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Positive cystic duct margin at index cholecystectomy in incidental gallbladder cancer is an important negative prognosticator

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ABSTRACT

Background: Prognostic factors following index-cholecystectomy in patients with incidental gallbladder cancer (IGBC) are poorly understood. The aim of this study was to assess the value of the initial cystic duct margin status as a prognosticator factor and to aid in clinical decision making to move forward with curative intent oncologic extended resection (OER).

Methods: This retrospective study included patients with IGBC who underwent subsequent OER with curative intent at 2 centers (USA and Chile) between 1999 and 2016., Patients with and without evidence of residual cancer (RC) at OER were included. Pathologic features were examined, and predictors of overall survival (OS) were analyzed.

Results: The study included 179 patients. Thirty-three patients (17%) had a positive cystic duct margin at the index cholecystectomy. Forty-two patients (23%) underwent resection of the common bile duct. OS was significantly worse in the patients with a positive cystic duct margin at index cholecystectomy (OS rates at 5 years, 34% vs 57%; $p = 0.032$). Following multivariate analysis, only a positive cystic duct margin at index cholecystectomy was predictive of worse OS in patients with no evidence of residual cancer (RC) at OER (hazard ratio, 1.7 95%CI 1.04–2.78; $p = 0.034$).

Conclusions: A positive cystic duct margin at index-cholecystectomy is a strong independent predictor of worse OS even if no further cancer is found at OER. In patients with positive cystic duct margin and no RC at OER common bile duct resection leads to improved outcomes.

Introduction

For patients with T1b-T3 incidental gallbladder cancer (IGBC) and no evidence of metastases, oncologic extended resection (OER) is recommended. OER includes resection of the gallbladder fossa, dissection of regional lymph nodes, and resection of the common bile duct in selected patients [1,2]. The goals of OER are to allow for accurate staging and to resect any residual cancer (RC), which is found in 39%–61% of patients [3–8]. Several groups have reported that the presence of RC is strongly correlated with poor survival akin to stage IV disease [3,5–10]. In contrast, patients with no RC at OER have 5-year survival up to 85% [3,6–8].

While an accurate prognosis can be predicted with the information derived from an OER after an index cholecystectomy (IC, the cholecystectomy that led to the discovery of IGBC), prognostic factors at IC are unclear. However, especially the information available from the IC may be important for decision-making regarding moving forward and extend of the OER. In this context, the authors have previously reported that lymph node station 12c

Abbreviations: IGBC, incidental gallbladder cancer; CDM, cystic duct margin; OER, oncologic extended resection; OS, overall survival; RC, residual cancer; IC, index cholecystectomy.

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(Calot's lymph node) which is frequently sampled during IC is an independent prognostic factor for metastasis to hepatoduodenal lymph nodes (N1 station) only. Further, it was found that patients who have a positive 12c lymph node only and are not found to have further positive lymph nodes have survival similar to N0 patients [11]. Another prognosticator in addition to lymph node station 12c available for prognostication following IC is the cystic duct margin. Pawlik et al. reported that patients with positive cystic duct margin are significantly more likely to have residual/additional cancer at the common bile duct (42% vs. 4.3%) [7]. Further, it has been reported that irrespective of the cystic duct margin status RC at OER is associated with a dismal prognosis [8]. Nevertheless, the effect of the combination of a positive cystic duct margin but no further RC at OER on prognosis is currently unknown.

Therefore, the aim of this study was to determine the independent prognostic value of the cystic duct margin in patients with in IGBC to help with the decision to move forward with OER, add a bile duct resection to the OER, and predict long term prognosis.

Patients and methods

Study population

Two-hundred patients with IGBC who underwent OER with curative intent at The University of Texas MD Anderson Cancer Center, Houston, Texas, USA, and Hospital Sotero del Rio, Santiago, Chile between 1999 and 2016 were identified [8]. IGBC was defined as gallbladder carcinoma diagnosed on final pathologic evaluation after open or laparoscopic cholecystectomy in a patient in whom gallbladder cancer was not suspected at the time of surgery [10]. The study was approved by the institutional review boards of both hospitals (Fig. 1).

Management before OER

Pathologists from the 2 institutions reviewed specimens and pathology reports from the index cholecystectomy to confirm the diagnosis of gallbladder carcinoma. Pathologists recorded the T category, grade and differentiation, presence of perineural and lymphovascular invasion, status of the cystic duct and liver bed margins, and presence of metastases in lymph node of the cystic duct (12c station). Before OER, all patients underwent computed tomography of the chest, abdomen, and pelvis and/or abdominal magnetic resonance imaging. Some patients treated at MD Anderson received preoperative chemotherapy or radiation therapy recommended following discussion at a multidisciplinary tumor board. At both institutions, OER was recommended to all patients with at least T1b disease without clinical evidence of remote organ metastases.

Pathologic assessment of the cystic duct margin at the index cholecystectomy

Cystic duct margin status at the index cholecystectomy was assessed during pathologic examination of the resected specimen in 179 (90%) of cases. Margin status was classified into negative if no tumor cell was identified at the margin or the distance of invasive carcinoma from the closest margin was > 1 mm. The margin was determined to be positive if high grade dysplasia or carcinoma in situ (n = 5) [12], or invasive carcinoma tumor cells were located within 1 mm of the mucosal transected margin. Experienced gastrointestinal pathologists who were blinded to the clinical

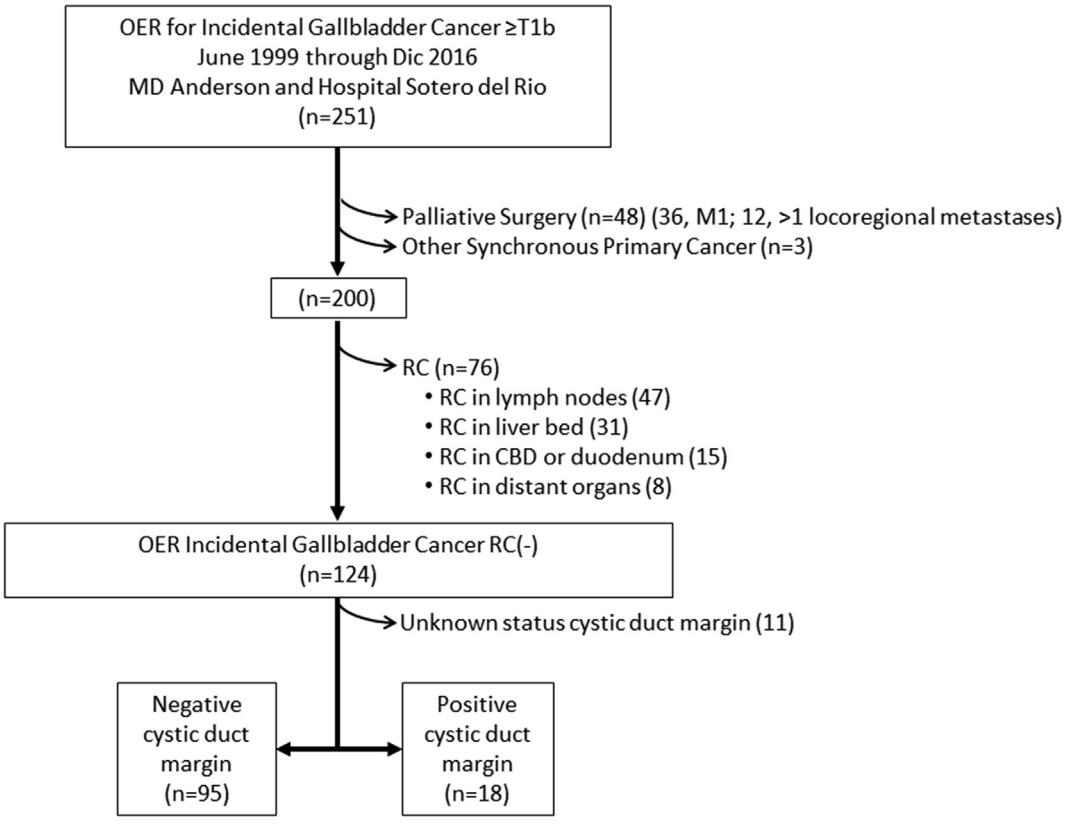

Fig. 1. CONSORT diagram. CBD, common bile duct; OER, oncologic extended resection; RC, residual cancer.

information re-reviewed all slides for this retrospective study [13,14].

OER procedures

The goals of OER were to permit accurate staging of disease and remove any potential RC. Details of OER have been described previously [8]. Briefly, OER included (1) open or laparoscopic exploration and, in selected patients, intraoperative frozen section analysis of aortocaval lymph nodes; (2) limited resection of the liver bed or anatomic resection of liver segments IVb and V or, in rare occasions, major liver resections and (3) dissection of the hepatoduodenal ligament, common hepatic artery, and retropancreatic lymph nodes.

Common bile duct resection was performed selectively in accordance with surgeons' preference and experience in the first period of the study. This changed in the latter part of the study when a common bile duct resection was performed routinely if the index cystic duct margin was found to be positive, re-resection of the cystic duct did not lead to a negative cystic margin or when it was not possible to evaluate the cystic duct stump histologically.

Pathological reassessment of the cystic duct margin at OER

At OER, patients with a positive cystic duct margin at IC were managed according to the results of frozen section of the stump (distal transection margin). If the remnant cystic duct stump was found to be positive on intraoperative frozen section bile duct resection was performed. OER was classified as R0, when resection led to macroscopically and microscopically tumor-free transection margins, or R1, when resection led to microscopically positive margins (cystic duct or otherwise). For pathological analysis, the extrahepatic bile duct of the resected specimen was opened longitudinally from the distal resection margin up to the proximal margin to accurately evaluate residual cancer. Next the resected specimens were fixed in 10% formalin and serially sectioned at less than 3–5 mm intervals.

Management after OER

Disease was staged according to the American Joint Committee on Cancer tumor-node-metastasis clinical staging system for gallbladder cancer, 7th edition [15]. RC was defined as any

Table 1
Patient characteristics overall and by status of the cystic duct margin.

Characteristic	Total	Negative cystic duct margin	Positive cystic duct margin	P value†
All patients	179	146 (73)	33 (17)	
Sex, M: F	53:147	40:106	9:24	0.781
Age, median (range), y	61 (32–83)	61 (32–83)	62 (34–77)	0.863‡
Body mass index ≥25 kg/m^2	129 (72)	102 (70)	27 (82)	0.174
ASA score ≥3	88 (49)	68 (47)	20 (61)	*0.022*
Index cholecystectomy				
Jaundice before surgery	12 (7)	9 (6)	3 (9)	0.664
Acute cholecystitis before surgery	85 (47)	72 (49)	13 (39)	0.290
Cholelithiasis at surgery	134 (75)	108 (74)	26 (79)	0.185
Well/moderately/poorly differentiated	26/122/31	25/98/23	1/24/8 (115179)	0.216
T stage, T1/T2/T3	25/119/35	20/101/25	5/18/10 (117739)	0.315
Perineural and/or lymphovascular invasion	79 (44)	61 (42)	18 (55)	0.887
Positive liver bed margin	24 (13)	18 (12)	6 (18)	0.226
Positive cystic duct (station 12c) lymph node	28 (16)	21 (14)	8 (24)	0.356
Oncologic extended resection (OER)				
Preoperative chemotherapy	13 (7)	6 (4)	7 (21)	*0.003*
Preoperative radiation therapy	6 (3)	2 (1)	4 (12)	*0.012*
Interval between index cholecystectomy and OER, median (range), days	73 (10–333)	74 (10–333)	83 (28–318)	*0.022*
Main procedures				
Segment VIb + V resection	171 (96)	142 (97)	29 (88)	*0.047*
Major liver resection	8 (4)	4 (3)	4 (12)	
Combined resection				
Common bile duct	42 (23)	24 (16)	18 (55)	*<0.001*
Adjacent organ	15 (8)	11 (8)	4 (12)	0.636
Hepatic artery and/or portal vein	9 (5)	6 (4)	3 (9)	0.369
Estimated blood loss, median (range), cc	200 (30–2000)	200 (30–1800)	275 (50–2000)	0.329‡
Operative time, median (range), min	240 (60–600)	238 (78–480)	300 (60–600)	0.186‡
Morbidity	30 (17)	20 (14)	10 (30)	*0.036*
Morbidity, Clavien-Dindo grade ≥ IIIa	14 (8)	8 (5)	6 (18)	*0.026*
90-day mortality	2 (1)	2 (1)	0 (0)	1.000
Postoperative hospital stay, median (range), days	6 (1–52)	6 (2–37)	6 (1–52)	0.616‡
Resection status, R1	15 (8)	11 (8)	4 (12)	
Residual cancer	66 (37)	51 (35)	15 (45)	0.316
Residual cancer in the common bile duct	13 (7)	11 (8)	2 (6)	0.906
Final N1 status	57 (32)	42 (29)	14 (42)	0.249
AJCC 7th edition stage, I/II/III/IV	17/79/61/22	14/69/49/14	3/10/12/8	0.279
Postoperative chemotherapy	40 (22)	27 (18)	13 (39)	0.019
Postoperative radiation therapy	10 (6)	7 (5)	3 (9)	0.360
Recurrence				
Locoregional				
Liver	25 (14)	17 (12)	8 (24)	*0.083*
Lymph node	15 (8)	11 (8)	4 (12)	0.679
Common bile duct	19 (11)	13 (9)	6 (18)	0.208
Distant	20 (11)	17 (12)	7 (21)	0.190

†χ2 test unless indicated otherwise.
‡Wilcoxon rank-sum test.
The italics means that the p value is equal or less than 0.05.

pathologically proven cancer tissue in lymph nodes, liver parenchyma, common bile duct, duodenum, or distant organs at the time of OER. Surgical complications were defined as any deviation from the normal postoperative course within 90 days after OER and were scored using the Clavien-Dindo classification [16]. Postoperative deaths were defined as deaths occurring within 90 days after surgery [17].

Statistical analysis

Continuous variables were compared using the Wilcoxon rank-sum test, and categorical variables were compared using the $\chi 2$ test or Fisher exact test where appropriate. Overall survival was measured from the date of OER to the date of death or last follow-up. Survival curves were generated using the Kaplan-Meier method, and differences between curves were evaluated with the log-rank test. Univariable and multivariable analyses to identify predictors of survival were performed by Cox proportional hazards regression models in patients with no RC. Variables with p-value <0.10 in the univariable analysis were entered in the multivariable analysis. A p-value <0.05 was considered statistically significant in all analyses. To assess the strength of the impact of a positive cystic duct margin on prognosis, subgroup analyses were performed comparing patients with and without resection of the common bile duct. Finally, to clarify if the resection of the common bile duct will benefit patients with positive cystic duct margin calculation of number needed to treat and harm was performed. Statistical analyses were performed with Stata 12 for Windows (StataCorp LP, College Station, Texas).

Results

Of 251 patients, 48 (19%) patients were excluded because they underwent palliative rather than curative surgery, 3 (1%) patients required a synchronous cancer resection and in 21 (8%) patients the cystic duct status was unknown. The remaining 179 patients constitute the study population (Fig. 1). In the entire cohort, Thirty-three patients (17%) had a positive cystic duct margin at the index cholecystectomy and forty-two (23%) underwent resection of the common bile duct. Data by status of the cystic duct margin are shown in Table 1. In the entire cohort, the positive cystic duct margin group had higher rates of preoperative chemotherapy and radiation therapy, common bile duct resection, morbidity, major morbidity (Clavien-Dindo grade $\geq$ IIIa) and postoperative chemotherapy.

Impact of positive cystic duct margin and common bile duct resection

Patients with a positive cystic duct margin had a worse 5-year OS rate than those with a negative cystic duct margin (34% vs 57%; p = 0.032) (Fig. 2A). Resection of the common bile duct failed to show improved OS (OS rate at 5 years, 42% vs 56%; p = 0.106) (Fig. 2B) or in subgroups with positive cystic duct margin (with and without RC) (Fig. 1C). However, resection of the common bile duct was associated with severe morbidity (Clavien-Dindo grade $\geq$ IIIa) (p = 0.018).

Predictors of OS in patient with no RC

On multivariable analysis of patients with no RC, the only independent predictor of poor OS was the presence of cystic duct margin invasion at the time of index cholecystectomy (hazard ratio [HR], 1.7; 95% CI, 1.0–2.8; p = 0.034) (Table 3).

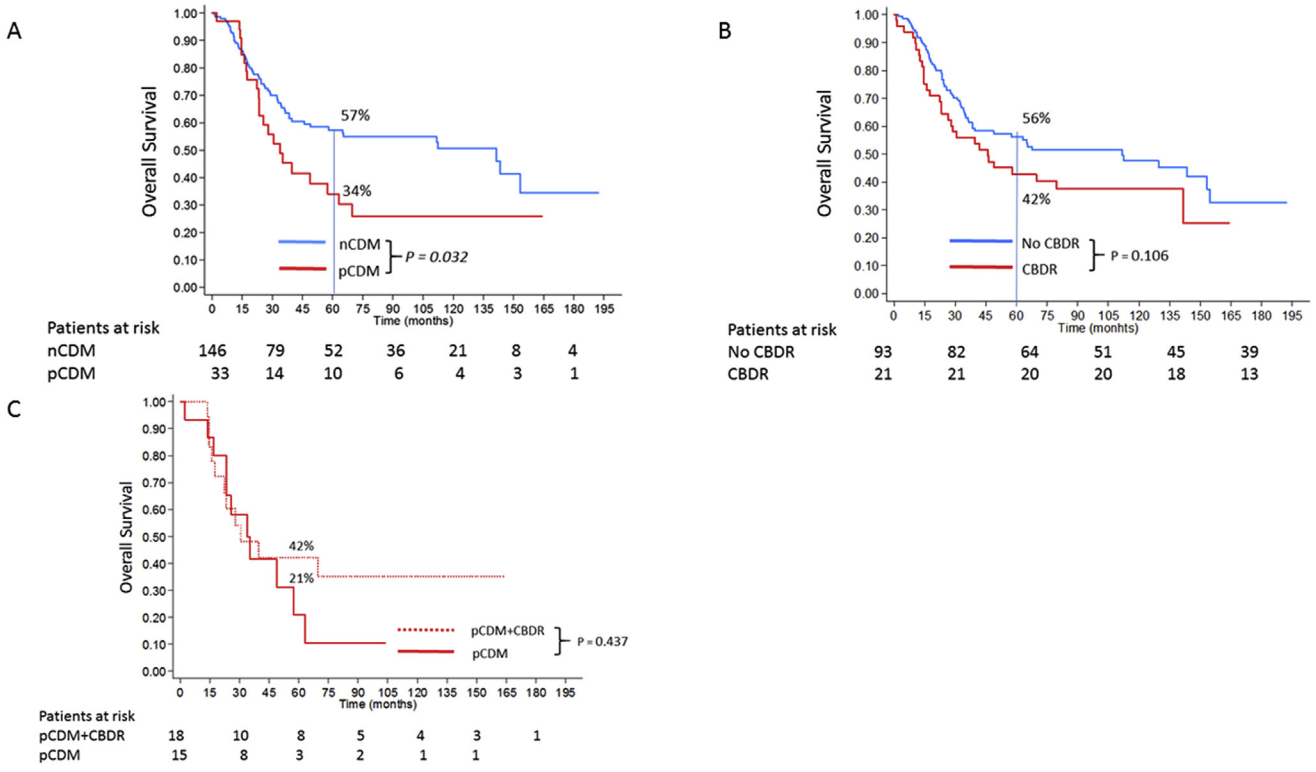

Fig. 2. OS in the entire cohort stratified by (A) cystic duct margin (CDM) status and (B, C) by common bile duct resection (CBDR). n, negative; p, positive.

Patient characteristic according to cystic duct margin status with no RC

Eighteen patients (16%) had a positive cystic duct margin at the index cholecystectomy. Table 2 lists the clinic-pathologic characteristic according to cystic duct margin status in this subpopulation with no RC. Compared to patients with a negative cystic duct margin, patients with a positive cystic duct margin had higher rates of poorly differentiated histology, preoperative radiation therapy, major liver resection, common bile duct resection, major morbidity (Clavien-Dindo grade ≥ IIIa) ($p = 0.054$), and recurrence. Also, recurrence patterns differed according to cystic duct margin status with higher rates of recurrence in the liver ($p = 0.005$) or common bile duct ($p = 0.012$) in the positive cystic duct margin group on detailed follow up imaging.

Impact of positive cystic duct margin and common bile duct resection on OS in patients with no RC

In patients with no RC ($n = 113$) the median follow-up time was 54 months (1–192) with an OS at 3- and 5-years were 83% and 74%.

Patients with a positive cystic duct margin had a worse 5-year OS rate than those with a negative cystic duct margin (49% vs 78%; $p = 0.012$) (Fig. 3A). Among patients with a positive cystic duct margin, those who underwent common bile duct resection had a 5-year OS rate (75%) similar to that of patients with a negative cystic duct margin (78%; $p = 0.964$), whereas those who did not undergo common bile duct resection had a dismal 5-year DSS rate, of only 26% $p = 0.034$ (Fig. 3C).

Number needed to treat and harm in positive cystic duct margin

Among patients with a positive cystic duct margin and common bile duct resection the risk difference of RC found at the OER is 22% more than patients without common bile duct resection. Therefore, the number needed to treat (resect) in patients with positive cystic duct is 4 patients to benefit 1 patient of the resection of the common bile duct and the number needed to harm in patients with positive cystic duct is 7 patients to harm 1 patient.

Discussion

In this study, prognostic factors available from the index cholecystectomy (IC) in patients with IGBC are analyzed. A positive cystic duct margin at IC is strongly correlated with patients requiring resection of the common bile duct, major liver resection,

Table 2
Patient characteristics without residual cancer by status of the cystic duct margin.

Characteristic	Total	Negative cystic duct margin	Positive cystic duct margin	P value†
All patients	113	95 (84)	18 (16)	
Sex, M: F	33:80	28:67	5:13	0.834
Age, median (range), y	61 (32–83)	60 (32–83)	64 (41–77)	0.642‡
Body mass index ≥25 kg/m^2	80 (71)	65 (68)	15 (83)	0.595
ASA score ≥3	54 (48)	42 (44)	12 (67)	*0.004*
Index cholecystectomy				
Jaundice before surgery	5 (4)	5 (5)	0 (0)	0.447
Acute cholecystitis before surgery	48 (42)	40 (42)	8 (44)	0.698
Cholelithiasis at surgery	81 (72)	67 (71)	14 (78)	0.394
Well/moderately/poorly differentiated	23/84/17	21/65/9	1/11/6	0.055
T stage, T1/T2/T3	20/83/10	16/73/6	4/10/4	0.055
Perineural and/or lymphovascular invasion	43 (38)	33 (35)	10 (56)	0.775
Positive liver bed margin	7 (6)	5 (5)	2 (11)	0.162
Positive cystic duct (station 12c) lymph node	13 (12)	11 (12)	2 (11)	0.775
Oncologic extended resection (OER)				
Preoperative chemotherapy	6 (5)	5 (5)	1 (6)	1.000
Preoperative radiation therapy	2 (2)	0 (0)	2 (11)	*0.027*
Interval between index cholecystectomy and OER, median (range), days	79 (10–333)	81 (10–333)	67 (33–177)	0.559‡
Main procedures				
Segment VIb + V resection	110 (97)	94 (99)	16 (89)	*0.040*
Major liver resection	3 (3)	1 (1)	2 (11)	
Combined resection	(0)			
Common bile duct	20 (18)	12 (13)	8 (44)	*0.007*
Adjacent organ	5 (4)	5 (5)	0 (0)	0.572
Hepatic artery and/or portal vein	3 (3)	2 (2)	1 (6)	0.554
Estimated blood loss, median (range), cc	200 (30–1500)	168 (30–1500)	275 (50–1200)	0.530‡
Operative time, median (range), min	233 (60–480)	237 (78–480)	180 (60–450)	0.293‡
Morbidity	18 (16)	13 (14)	5 (28)	0.074
Morbidity, Clavien-Dindo grade ≥ IIIa	10 (9)	6 (6)	4 (22)	0.052
90-day mortality	0 (0)	0 (0)	0 (0)	1.000
Postoperative hospital stay, median (range), days	5 (1–35)	5 (2–35)	5 (1–19)	0.330‡
Final N1 status	13 (12)	11 (12)	2 (11)	0.710
AJCC 7th edition stage, I/II/III/IV	17/74/10/12	14/64/7/10	3/10/3/2	0.279
Postoperative chemotherapy	40 (35)	27 (28)	13 (72)	*0.019*
Postoperative radiation therapy	10 (9)	7 (7)	3 (17)	0.360
Recurrence	21 (19)	13 (14)	8 (44)	*0.003*
Locoregional				
Liver	9 (8)	4 (4)	5 (28)	*0.010*
Lymph node	5 (4)	4 (4)	1 (6)	0.743
Common bile duct	6 (5)	4 (4)	2 (11)	*0.019*
Distant	6 (5)	6 (6)	0 (0)	1.000

†$\chi 2$ test unless indicated otherwise.
‡Wilcoxon rank-sum test.
The italics means that the p value is equal or less than 0.05.

Table 3
Univariable and multivariable analysis of overall survival in patients without residual cancer after oncologic extended resection (OER).

Characteristic	Univariable Analysis†			Multivariable Analysis††**		
	Hazard ratio	95% Confident Interval	Pvalue	Hazard ratio	95% Confident Interval	Pvalue
Sex, M: F	0.64	0.29–1.40	0.272			
Age ≥60, y	2.18	1.13–4.21	*0.020*	1.41	0.90–2.21	0.133
Body mass index ≥25 kg/m^2	1.17	0.55–2.48	0.677			
ASA score ≥3	1.91	0.94–3.86	0.070	1.1	0.69–1.73	0.679
Index cholecystectomy						
Jaundice before surgery	1.12	0.34–3.66	0.843			
Acute cholecystitis before surgery	1.26	0.66–2.41	0.482			
Well/moderately/poorly differentiated	1.51	0.37–6.05	0.560			
T stage, T1/T2/T3	1.40	0.44–4.40	0.562			
Perineural and/or lymphovascular invasion	1.41	0.65–3.03	0.379			
Positive liver bed margin	0.41	0.05–3.05	0.387			
Positive cystic duct margin	2.45	1.19–5.05	*0.015*	1.70	1.04–2.78	*0.034*
Positive cystic duct margin with HGD and Cis	2.89	1.44–5.78	*0.003*	1.77	1.09–2.85	*0.019*
Positive cystic duct (station 12c) lymph node	1.36	0.60–3.11	0.455			
Oncologic extended resection (OER)						
Preoperative chemotherapy	0.83	0.11–6.15	0.858			
Interval between index cholecystectomy and OER, ≥60, days	0.71	0.38–1.35	0.305			
Combined resection						
Common bile duct	0.91	0.41–1.98	0.815			
Adjacent organ	1.01	0.24–4.20	0.991			
Morbidity, Clavien-Dindo grade ≥ IIIa	1.69	0.74–3.83	0.208			
Final N1 status	1.45	0.60–3.47	0.404			
AJCC 7th edition stage, I/II vs. III/IV	1.15	0.33–3.99	0.822			
Postoperative chemotherapy	1.49	0.65–3.38	0.340			

† Cox regression model.
†† Multivariate Cox regression.
** The model was constructed including 39 death.
The italics means that the p value is equal or less than 0.05.

total morbidity, Clavien-Dindo grade IIIa or greater complications, and locoregional recurrence, and \ worse survival than patients with a negative cystic duct margin. In patients with IGBC and no RC following OER, the initial cystic duct margin status at time of IC acts as an important independent predictor of overall survival. In patients with a negative cystic duct margin at IGBC and no RC at OER outcomes are favorable independent of T stage, histologic differentiation, perineural and lymphovascular invasion, and status of the liver bed margin and cystic duct lymph node. Conversely in patients with comparable histopathological features but a positive cystic duct margin, the survival is poor.

Previous studies have established that patients with IGBC without RC at OER can be expected to have good survival after resection [3,6–8]. In agreement with those findings, 95 patients with a negative cystic duct margin had higher 5-year OS rates than the 18 patients with a positive cystic duct margin (OS rate at 5 years, 78% vs 49%). Moreover, a positive cystic duct margin at index cholecystectomy despite no RC at OER was strongly correlated with recurrence at the common bile duct (p = 0.012) or liver bed (p = 0.005). In this context, Yokoyama et al. [18] had reported a series of 44 patients with gallbladder cancer with positive cystic duct in whom the median overall survival was only 16 months.

Several mechanisms may explain the negative impact of a positive cystic duct margin on OS. First, the cystic duct has lymphatic network which may increase the risk for early metastasis to the hepatoduodenal lymph nodes [18–20]. Second, in addition to lymphatic spread, gallbladder cancer can disseminate superficially along the bile duct wall. This may explain the significant rates of common bile duct recurrence seen in this study. Third, intraductal (not superficial or lymphatic) spread of gallbladder cancer through the lumen of the cystic duct into the common bile duct has been documented [21–23].

Whether the common bile duct should be resected in patients

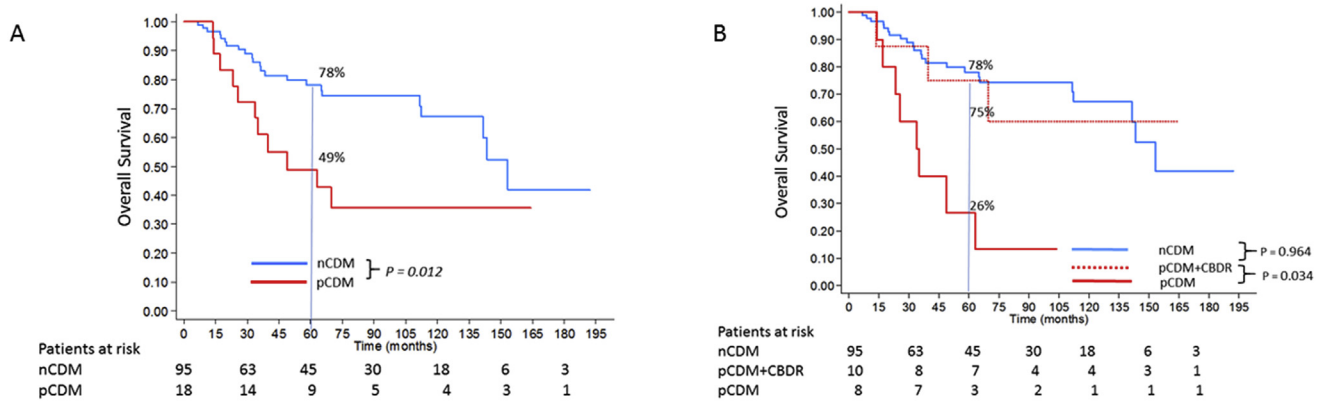

Fig. 3. OS in the patients with no residual cancer (RC) stratified by (A) cystic duct margin (CDM) status, (B) combinations of positive CDM and CBDR status. n, negative; p, positive.

with a positive cystic duct margin at index cholecystectomy has not conclusively been established [2]. In a previous study [11] and earlier reports [7,24,25], common bile duct resection did not increase the median number of lymph nodes sampled. In this study reported here, common bile duct resection did not improve OS in the entire cohort (Fig. 2B). However, in the subset of patients with a positive cystic duct margin at index cholecystectomy but no RC at OER, common bile duct resection ($n = 10$) lead to improved OS compared to patients without a common bile duct resection (OS at 5 years, 75% vs 26%; $p = 0.034$) (Fig. 3B). Although this subset included a limited number of patients, the between-group difference in OS was large and suggests a therapeutic benefit from common bile duct resection in case of a positive cystic duct margin. This finding is consistent with reports demonstrating a benefit of extrahepatic bile duct resection in selected patients [24,26–29].

While this study demonstrates a benefit of bile duct resection, the data shown here demonstrates that resection of the extrahepatic bile duct should be reserved for select patients, only: In the entire cohort of 200 patients (with and without RC at OER), resection of the common bile duct failed to show improved overall survival (OS rate at 5 years, 42% vs 56%; $p = 0.106$) (Fig. 2B) or in subgroups with positive (with and without RC) duct margins (Fig. 2C). However, it was associated with severe morbidity (Clavien-Dindo grade $\geq$ IIIa). Therefore, as an improved survival rate of common bile duct resection was only seen in patients with a positive cystic duct margin and no RC, common bile duct resection may be limited to select early stage patients with a positive cystic duct margin. For risk/benefit stratification a number needed to treat analysis was performed. This analysis shows that 4 common bile duct resections need to be performed (in patients with a positive cystic duct margin) to benefit 1 patient only and 7 common bile duct resection in this cohort leads to harm in 1 patient. Therefore, a careful risk benefit stratification should be performed prior to performing a common bile duct resection in patients with a positive cystic duct margin. Nevertheless, based on the data provided here, all pathology specimens from the IC should be carefully examined by an experienced pathologist to assess the status of the cystic duct margin as it may inform surgeons to add a bile duct resection at time of OER in select cases.

The current study has limitations. First, it is limited by its retrospective nature and associated biases. Second, cystic duct margin status at the time of index cholecystectomy was unknown for 21 (10%) patients. Third, the number of patients with a positive cystic duct margin was relatively small. Therefore, the impact of common bile duct resection on survival may need to be confirmed in a larger cohort. Despite some of these limitations the study conclusively shows the importance of the cystic duct margin status as a prognosticator and implication for decision making regarding OER.

Conclusion

In conclusion, in patients with IGBC a positive cystic duct margin at index cholecystectomy is a strong and independent predictor of worse OS in incidental gallbladder cancer even if no further RC is found at the later OER. Therefore, the cystic duct margin status at time of index cholecystectomy should be reported for each patient with IGBC. A positive margin at index cholecystectomy should prompt consideration for clearance of the cystic duct stump or common bile duct resection at OER and/or multimodal postoperative therapy to achieve optimal oncologic outcome.

Disclosure

None of the authors have declared any conflict of interest.

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