

# Clinical effect of a positive surgical margin after hepatectomy on survival of patients with intrahepatic cholangiocarcinoma

Chun-Nan Yeh<sup>1</sup>  
Feng-Jen Hsieh<sup>1</sup>  
Kun-Chun Chiang<sup>1</sup>  
Jen-Shi Chen<sup>2</sup>  
Ta-Sen Yeh<sup>1</sup>  
Yi-Yin Jan<sup>1</sup>  
Miin-Fu Chen<sup>1</sup>

<sup>1</sup>Department of General Surgery,  
<sup>2</sup>Department of Medical Oncology,  
Chang Gung Memorial Hospital,  
Chang Gung University, Taoyuan,  
Taiwan

**Background:** Several unfavorable prognostic factors have been proposed for peripheral cholangiocarcinoma (PCC) in patients undergoing hepatectomy, including gross type of tumor, vascular invasion, lymph node metastasis, a high carbohydrate antigen 19-9 level, and a positive resection margin. However, the clinical effect of a positive surgical margin on the survival of patients with PCC after hepatectomy still needs to be clarified due to conflicting results.

**Methods:** A total of 224 PCC patients who underwent hepatic resection with curative intent between 1977 and 2007 were retrospectively reviewed. Eighty-nine patients had a positive resection margin, with 62 having a microscopically positive margin and 27 a grossly positive margin (R2). The clinicopathological features, outcomes, and recurrence pattern were compared with patients with curative hepatectomy.

**Results:** PCC patients with hepatolithiasis, periductal infiltrative or periductal infiltrative mixed with mass-forming growth, higher T stage, and more advanced stage tended to have higher positive resection margin rates after hepatectomy. PCC patients who underwent curative hepatectomy had a significantly higher survival rate than did those with a positive surgical margin. When PCC patients underwent hepatectomy with a positive resection margin, the histological grade of the tumor, nodal positivity, and chemotherapy significantly affected overall survival. Locoregional recurrence was the most common pattern of recurrence.

**Conclusion:** A positive resection margin had an unfavorable effect on overall survival in PCC patients undergoing hepatectomy. In these patients, the prognosis was determined by the biology of the tumor, including differentiation and nodal positivity, and chemotherapy increased overall survival.

**Keywords:** surgical margin, hepatectomy, cholangiocarcinoma

## Introduction

Peripheral cholangiocarcinoma (PCC) is a malignant tumor of the liver, arising from the second or more distal branches of the intrahepatic bile ducts.<sup>1</sup> The incidence of PCC varies widely in different regions, but generally accounts for 5%–30% of primary liver cancers.<sup>1</sup> In a report from the Japan Liver Cancer Society, histologically proven PCC represented 3.58% of all primary liver cancers.<sup>1</sup>

Because of causative factors like liver flukes and hepatolithiasis, the incidence of PCC is ten times higher in Oriental countries.<sup>2–4</sup> Due to its intrahepatic location, early symptoms are rare and most patients present with advanced tumors and have dismal survival.<sup>5,6</sup> Hepatic resection provides the only chance of cure for PCC; however, most of the tumors are detected at an advanced stage, making curative resection challenging.<sup>6</sup> In addition, there are no definitive guidelines for adjuvant chemotherapy or radiotherapy, leaving PCC patients with few treatment options.<sup>7–9</sup> Although liver

Correspondence: Yi-Yin Jan  
Department of General Surgery, Chang  
Gung Memorial Hospital, Chang Gung  
University, 5 Fu-Hsing Street, Kwei-Shan,  
Taoyuan 333, Taiwan  
Tel +886 3 328 1200 extension 3219  
Fax +886 3 328 5818  
Email janyy@adm.cgmh.org.tw

transplantation represents a possible alternative, high recurrence rates and a shortage of organs make this an unsuitable choice of treatment.<sup>10–12</sup>

Several unfavorable prognostic factors have been identified in PCC patients undergoing hepatectomy, including gross type of tumor, vascular invasion, lymph node metastasis, a high carbohydrate antigen 19-9 level, and a positive resection margin.<sup>13–18</sup> We previously reported that an absence of physical findings, presence of mucobilia, an early-stage tumor, and curative resection were independent prognostic factors for long-term survival.<sup>19</sup> Among these, the resection margin is the only factor that can be improved upon by hepatic surgeons. The presence of a positive resection margin varies from 15% to 68% in PCC cases.<sup>20–24</sup> However, the impact of a positive surgical margin on PCC is conflicting.<sup>13–24</sup> In this study, we investigated clinicopathological features and recurrence patterns in PCC patients who underwent hepatectomy with a positive resection margin and further clarified the effect of a positive resection margin (both gross and microscopic) on the prognosis.

## Materials and methods

Between 1977 and 2007, 224 patients with histopathologically confirmed PCC underwent hepatic resection with curative intent at the Department of Surgery, Chang Gung Memorial Hospital, Taoyuan, Taiwan. This study retrospectively reviewed prospectively collected data for 224 (101 male and 123 female) patients with histologically confirmed PCC (adenocarcinoma), including 172 PCC patients with a non-intraductal papillary growth type and 52 PCC patients with an intraductal papillary growth type, who underwent hepatectomy. Curative resection was defined as a negative resection margin determined by histopathological examination. A positive resection margin was defined by either gross or histological examination. Tumors with a microscopically positive margin were defined as R1 and those with a grossly positive margin as R2. Among the 224 resected patients, 89 (39.7%) had a positive margin. The clinicopathological features and outcomes were analyzed using patients with a negative margin for comparison. Tumors were evaluated before surgery by ultrasonography, computed tomography (CT) scanning, and magnetic resonance cholangiopancreatography as appropriate. Tumor stage was defined according to the 7th edition of the American Joint Committee on Cancer classification. Patients with lymph node metastasis and positive resection margins received adjuvant chemotherapy and/or radiotherapy. This retrospective study was approved by the institutional review board at Chang Gung Memorial Hospital (clinical study number 99-2886B).

## Follow-up

Follow-up included physical examination, blood chemistry tests, and detection of tumor markers (carbohydrate antigen 19-9 and carcinoembryonic antigen) every 3 months. Abdominal ultrasonography was repeated at each visit. In the event of suspicious lesions on abdominal ultrasonography or elevated tumor markers, a comprehensive assessment for metastasis was done using CT or magnetic resonance imaging.

## Statistical analyses

All data are presented as percentages of patients or as the mean and standard deviation. Numerical data were compared by analysis of variance tests. The Pearson's chi-square test and Fisher's Exact test were used for nominal variables. Multiple variance analysis of multinomial logistic regression test was used for multivariate analysis. The survival rate was calculated and plots were constructed using the Kaplan–Meier method, and data were compared between groups using the log-rank test. The Cox proportional hazards model was employed for multivariate regression analysis. Statistical Package for the Social Sciences version 13.0 software (SPSS Inc, Chicago, IL, USA) was used for the statistical analysis.  $P \leq 0.05$  was considered to be statistically significant.

## Results

### Demographic and clinicopathological data

The distribution of operative procedures performed in the 224 PCC patients is shown in Table S1. Left hepatectomy was the most common operative procedure (61.6%). Sixteen patients (7.1%) underwent hepatectomy including caudate lobe resection. The liver parenchyma was the most common site of positive margin, followed by the bile duct and soft tissues (Table S2). Table 1 shows the demographic data, laboratory data, and pathological features of the 224 patients undergoing resection with negative (R0), microscopically positive (R1), and grossly positive (R2) margins. In total, there were 101 men and 123 women with a median age of 60 (range 22–89) years. Mucobilia was seen in 27 patients, and 95 had associated intrahepatic stones. A total of 52 patients had intraductal papillary tumor growth. Of the 224 patients who underwent resection, 89 had positive resection margins. Patients with a positive resection margin were further divided into R1 (n=62) and R2 (n=27) margins.

### Comparison of clinicopathological data in patients with R0, R1, and R2 resection margins

The differences in clinicopathological characteristics between PCC patients with R0, R1, and R2 resection

**Table 1** Clinicopathological manifestation of intrahepatic cholangiocarcinoma 224 patients undergoing resection with negative, microscopically positive and grossly positive resection margins

	R0 (N=135)	R1 (N=62)	R2 (N=27)	P-value
Age (yrs)	58.8	59.3	57.3	0.453
Sex (M/F)	63/72	25/37	13/14	0.668
CEA (ng/mL)	3.8	4.4	4.2	0.526
CA19-9 (U/mL)	43.4	86.0	232.8	0.174
Size (cm)	5.0	5.0	5.7	0.057
Mucobilia	17 (12.6)	6 (9.7)	4 (14.8)	0.755
IHD stones	46 (34.1)	35 (56.5)	14 (51.9)	0.007
Gross type				<0.0001
IP	36 (26.7)	16 (25.8)	0 (0.0)	
MF	57 (42.2)	17 (27.4)	5 (18.5)	
MF-PI	16 (11.9)	12 (19.4)	12 (44.4)	
PI	26 (19.3)	17 (27.4)	10 (37.0)	
Tumor number				0.542
Single	117 (86.7)	51 (82.3)	22 (81.5)	
Daughter or satellite	13 (9.6)	5 (8.1)	3 (11.1)	
Multiple	5 (3.7)	6 (9.7)	2 (7.4)	
Tumor number				0.232
Single	130 (96.3)	56 (90.3)	25 (92.6)	
Multiple	5 (3.7)	6 (9.7)	2 (7.4)	
Histological grade				0.319
Well	33 (24.4)	14 (22.6)	7 (25.9)	
Moderate	52 (38.5)	22 (35.5)	8 (29.6)	
Poor	34 (25.2)	14 (22.6)	11 (40.7)	
Others	16 (11.9)	12 (19.4)	1 (3.7)	
T stage				<0.0001
T1/T2	74 (54.8)	16 (25.8)	0	
T3/T4	61 (45.2)	46 (74.2)	27 (100)	
Nodal status				0.085
Negative	108 (80.0)	43 (69.4)	17 (63.0)	
Positive	27 (20.0)	19 (30.6)	10 (37.0)	
Staging				<0.0001
I/II	65 (48.1)	9 (14.5)	0	
III/IVA	70 (51.9)	53 (85.5)	27 (100.0)	

**Abbreviations:** yrs, years; M, male; F, female; CA, carbohydrate antigen; CEA, carcinoembryonic antigen; T, tumor; IHD, intrahepatic duct; IP, intra-ductal papillary; MF, mass-forming; MF-PI, mass-forming mixed with periductal infiltrating; PI, periductal infiltrating.

margins are shown in Table 1. The main differences between the three groups of patients were in tumor size, the rate of association with hepatolithiasis, gross tumor type, T stage, and disease staging. Larger tumor size, a positive association with hepatolithiasis, presence of periductal infiltrative growth, higher T stage, and advanced tumor staging were associated with a higher rate of positive resection margin.

However, further multivariate analysis using multinomial logistic regression revealed that PCC patients with R1 and R2 resection could be independently differentiated from those with R0 resection on the basis of a significantly higher rate of association with hepatolithiasis and advanced tumor staging (Tables S3 and S4).

## Prognostic factors for survival of patients with a positive surgical margin

The duration of follow-up ranged from 1.12 to 95.90 months (median 7.36 months). Median survival for the resection group was 15.2 months and overall survival rates for 1, 3, and 5 years were 58.9%, 27.5%, and 16.5%, respectively. Among 224 PCC patients underwent hepatic resection with curative intent, including 135 patients with curative resection R0, R1 (n=62), and R2 (n=27). Nine patients who died within 1 month of surgery and one patient who was lost to follow-up were excluded from the analysis of survival rate. A total of 214 PCC patients with 130 curative resections were included in the survival analysis. Of 89 patients with positive surgical margins after resection, 62 had R1 and 27 had R2 margins. The survival analysis was performed for 84 patients (four patients were excluded because of perioperative mortality and one patient was lost to follow-up). Patients with a negative surgical margin (n=130) had a median survival of 26.1 months and 1-year, 3-year, and 5-year overall survival of 78.5%, 43.3%, and 28.6%, respectively. However, patients (n=84) with an R1 margin and R2 margin had a median survival of 11.4 and 5.8 months, respectively, and 1-year, 3-year, and 5-year overall survival of 47.5%, 6.8%, and 4.5%, and 24.0%, 6.0%, and 0%, respectively. The non-resection group of patients (n=184) had a median survival of 3.6 months and one-year, 3-year, and 5-year overall survival rates of 13.6%, 1.9%, and 0.6%, respectively. PCC patients who underwent hepatectomy had significantly superior survival when compared to those who had an unresectable tumor. Further, patients with PCC who underwent curative resection had significant better survival than those who did not undergo curative resection. PCC patients with positive microscopic resection after hepatectomy had significantly better survival than those with a macroscopic resection margin (11.4 months versus 5.8 months;  $P=0.0012$ ). It is worth noting that patients with an R2 resection margin had survival rates similar to those of patients without hepatectomy (Table 2 and Figure 1).

Univariate analysis identified carcinoembryonic antigen values more than 5 ng/mL, lymph node positivity, positive microscopic resection, histological tumor grade, and absence of chemotherapy as adversely affecting survival in patients undergoing surgery with a positive resection margin (Table 3). Tumor size, tumor number, vascular, perineural, and lymphatic invasion did not affect survival. Multivariate Cox proportional hazard analysis identified tumor differentiation, negative lymph node metastasis, and chemotherapy to be independently favorable prognostic factors (Table S5 and Figure 2A–C).

**Table 2** Long term survival of 398 patients with intrahepatic cholangiocarcinoma

	Median (m)	95% CI of median	1-year (%)	3-year (%)	5-year (%)
All (n=398)	7.9	6.5–9.2	40.5	16.5	10.4
Resection (n=214)					
R0 (n=130)	26.1	14.9–37.4	78.5	43.3	28.6
R1 (n=59)	11.4	8.2–14.7	47.5	6.8	4.5
R2 (n=25)	5.8	4.2–7.3	24.0	6.0	0.0
Non-resection (n=184)	3.6	3.1–4.2	13.6	1.9	0.6

Resection versus non-resection  $P < 0.0001$

	R0	R1	R2
R1	<0.0001		
R2	<0.0001	<b>0.013</b>	
Non-resection	<0.0001	<0.0001	<b>0.092</b>

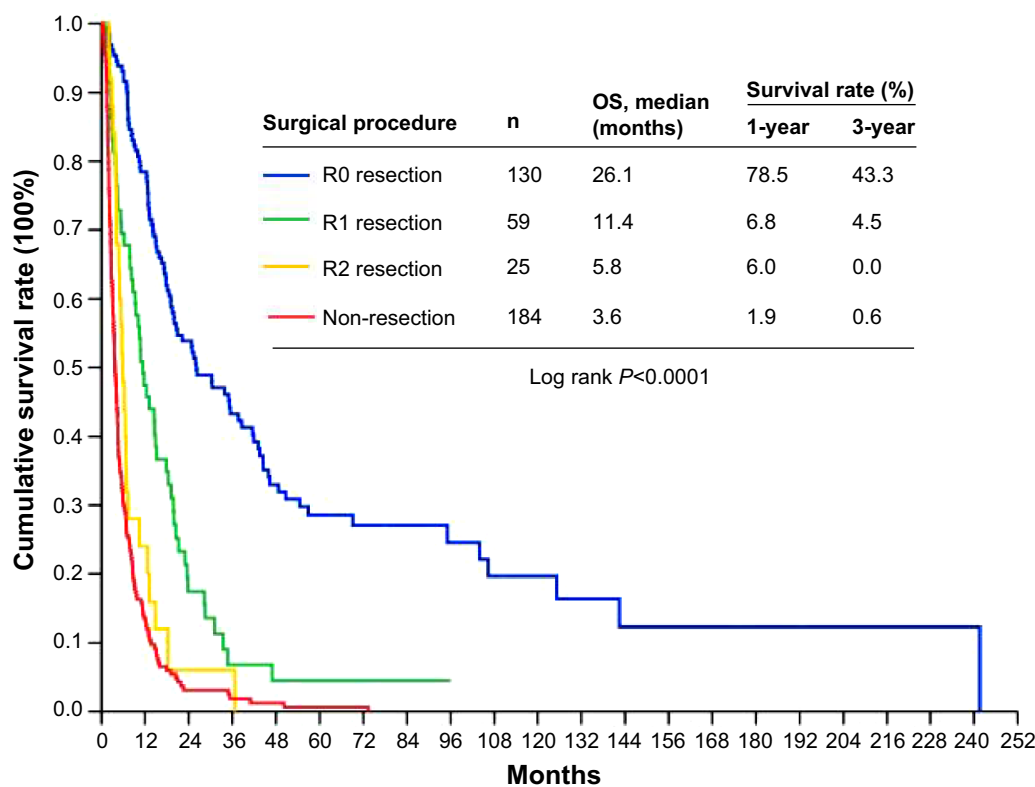
**Note:** Bold values indicate significance.

**Abbreviation:** CI, confidence interval.

### Recurrence pattern

Recurrences were documented in 89 patients during follow-up at a total of 63 specific sites, as summarized in Table S6. We divided the recurrence sites into three main areas, ie, locoregional, peritoneal, and distant. All recurrences

were documented clinically, radiologically, and histologically. Figure S1 illustrates the pattern of recurrence. Overall, 35 patients had recurrences involving a single area, eleven had recurrences involving two areas, and two had recurrences involving all three areas. Thirty-three patients had



**Number at risk**

	0	12	24	36	48	60	72	84	96	108	120	132	144	156	168	180	192	204	216	228	240	252
R0 resection	102	65	44	31	22	17	14	10	8	6	4	3	3	3	2	2	1	1	1	1	1	0
R1 resection	28	9	3	2	2	2	2	-														
R2 resection	6	1	1	0																		
Non-resection	25	5	3	2	1	1	0															

**Figure 1** Difference in overall survival rates of 398 PCC patients divided into R0, R1, and R2 resection groups and a nonresection group.

**Abbreviations:** OS, overall survival; PCC, peripheral cholangiocarcinoma.

**Table 3** Univariate and multivariate analysis of factors influencing the overall survival in resected intrahepatic cholangiocarcinoma with positive resection margin

Factors	(N)	Median survival (ms)	95% CI of median	1-year (%)	3-year (%)	P-value
Age (yrs)	≤65 (62)	8.7	5.6–11.8	37.7	5.0	0.618
	>65 (22)	11.7	2.6–20.9	50.0	10.1	
Gender	Male (38)	10.7	4.9–16.5	50.0	9.8	0.164
	Female (46)	7.3	4.1–10.5	32.6	3.2	
CA 19-9 (U/mL)	≤37 (9)	17.8	4.6–31.1	66.7	16.7	0.110
	>37 (23)	10.8	5.0–16.7	47.8	7.0	
CEA (ng/mL)	≤5 (34)	11.7	8.2–15.2	50.0	8.8	0.031
	>5 (21)	5.8	0.0–14.4	33.3	0.0	
Tumor size (cm)	≤5 (30)	9.3	5.6–12.9	36.7	0.0	0.464
	>5 (30)	6.2	0.0–14.1	43.3	11.4	
Tumor number	Single (69)	9.4	6.1–12.7	40.6	5.5	0.307
	Daughter/satellite (7)	3.8	2.4–5.3	28.6	0.0	
	Multiple (8)	10.5	0.0–26.5	50.0	25.0	
T stage	T1/T2 (15)	14.4	1.7–27.1	53.3	6.7	0.505
	T3/T4 (69)	8.7	4.9–12.5	37.7	6.6	
Nodal status	Negative (58)	10.8	8.0–13.6	46.6	7.0	0.017 <sup>a</sup>
	Positive (26)	5.3	3.6–7.0	26.9	4.5	
Stage	I/II (9)	19.9	3.8–36.1	66.7	0.0	0.375
	III/IVA (75)	8.3	4.9–11.6	37.3	7.7	
Margin	R1 (59)	11.4	8.2–14.7	47.5	6.8	0.013
	R2 (25)	5.8	4.2–7.3	24.0	6.0	
Gross type	IP (15)	14.4	9.8–19.0	60.0	0.0	0.190
	MF (22)	10.7	0.0–21.7	50.0	6.6	
	MF-PI (23)	5.0	3.2–6.8	17.4	8.7	
	PI (24)	10.5	6.8–14.1	41.7	8.3	
Histological grade	Well (19)	19.2	10.3–28.1	63.2	14.6	<0.0001 <sup>b</sup>
	Moderate (29)	7.9	4.4–11.4	31.0	0.0	
	Poor (24)	5.3	4.0–6.6	20.8	0.0	
	Others (12)	13.2	3.3–23.1	66.7	16.7	
IHD stones	No (36)	10.5	6.8–14.3	47.2	9.5	0.238
	Yes (48)	7.9	4.5–11.3	35.4	4.4	
Vascular invasion	No (65)	9.3	4.6–13.9	43.1	6.6	0.304
	Yes (19)	9.4	4.8–14.0	31.6	5.3	
Lymphatic invasion	No (59)	11.4	6.6–16.3	47.5	5.0	0.070
	Yes (25)	6.3	3.4–9.2	24.0	8.0	
Perinueral invasion	No (43)	9.3	3.7–14.8	39.5	6.9	0.546
	Yes (41)	10.2	6.9–13.5	41.5	5.6	
Chemotherapy	No (45)	5.3	3.4–7.2	28.9	5.5	0.024 <sup>c</sup>
	Yes (39)	12.7	9.1–16.3	53.8	7.3	
Radiotherapy	No (63)	9.3	5.0–13.5	38.1	7.3	0.979
	Yes (21)	11.7	3.5–19.9	47.6	4.8	

**Note:** <sup>a-c</sup>mean significance in cox's proportional hazards analysis, P=0.007, 0.008, and 0.028, respectively.

**Abbreviations:** yrs, years; CA, carbohydrate antigen; CEA, carcinoembryonic antigen; T, tumor; IHD, intrahepatic dust.

locoregional involvement. Distant sites were involved in nine patients. The liver and bile duct were the most common sites of locoregional recurrence. Peritoneal recurrence was detected in 23 patients (Table S6).

## Discussion

Intrahepatic PCC is an aggressive disease with a 5-year survival rate of 25% even after aggressive surgical resection.<sup>2,16,25</sup>

Our previous study, one of the largest in the world, showed a 5-year survival of 28.6% after R0 resection. An absence of physical findings, presence of mucobilia, an early-stage tumor, and curative hepatic resection were the four independent prognostic factors contributing to long-term survival.<sup>19</sup> Among these, the resection margin is the only factor that hepatic surgeons can improve. In this study, we attempted to identify the clinicopathological features and recurrence

patterns associated with positive surgical margins. All these data can show the clinical effect of a positive surgical margin on overall survival.

The rate of R0 in hepatic cancers varies from 30% to 80%.<sup>2,11,12,18,19,22-29</sup> R0 resection is the only way to obtain an acceptable long-term result, and has a 5-year survival rate of 36%–54%.<sup>2,12,28,29</sup> Lang et al reported 5-year survival of 28% for 54 PCC patients; however, survival was 48% for the R0 resection patients and 0% for R1/R2 patients.<sup>15</sup> Similarly, Uenishi et al reported 5-year survival of 39% for PCC patients with radical resection and 0% for those with R1 resection.<sup>22</sup> In our study, radical resection was achieved in 60.3% of PCC patients, with a median survival of 31 months for R0 resection compared with 11.4 months for R1 patients and 5.8 months for R2 patients (5-year survival for R0 was 28.6% versus 0% for R2;  $P < 0.05$ , Figure 1).

A positive surgical margin was reported in 15%–68% of PCC patients after hepatectomy in different studies.<sup>20-22</sup> In our cohort, 89 (39.7%) of 224 patients who underwent hepatectomy had positive resection margins. The liver parenchyma is the most common site for a positive resection margin. An adequate hepatic reserve remnant represents a problem for curative resection and is a possible cause of hepatic failure after hepatectomy. In this case, portal vein embolization is a potential solution. For the bile duct margin, the use of intraoperative frozen sections to determine the extent of the resection margin might help to solve part of the problem.

We used univariate analysis to identify clinicopathological features associated with a positive resection margin, such as the presence of nonpapillary histology ( $P = 0.050$ ), intrahepatic stones ( $P = 0.001$ ), and a higher tumoral T stage ( $P < 0.001$ ). Although intraoperative assessment of the margin was done

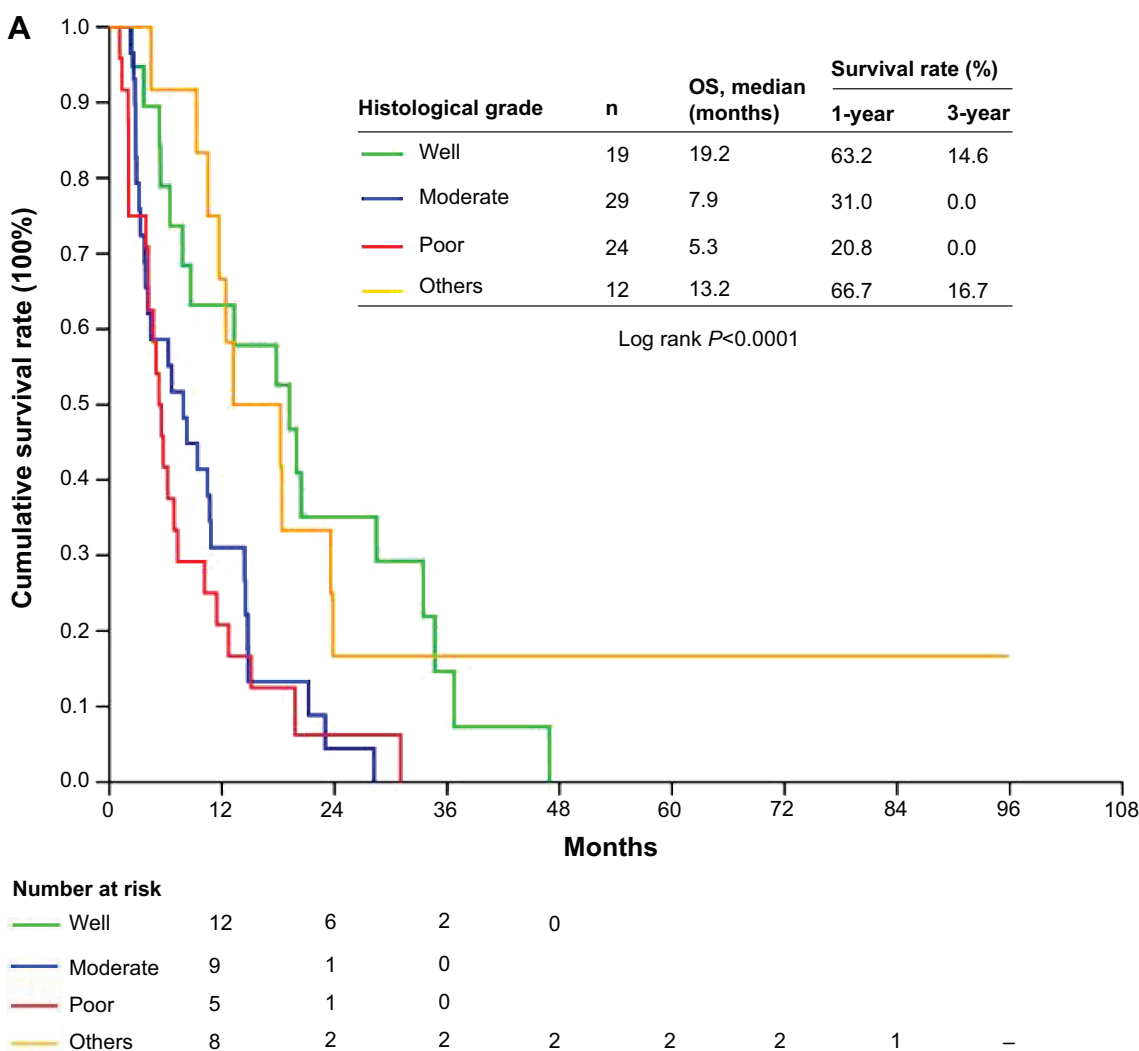
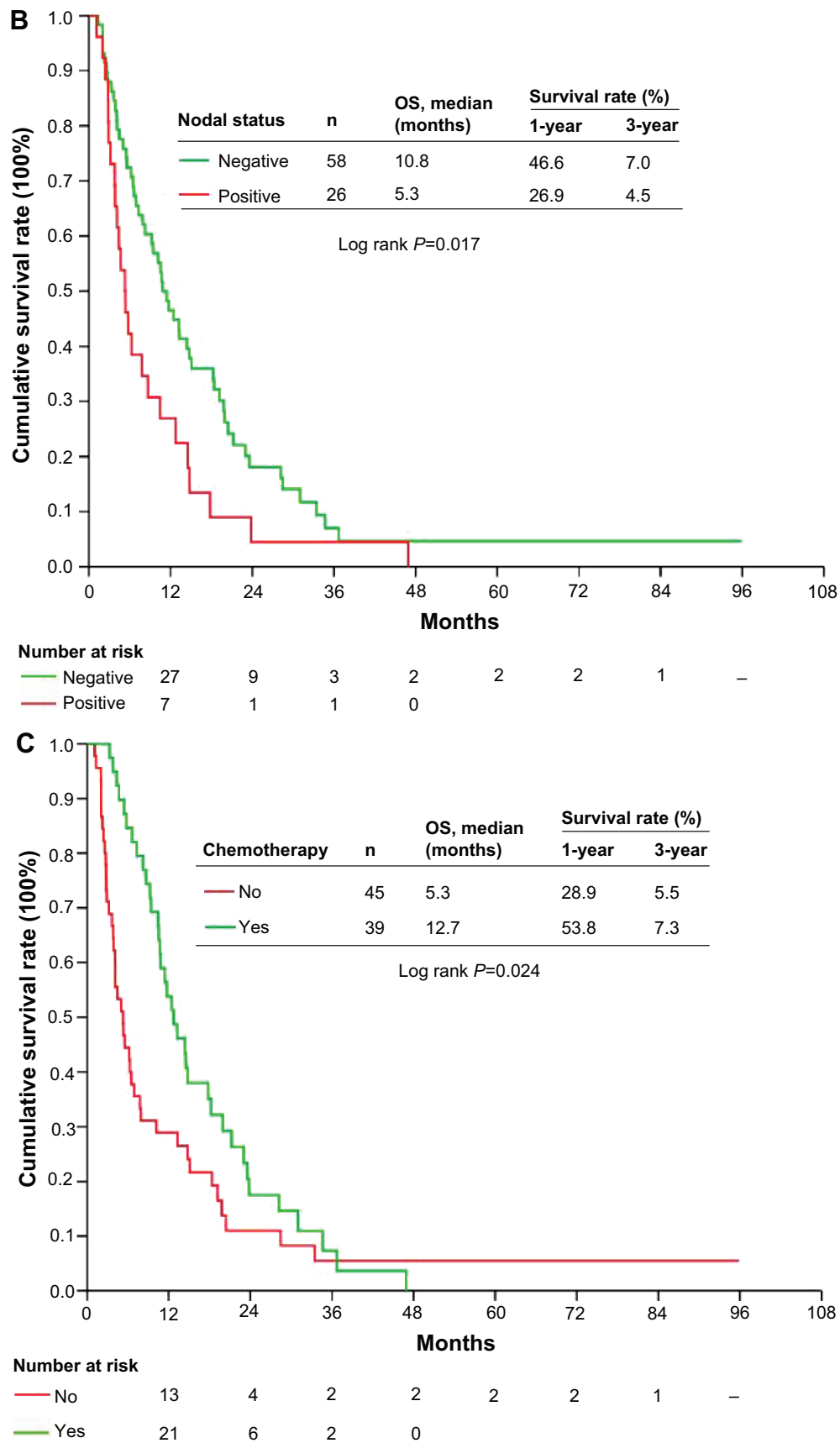


Figure 2 (Continued)



**Figure 2** Overall survival (OS) rates for 84 peripheral cholangiocarcinoma patients with a positive resection margin based on tumor differentiation (A), nodal status (B), and postoperative chemotherapy (C).

using ultrasonography, 39.7% of the patients had a positive resection margin. A positive surgical margin did not correlate with tumor size. Intraductal papillary tumors tend to be well differentiated, with cancer cells confined to the mucosal layer of the affected bile duct and less frequent lymphatic, venous, or perineural involvement.<sup>19,27</sup> This may explain the low level of margin positivity for intraductal tumors in our series.

Hepaticolithiasis was associated with increased margin positivity. Chen et al proposed that hepaticolithiasis prevented precise diagnosis of PCC preoperatively, making margin assessment difficult.<sup>28</sup> It was also reported that a higher T stage was associated with higher margin positivity. Patients with T3 tumors tended to have more R1 than R2 resections, which can be explained by the frequent presence of intrahepatic metastasis. T4 tumors had a high incidence of R2 resection. Shimada et al found that the positive margin correlated better with the presence of intrahepatic metastasis than with the size of the tumor. This was attributed to the difficulty in recognizing small multiple tumors during hepatic resection.<sup>21</sup>

PCC patients who undergo curative resection obviously had superior survival when compared with those who had R1 and R2 resection (median survival of 26.1 months for R0, 11.3 months for R1, and 5.8 months for R2). It is worth noting that patients with R2 resection had survival similar to that of patients without hepatectomy. The clinical effect of a positive surgical margin is inconclusive. Lang et al, Jan et al, and de Jong et al found a positive surgical margin to be an important prognostic factor; however, the findings of Shimada et al, Tamandl et al, and Farges et al, were inconclusive.<sup>15,19,21,23,24,28</sup>

Shirai et al found that tumors with a positive resection margin, higher T stage, positive nodal status, less differentiated status, and no chemotherapy contributed to an adverse prognosis.<sup>20</sup> In contrast with their results, perineural invasion was not found to be a prognostic factor in our study. However, lower histological differentiation grade ( $P < 0.0001$ ), presence of positive lymph nodes ( $P < 0.0001$ ), and absence of chemotherapy ( $P = 0.0001$ ) were three independent adverse prognostic factors (Figure 2A–C). The median survival for patients with well differentiated, moderately differentiated, and poorly differentiated tumors was 19.2, 7.9, and 5.3 months, respectively, making tumor biology one of the most important predictors for survival (Figure 2A), in agreement with the reports of Yamashita et al and Shirabe et al.<sup>29,30</sup>

We found that patients with a negative lymph node status had a median survival of 10.8 months compared with 5.3 months in patients with a positive status (Figure 2B).

This finding supports the idea that the presence of lymph node metastasis is one of the strongest prognostic predictors.<sup>2,21,24,30,31</sup> Inoue et al suggested that hepatectomy is contraindicated in the presence of lymph node metastasis at the time of sampling.<sup>32</sup> On the contrary, Weber et al reported long-term survivors with lymph node metastasis.<sup>33</sup> Given that preoperative assessment of lymph node involvement is difficult, aggressive lymph node dissection might be the safest approach. However, the role of lymph node dissection is still unclear and needs further investigation.

The effect of chemotherapy in the treatment of PCC is not well defined. Although response rates of 20%–30% have been reported, clinical trials have failed to show consistent benefits.<sup>7</sup> The Mayo Clinic obtained excellent results with neoadjuvant chemoradiotherapy followed by transplantation for hilar cholangiocarcinoma.<sup>34</sup> Based on the current literature, patients with good performance status might benefit from chemotherapy.<sup>7</sup> There are very limited data on the efficacy of chemotherapy for PCC patients. Only a small number of PCC cases, together with extrahepatic cholangiocarcinoma, gall bladder carcinoma, and ampullary carcinoma, have been reported, mainly because of the rarity of these diseases. A variety of confounding factors influence the effect of chemotherapy and complicate the evaluation, such as control of cholangitis, liver function, and performance status. In this article, one of the authors (JSC) used chemotherapy during the study period and achieved a response rate of around 30% and a median survival of more than 1 year for PCC patients.<sup>35–39</sup> Key drugs currently available for chemotherapy are gemcitabine, fluoropyrimidines, and platinum-based drugs. Further investigations are required for the development of new agents, such as molecular targeting drugs and combined therapy with surgery.<sup>40</sup> Although our center has used a variety of chemotherapies for advanced PCC over the last three decades with variable outcomes, use of palliative chemotherapy for PCC with a positive margin after hepatectomy does have a survival benefit (Figure 2C). This result is in agreement with a recent meta-analysis showing that chemotherapy is beneficial for PCC.<sup>41</sup>

We analyzed the recurrence pattern in PCC patients with a positive resection margin, and found that the locoregional area was the most common site of recurrence, followed by the peritoneal and distant areas (Figure S1). In agreement with the results of Weber et al the liver was the most common site of recurrence, followed by the lymph nodes, and distant sites such as the lungs and bone.<sup>33</sup> All recurrences occurred within a median of 13 months, suggesting that aggressive tumor biology might contribute to the low



survival rate in PCC patients with positive resection margins. Therefore, postoperative chemotherapy in patients with resected PCC with positive and negative margins should be aggressive.

In conclusion, more advanced tumor stage, a higher T stage, associated hepatolithiasis, and periductal infiltrative tumor growth are the main factors independently associated with a positive resection margin. A positive resection margin has an unfavorable effect on overall survival in PCC patients undergoing hepatectomy. PCC patients with R2 resection had survival similar to that of patients without hepatectomy. In patients with a positive margin, the prognosis was determined by tumor biology, including tumor differentiation and nodal positivity. Chemotherapy was useful for increasing overall survival in these patients.

## Author contributions

All authors contributed toward data analysis, drafting and revising the paper and agree to be accountable for all aspects of the work.

## Disclosure

The authors report no conflicts of interest in this work.

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## Supplementary materials

**Table S1** Type of hepatic resection in 224 patients with intrahepatic cholangiocarcinoma

Surgical procedure	Case number	%
Left hepatectomy	138/224	61.6
Segment 1, 2, 3, 4	7	
Segment 1, 2, 3, 4 + BR	1	
Segment 2, 3, 4	74	
Segment 2, 3, 4 + BR	2	
Segment 1, 2, 3	1	
Segment 2, 3	45	
Segment 1, 4	1	
Segment 1	1	
Segment 3	1	
Segment 4	5	
Right hepatectomy	51/224	22.8
Segment 4, 5, 6, 7, 8	3	
Segment 4, 5, 6, 7, 8 + BR	2	
Segment 5, 6, 7, 8	19	
Segment 5, 6, 7, 8 + BR	4	
Segment 5, 6, 7	3	
Segment 6, 7, 8	1	
Segment 4, 5	5	
Segment 5, 6	4	
Segment 6, 7	6	
Segment 7, 8	1	
Segment 5	2	
Segment 6	1	
Bilateral hepatectomy	24/224	10.7
Segment 1, 2, 4, 5, 8	1	
Segment 1, 2, 3, 4, 5, 8 + BR	1	
Segment 1, 5, 6, 7, 8	1	
Segment 1, 5, 6, 7, 8 + BR	1	
Segment 2, 3, 4, 5, 8	2	
Segment 4, 5, 6, 7, 8	1	
Segment 2, 3, 4, 6	1	
Segment 2, 3, 4, 8	1	
Segment 2, 3, 5	1	
Segment 3, 5, 6	1	
Segment 4, 5, 6	3	
Segment 4, 5, 8	7	
Segment 1, 6	1	
Segment 3, 8	1	
Partial hepatectomy	11/224	4.9

**Abbreviation:** BR, bile duct resection.

**Table S2** Resection margin involved in intrahepatic cholangiocarcinoma

	(n=89)
<b>Liver tissue (main part)</b>	61 (68.5)
LT only	36
LT + HD	15
LT + ST	8
LT + HD + ST	2
<b>Hepatic duct (main part)</b>	29 (32.6)
HD only	11
HD + LT	15
HD + LT + ST	2
HD + ST	1
<b>Soft tissue (main part)</b>	27 (30.3)
ST only	16
ST + HD	1
ST + LT	8
ST + LT + HD	2

**Note:** Values in parentheses are percentages.

**Abbreviations:** LT, liver tissue; HD, hepatic duct tissue; ST, soft tissue.

**Table S3** Multiple variance analysis of multinomial logistic regression in the R1 resection group compared with R0 used as reference

R1/R0	B	OR	95% CI of OR		P-value
			Lower	Upper	
<b>Factors</b>					
<b>IHD stones</b>					
With/without	1.101	3.006	1.446	6.249	<b>0.003</b>
<b>Gross type</b>					
MF/IP	-0.991	0.371	0.121	1.141	0.084
MF-PI/IP	-0.405	0.667	0.250	1.779	0.418
PI/IP	-0.605	0.546	0.165	1.813	0.323
<b>T stage</b>					
T3, 4/T1, 2	0.172	1.187	0.346	4.080	0.785
<b>Staging</b>					
III, IV/I, II	2.081	8.014	2.163	29.688	<b>0.002</b>

**Note:** Bold values indicate significant association.

**Abbreviations:** CI, confidence interval; OR, odds ratio; IHD, intrahepatic duct; IP, intraductal papillary; MF, mass-forming type; IP, intra-ductal papillary type; T, tumor.

**Table S4** Multiple variances analysis of multinomial logistic regression of the R1 and R2 resection group compared with R0 as reference

R1 + R2/R0	B	OR	95% CI of OR		P-value
			Lower	Upper	
<b>Factors</b>					
<b>Associated with IHD stones</b>					
With/without	1.060	2.887	1.474	5.654	<b>0.002</b>
<b>Gross type*</b>					
MF/IP	-0.687	0.503	0.172	1.474	0.210
MF-PI/IP	-0.222	0.801	0.308	2.087	0.650
PI/IP	-0.075	0.928	0.302	2.852	0.896
<b>T stage*</b>					
T3, 4/T1, 2	0.485	1.624	0.488	5.404	0.429
<b>Staging*</b>					
III, IV/I, II	1.998	7.376	2.027	26.846	<b>0.002</b>

**Note:** \*Maximum likelihood estimation does not exist when quasi-complete separation of the factor occurs. Bold values indicate significant association.

**Abbreviations:** CI, confidence interval; OR, odds ratio; IHD, intrahepatic duct; IP, intraductal papillary; T, tumor.

**Table S5** Cox's proportional hazards analysis

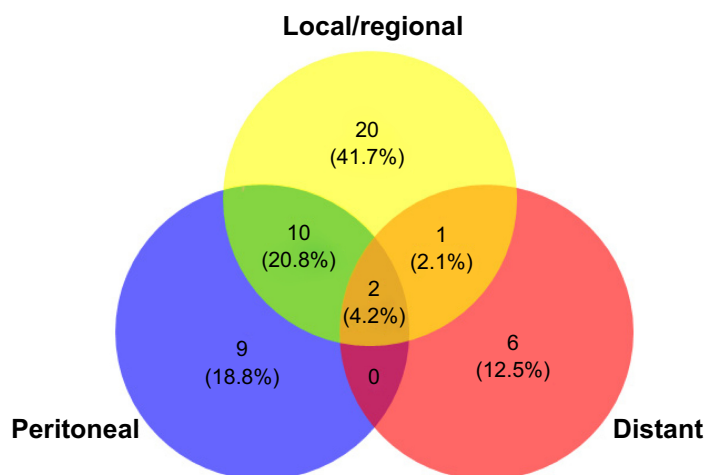
Factors	Hazard ratio (95% CI)	P-value
CEA (>5/≤5 ng/mL)		0.459
Nodal status (positive/negative)	2.372 (1.269–4.433)	0.007
Margin		0.086
Histological grade		
Moderate/well	3.061 (1.336–7.012)	0.008
Poor/well	2.929 (1.268–6.763)	0.012
Others/well	1.275 (0.504–3.226)	0.609
Chemotherapy (no/yes)	1.932 (1.092–3.481–4.122)	0.028

**Abbreviations:** CEA, carcinoembryonic antigen; CI, confidence interval.

**Table S6** Specific sites of recurrence within the three areas

<b>Locoregional</b>	33
Liver and/or bile duct	33
<b>Distant</b>	9
Scalp	1
Neck LN	2
Lung	1
Bone	1
Spine	1
Abdominal wall	3
<b>Intra-abdominal carcinomatosis</b>	21 (42%)

**Abbreviation:** LN, lymph nodes.

**Figure S1** Plot of recurrence patterns in 63 peripheral cholangiocarcinoma patients with a positive resection margin and clinically, radiologically, or histologically documented recurrences.

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