545–8.774)	0.003
pM classification	pM0	34	28.5	<0.001	1.000	
	pM1	7	0		4.240 (1.634–11.005)	0.003
Histological type	Adenocarcinoma	39	24.9	0.019		
	Adenosquamous carcinoma	2	0			
Histological grade	G1	9	55.6	0.148		
	G2 plus G3	32	15.6			
Lymphatic vessel invasion	Absent	17	41.2	0.009		
	Present	24	11.1			
Venous invasion	Absent	22	39.4	0.002		
	Present	19	5.3			
Perineural invasion	Absent	4	75.0	0.028		
	Present	37	18.0			
Residual tumor status	R0	26	37.8	0.017		
	R1 plus R2	15	0			

HR hazard ratio, *CI* confidence interval, *CD* Clavien-Dindo classification, *pT classification* pathological primary tumor classification, *pN classification* pathological regional lymph nodes classification, *pM classification* pathological distant metastasis classification, *G1* well differentiated, *G2* moderately differentiated, *G3* poorly differentiated, *R0* no residual tumor, *R1* microscopic residual tumor, *R2* macroscopic residual tumor

lymphadenectomy for CDC being performed in a similar manner. In this study, almost all patients with pN1/2 disease (92.3%) had pT3/4 tumor, which is an established adverse prognostic factor [15, 16]. The high frequency of pT3/4 tumor may partly explain the poor surgical outcomes of patients with pN1/2 disease in this series. Thus, the



◀**Fig. 2** Kaplan–Meier overall survival (OS) estimates in the 41 patients who underwent radical resection for primary cystic duct carcinoma. **a** By pN classification. OS after resection was significantly worse in patients with pN1/2 disease (median OS, 16.8 months; 5-year OS, 7.7%) than in patients with pN0 disease (median OS, 75.3 months; 5-year OS, 50.4%; $P < 0.001$). **b** By pM classification. OS after resection was significantly worse in patients with pM1 disease (median OS, 5.4 months; 5-year OS, 0%) than in patients with pM0 disease (median OS, 29.3 months; 5-year OS, 28.5%; $P < 0.001$). **c** By combined pN and pM classification. OS after resection differed significantly among the groups (pN0pM0: median OS, 75.3 months, 5-year OS, 54.5%; pN1/2pM0 or pN0pM1: median OS, 17.7 months, 5-year OS, 9.5%; pN1pM1: median OS, 5.2 months, 5-year OS, 0%; $P < 0.001$)

causes of the poor outcomes for patients with pN1/2 disease are not simply attributable to nodal metastasis but also to concomitant factors associated with poor prognosis.

What are the implications of distinguishing primary CDC from other biliary tract cancers? Based on results of this and previous studies [3–6], primary CDC is characterized by locally advanced disease with aggressive histopathological characteristics at surgery with poor OS despite ensuring extensive resection. Therefore, clear distinguishing factors may be helpful for planning the optimal treatment strategy, including neoadjuvant and adjuvant chemotherapy especially in patients with pN1/2 and/or pM1 disease. We believe that clinical application of our definition of primary CDC would help to improve surgical outcomes in this disease entity.

This study is one of the largest series on surgical outcomes of primary CDC diagnosed using the clinically rational definition and is the first to perform multivariate analysis of OS and DSS. However, there are some limitations that should be considered. Although this study involved multiple institutions, it had a small number of patients over a long period of time. Nevertheless, we believe that compared with previous studies, this study more clearly defines the clinicopathological characteristics and the role of surgery in patients with primary CDC. Due to the lack of established adjuvant chemotherapy during the study period, only 7.3% of patients received adjuvant chemotherapy, partly explaining the poor OS in patients with advanced primary CDC. We deem that patients with pN1/2 and/or pM1 are potential candidates for adjuvant chemotherapy. It is anticipated that the use of adjuvant chemotherapy may improve the prognosis after resection for such patients [17].

In conclusion, primary CDC is characterized by locally advanced disease with aggressive histopathological characteristics at surgery, leading to treatment that involves extensive resection. Radical resection provides potential benefits for patients with pN0pM0 disease, whereas pN1/2 and/or pM1 status appear to have strong adverse effects on survival.

Table 5 Reports on primary cystic duct carcinoma defined as a part of gallbladder carcinoma with the tumor centre located in the cystic duct

First author	Year	No. of patients	Preoperative jaundice (%)	Extensive resection* (%)	Morbidity (%)	Mortality (%)	Adjuvant therapy (%)	Organ invasion† (%)	Nodal involvement (%)	Distant metastasis (%)	Perineural invasion (%)	R0 resection (%)	Median survival (months)	5-year survival rate (%)
Yokoyama	2008	44	–	84.1	–	–	–	–	38.6	–	90.9	–	15.7	–
Nakata	2009	15	66.7	66.7	40.0	0	–	60.0	33.3	0	73.3	–	28.8	40.0
Nakanishi	2018	47	–	78.7	–	–	–	100	51.1	8.5	95.7	85.1	23.0	–
This study	2020	41	75.6	68.3	85.4	7.3	7.3	75.6	63.4	17.1	90.2	63.4	23.7	23.6

†Organ invasion was defined as involvement of contiguous organs or structures such as the extrahepatic bile ducts, liver, pancreas, portal vein, hepatic artery, inferior vena cava, duodenum, transverse colon, and omentum

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interests.

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