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Significance of Ductal Margin Status in Patients Undergoing Surgical Resection for Extrahepatic Cholangiocarcinoma

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Abstract
Objectives The objective of this study was to determine whether carcinoma in situ at the bile duct margin is prognostically different from residual invasive carcinoma in patients with extrahepatic cholangiocarcinoma.
Summary Background Data Although there are many reports that the ductal margin status at bile duct resection stumps is a prognostic indicator in patients with extrahepatic cholangiocarcinoma, some patients who undergo resection with microscopic tumor involvement of the bile duct margin survive longer than expected.
Methods A retrospective clinicopathological analysis of 128 patients who had undergone surgical resection for extrahepatic cholangiocarcinoma was conducted. The status of the bile duct resection margin was classifiedas negative in 105 patients (82.0%), positive for carcinoma in situ in 12 patients (9.4%), and positive for invasive carcinoma in 11 patients (8.6%).
Results Ductal margin status was an independent prognostic indicator by both univariate ($p = 0.0022$) and multivariate ($p = 0.0105$) analyses, along with lymph node metastasis. There was no significant difference between patients with a negative ductal margin and those with a positive ductal margin with carcinoma in situ ($p = 0.5247$). The 5-year survival rate of patients with a positive ductal margin with carcinoma in situ (22.2%) was significantly better ($p = 0.0241$) than with invasive carcinoma (0%). There was a significant relationship between local recurrence and ductal margin status ($p = 0.0401$).
Conclusions Among patients undergoing surgical resection for extrahepatic cholangiocarcinoma, invasive carcinoma at the ductal resection margins appears to have a significant relation to local recurrence and also a significant negative impact on survival, whereas residual carcinoma in situ does not. Discrimination whether carcinoma in situ or invasive carcinoma is present is important in clinical setting in which the resection margin at the ductal stump is positive.

Despite the overall advances in the ability to diagnose and treat extrahepatic cholangiocarcinoma, the prognosis for patients with this malignancy remains poor [1–4]. It has long been recognized that complete removal of cancer tissues offers patients the only chance for cure and long-term survival [5–7]. It is sometimes very difficult to achieve a free bile duct margin because of the rather short length of the bile duct and because the extent of microscopic spread is variable [8]. Although there are many reports that the ductal margin status at bile duct resection stumps is a prognostic indicator, some patients who undergo resection with microscopic tumor involvement of the bile duct margin survive longer than expected [9–12]. We hypothesized that carcinoma in situ at the bile duct margin is prognostically different from residual invasive carcinoma. In the present study, patients were divided into three categories according to their ductal margin status: negative

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ductal margin, positive ductal margin with carcinoma in situ, or positive ductal margin with invasive carcinoma. The aim of this study was to determine whether residual carcinoma in situ at bile duct margins differs prognostically from residual invasive carcinoma in patients with extrahepatic cholangiocarcinoma.

Patients and methods

Patient population

The present study retrospectively analyzed 128 consecutive patients (96 men and 32 women) with extrahepatic cholangiocarcinoma who underwent surgical resection at Iwate Medical University Hospital between January 1985 and April 2005. The mean patient age was 66.1 years (range: 38–84 years).

Primary tumor location

The predominant sites of the primary tumor were the hilar bile duct in 25 patients (19.5%), proximal bile duct in 24 patients (18.8%), middle bile duct in 41 patients (32.0%), distal bile duct in 33 patients (25.8%), and diffuse areas (in which carcinomas exist from the hilar/proximal to distal bile ducts) in 5 patients (3.9%). The location of the primary tumor was classified as hilar or nonhilar according to the classification of Bismuth et al. [13, 14], in which a hilar cholangiocarcinoma was defined as a tumor involving the primary ductal confluence with or without extension into the more proximal bile ducts.

Surgical resection procedures

Surgical resection procedures were dependent on the location of the primary tumor. Seventy-nine patients underwent a Whipple procedure or a pylorus-preserving pancreatoduodenectomy (PPPD), 27 patients underwent hepatectomy with bile duct resection, 14 patients underwent bile duct resection, and 8 patients underwent a combined hepatectomy and pancreatoduodenectomy (HPD). Systematic regional lymphadenectomies were performed in all 128 patients; included lymph nodes were those in the hepatoduodenal ligament, posterior pancreatoduodenal nodes, and nodes along the common hepatic artery. Radical lymphadenectomy including the para-aortic lymph nodes, which are the final regional lymph nodes involved in biliary tract carcinoma, was performed in 76 patients. Four patients (3.1%) died within 30 days after surgical resection, and nine patients died in the hospital, giving a surgical mortality rate of 7.0%.

Pathological examination

Resected specimens were submitted to the Department of Clinical Pathology in our hospital for histological evaluation, in which experienced pathologists (N.U. and T.S.) independently examined all specimens without knowledge of the clinical details. Histologic findings were described in accordance with two staging systems: the TNM staging of the American Joint Committee on Cancer (AJCC) [15] and The General Rules for Surgical and Pathological Studies on Cancer of the Biliary Tract of the Japanese Society of Biliary Surgery (JSBS) [16]. Primary tumor status, lymph node category, and histopathologic tumor grade were classified based on the AJCC-TNM classification system. Furthermore, histopathological factors of lymphatic permeation, venous permeation, perineural permeation, tumor growth pattern, and stroma of tumors were examined and recorded in accordance with JSBS guidelines.

The extent of the primary tumor was determined through the examination of multiple sections (median, 13 sections; range: 3–49 sections) of the entire lesion for each resected specimen. Histopathologic grade was determined based on areas having the highest grade [15].

Histological assessment of the ductal resection margin

The status of the ductal resection margin was assessed histologically by both frozen-section examination of the ductal stumps and pathologic examination of the resected specimens. Margin status was classified as negative, positive with carcinoma in situ, or positive with invasive carcinoma (Fig. 1). In the present study, severe dysplasia was

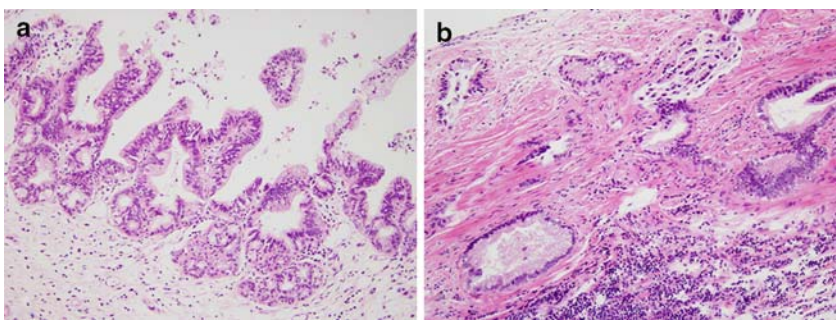

Fig. 1 Microphotographs of the positive resection margin at the bile duct stump (hematoxylin and eosin staining). (**a**) Carcinoma in situ (original magnification ×100). (**b**) Invasive carcinoma (original magnification ×100)

included in the category of carcinoma in situ because it is usually difficult or even impossible to distinguish between these two epithelial lesions, as described by Albores-Saavedra et al. [17–20] and Wakai et al. [21]. Mild to moderate dysplasia that was inflammatory, regenerative, or hyperplastic in nature was excluded. Carcinoma in situ or severe dysplastic epithelium may extend into intramural glands such as the sacculi of Beale or metaplastic pyloric-type glands. Discrimination between such intramural epithelial lesions (pseudoinvasion) and invasive carcinoma was made on the basis of the histologic criteria proposed by Albores-Saavedra et al. [17].

Patient follow-up and statistical analysis

Patients were followed regularly in outpatient clinics every 1–6 months, and follow-up information for all 128 patients was obtained from routine clinic appointments and telephone calls to the patients and their referring physicians. The sites of initial disease recurrence were determined from cross-sectional imaging studies (computed tomography—CT—or magnetic resonance imaging—MRI). They were classified as local disease recurrence (hepatic resection margin, bilioenteric anastomosis, or porta hepatis), regional disease recurrence (retroperitoneal lymph nodes), and distant disease recurrence (intrahepatic, peritoneum, or extra-abdominal sites).

The majority of patients ultimately underwent biopsy confirmation of cancer recurrence. At the time of the last follow-up, 53 patients had died of tumor recurrence and 34 patients had died of other causes with no evidence of tumor recurrence. One patient was alive with liver metastasis, and the remaining 32 patients were alive without disease. The follow-up period was defined as the interval between the date of surgical resection and that of the last follow-up. Survival curves were calculated using the Kaplan-Meier method [22], and differences between curves were evaluated using the log-rank test. Values of $p < 0.05$ were considered statistically significant. Only variables that were statistically significant by univariate analysis were included in the multivariate analysis, which was performed using a Cox proportional hazards model [23]. Data were analyzed using StatView 5.0J software (SAS Institute Inc., Cary, NC).

Results

Of 128 patients undergoing surgical resection, the bile duct resection margin was negative in 105 patients (82.0%), positive with carcinoma in situ in 12 patients (9.4%), and positive with invasive carcinoma in 11 patients (8.6%). Regarding clinicopathological characteristics between these three groups, patients whose tumors existed at the hilar or proximal bile ducts had a significantly higher rate of a positive ductal margin (33.3%) than patients whose tumors existed at the middle or distal bile ducts (7.79%) ($p = 0.0003$; Table 1).

Prognostic factors after surgical resection

Overall survival rates were 31.9% at 5 years and 14.9% at 10 years for all 128 patients. By univariate analysis, the histologic grade, venous permeation, stroma of tumors, pathologic lymph node metastasis (pN) category, TNM-stage, and ductal margin status were found to be significant prognostic factors (Table 2). Other factors, such as the predominant tumor location and pathological primary tumor (pT) category, were not found to be significant predictors of survival. A multivariate analysis was then performed using the six variables that proved to be significant in the univariate analysis and ductal margin status ($p = 0.0105$) and pN category ($p < 0.0001$) remained independent predictors of survival (Table 3).

Relationship between bile duct margin status and prognosis

The 5-year and 10-year survival rates were significantly better in patients with negative ductal margins (35.5% at 5 years and 17.0% at 10 years) than in those with positive ductal margins (12.2% at 5 years and 0% at 10 years) ($p = 0.0249$) (Fig. 2A). When patients with positive ductal margins were subdivided into those with carcinoma in situ and those with invasive carcinoma, the survival rates in patients with positive ductal margins with carcinoma in situ were 55.5% at 3 years and 22.2% at 5 years (with longest follow-up of 71 months), and the survival rates in patients with positive ductal margins with invasive carcinoma were 13.6% at 3 years and 0% at 5 years. There was no statistically significant difference in the survival rates between patients with negative ductal margins and those with positive ductal margins with carcinoma in situ ($p = 0.5247$) (Fig. 2B). Statistically significant differences in the survival rates were demonstrated between patients with positive ductal margins with carcinoma in situ and those with invasive carcinoma by means of the log-rank test ($p = 0.0241$) (Fig. 2C).

Relationship between local recurrence rate and ductal margin status

Local recurrence was found in 10 of the 128 patients (7.81%). When local recurrence was investigated according to the ductal margin status, local recurrence was observed in 6 of 105 patients (5.71%) with negative ductal

Table 1 Clinicopathological characteristics of 128 patients who underwent surgical resection according to ductal margin status

Variable	Number of patients			*p* Value
	Negative ductal margin	Positive ductal margin with		
		Carcinoma in situ	Invasive carcinoma	
Age (years)				
< 65	40	6	4	0.7125
> 65	65	6	7	
Sex				
Female	79	9	9	0.8601
Male	26	3	2	
Predominant location				
Hilar plus proximal	34	7	10	0.0003
Middle plus distal	71	5	1	
Histologic grade				
G1	44	4	2	
G2	45	5	3	0.1855
G3 or G4	16	3	6	
Lymphatic permeation				
Absent	11	1	1	0.9660
Present	93	11	11	
Venous permeation				
Absent	42	3	1	0.0898
Present	63	9	10	
Perineural permeation				
Absent	23	2	1	0.5716
Present	82	10	10	
Growth pattern				
α (expanding growth)	12	0	0	
β (intermediate growth)	56	7	5	0.4248
γ (infiltrating growth)	37	5	6	
Stroma of tumor				
Medullary	8	0	1	
Intermediate	73	7	4	0.1168
Scirrhous	24	5	6	
PT classification				
PTis plus pT1 plus pT2	47	7	6	0.5825
pT3 plus pT4	58	5	5	
pN classification				
pN0	72	9	8	
pN1	28	3	3	0.8797
pN2	5	0	0	
TNM stage				
0 plus 1	38	6	5	
II	54	6	5	0.6777
III plus IV	13	0	1	

G1 well differentiated; *G2* moderately differentiated; *G3* poorly differentiated; *G4* undifferentiated; *pT classification* pathologic primary tumor classification; *pN classification* pathologic lymph node metastasis classification

margins, 1 of 12 patients (8.33%) with positive ductal margins with carcinoma in situ, and 3 of 11 patients (27.3%) with positive ductal margins with invasive carcinoma. There was a significant relationship between local recurrence and ductal margin status ($p = 0.0401$, chi-square test) (Table 4).

Table 2 Univariate analysis of survival according to clinicopathologic factors

Characteristic	Number of patients	Median survival (days)	Five-year survival rate (%)	Ten-year survival rate (%)	*p* Value
Overall	128	1,706	31.9	14.9	–
Predominant location					
Hilar plus proximal	51	1,545	22.2	15.5	0.3050
Middle plus distal	77	1,668	37.3	14.0	
Histologic grade					
G1	50	1485	38.5	17.7	
G2	53	884	32.1	17.1	0.0470
G3 or G4	25	616	19.4	6.5	
Lymphatic permeation					
Absent	13	2190	72.7	27.3	0.0555
Present	115	851	27.3	13.3	
Venous permeation					
Absent	46	1806	48.0	21.9	0.0067
Present	82	728	21.2	9.6	
Perineural permeation					
Absent	26	1307	44.9	16.9	
Present	102	851	28.4	14.6	0.3244
Growth pattern					
α (expanding growth)	12	1694	37.0	24.7	
β (intermediate growth)	68	1806	36.1	19.4	0.2153
γ (infiltrating growth)	48	1385	25.4	7.2	
Stroma of tumor					
Medullary	9	1973	63.5	33.9	
Intermediate	84	1862	34.2	19.0	0.0124
Scirrhous	35	1001	18.2	0	
PT					
PTis plus pT1 plus pT2	60	1283	34.2	21.4	0.1414
pT3 plus pT4	68	851	30.1	10.3	
pN					
pN0	89	2170	45.5	21.0	
pN1	34	699	6.1	–	<0.0001
pN2	5	301	0	0	
TNM stage					
0 plus 1	49	1611	44.4	27.8	
II	65	777	26.8	9.7	0.0122
III plus IV	14	722	21.4	–	
Ductal margin status					
Negative	105	992	35.5	17.0	
Positive with carcinoma in situ	12	1,097	22.2	0	0.0022
Positive with invasive carcinoma	11	373	0	0	

Discussion

Extrahepatic cholangiocarcinoma, including hilar cholangiocarcinoma, remains one of the most difficult management problems in terms of staging and radical treatment. A microscopically tumor-free surgical margin is usually necessary for prolonged survival because complete eradication of the carcinoma is essential for cure. But extrahepatic cholangiocarcinoma often shows extensive microscopic spread along the bile duct beyond the macroscopic spread of the tumor mass. This microscopic extension, which may include aggressively infiltrating and/

Table 3 Multivariate analysis of survival

Variables	Hazard ratio	95% CI	*p* Value
Histologic grade			
G1	0.732	0.381–1.406	0.5075
G2	0.688	0.364–1.302	
G3 or G4	0	–	
Venous permeation			
Absent	0.762	0.466–1.247	0.2799
Present	0	–	
Stroma of tumor			
Medullary	0.729	0.242–2.192	0.7651
Intermediate	1.038	0.579–1.861	
Scirrhous	0	–	
Ductal margin status			
Negative	0.260	0.109–0.624	0.0105
Positive with carcinoma in situ	0.344	0.123–0.957	
Positive with invasive carcinoma	0	–	
pN classification			
pN0	0.066	0.016–0.027	<0.0001
pN1	0.344	0.058–0.744	
pN2	0	–	
TNM-stage			
0 plus I	1.405	0.520–3.798	0.1846
II	2.003	0.820–4.892	
III plus IV	0	–	

95% CI 95% confidence interval

or relatively noninvasive cancer cells, can result in residual tumor at the resection margin, even after a macroscopically successful radical resection.

There are several reports that some patients who undergo resection with microscopic tumor involvement at the bile duct margin survive longer than expected [9–12]. Few previous studies have considered the microscopic margin status of invasive and noninvasive carcinoma separately. We hypothesized that carcinoma in situ at the bile duct margin is prognostically different from residual invasive carcinoma, and we investigated this hypothesis clinocopathologically.

When investigating the rate of tumor-free margin at the bile duct stump from previously published reports, the University of California-San Francisco group reported that only 22% of grossly resected tumors had microscopically negative margins in patients with extrahepatic cholangiocarcinoma [24]. In their study, Ebata et al. [25] reported that tumor was present microscopically at the resection margin in 31.6% of patients undergoing resection for extrahepatic cholangiocarcinoma, and Jang et al. [11] reported that 15.9% of resected tumors had microscopic tumor involvement at the bile duct resection margin. In the present study, the bile duct resection margin was pathologically negative in 105 patients (82.0%) among the 128 patients with resected tumors. Compared to the previous reports, the margin-free rate of carcinoma at the bile duct stump is favorable in the current series, which suggests that the quality of preoperative diagnosis, including the selection of operation procedure, is appropriate and that the operation itself is acceptable in our facility.

Surgeons need to achieve a tumor free resection margin when performing curative operations for extrahepatic cholangiocarcinoma; multivariate analysis has demonstrated that a negative surgical margin is an independent predictor of prolonged survival after surgical resection. In the present study, ductal margin status was an independent prognostic factor by both univariate and multivariate analyses, along with lymph node metastasis.

Wakai et al. [21] investigated the relationship between bile duct margin status and prognosis in 84 patients undergoing surgical resection for extrahepatic cholangiocarcinoma. They reported that the prognosis of patients with residual carcinoma in situ at the ductal stumps is significantly better than the prognosis of those with invasive carcinoma. We also demonstrated that residual carcinoma in situ differs prognostically from invasive carcinoma at the ductal resection margins in 128 patients with this disease. To the best of our knowledge, Wakai's report was the first one that considered the microscopic margin status of invasive and noninvasive carcinoma separately, and the present study is the second, but the larger,

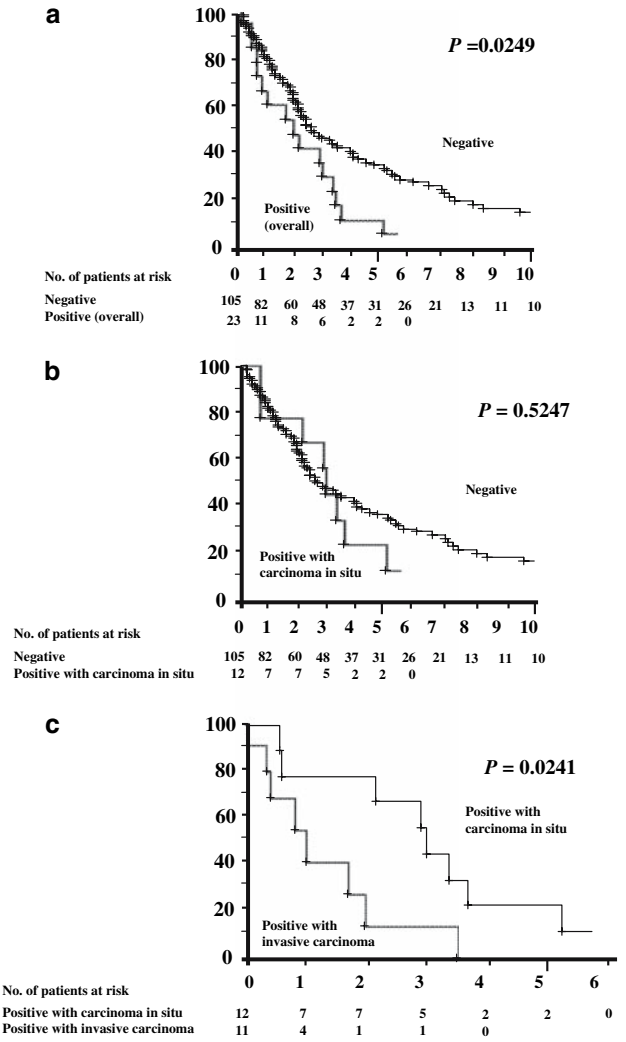

Fig. 2 Kaplan-Meier estimated survival curves according to the ductal resection margin status. (**A**) There is a statistically significant difference between patients with negative ductal margins and those with positive ductal margins via the log-rank test ($p = 0.0249$). (B) There is no statistically significant difference between patients with negative ductal margins and those with positive ductal margins with carcinoma in situ via the log-rank test ($p = 0.5247$). (**C**) A statistically significant difference was observed between patients with positive ductal margins with carcinoma in situ and those with invasive carcinoma via the log-rank test ($p = 0.0241$)

study concerning this issue. Furthermore, we first demonstrated that there was a statistically significant relationship between local recurrence and ductal margin status in this disease.

Wakai et al. [21] also reported that they observed four 5-year survivors with positive ductal margins and that all four patients with residual carcinoma at the ductal stumps died of local recurrence. In the present study we observed six 3-year survivors, including two 5-year survivors, and four of those six patients died of disease (Table 5). The sites of recurrence were local recurrence, peritoneal carcinomatosis, liver metastasis, lung metastasis, and abdominal wall recurrence, including duplication patients. To our knowledge, there have been few previous detailed reports concerning the sites of recurrence in patients with extrahepatic cholangiocarcinoma. We previously reported that the sites of recurrence of extrahepatic cholangiocarcinoma were various, such as liver metastasis, carcinomatous peritonitis, lymph node recurrence, local recurrence, metastasis involving the abdominal wall, and metastasis of the bone, pleura, and brain [26]. We think Wakai's report, in which all four patients with residual carcinoma at the ductal stumps died of local recurrence, is curious because most resected tumors are advanced disease. In view of the finding that the rate of local recurrence is significantly higher in patients with positive ductal margins than in patients with negative margins, patients should be followed postoperatively for possible local recurrence, especially patients with positive ductal margins, and also for other sites where recurrence has been previously reported.

Table 4 Local recurrence rate in 128 patients undergoing resection stratified by ductal margin status

	Local recurrence		Total
	(–)	(+)	
Negative	99	6	105
Positive with carcinoma in situ	11	1	12
Positive with invasive carcinoma	8	3	11
Total	118	10	128

$p = 0.0401$, chi-square test

Hilar cholangiocarcinoma remains a difficult challenge for surgeons. Achieving negative surgical margins when resecting this relatively uncommon tumor is technically demanding, because of the close proximity of the bile duct bifurcation to the vascular inflow of the liver. Bismuth et al. [13] demonstrated a close correlation between tumor clearance at operation and prognosis, thereby emphasiszing the importance of achieving a tumor-free surgical margin. A recent advance in surgical treatment is reflected in the increased number of patients who can be offered potentially margin-free resection, especially the increased oncologic clearance of patients that would previously have been treated with bile-duct resection only. Boerma [27] and Ogura et al. [28] indicated that there was a statistically significant difference in prognosis between patients with and without hepatectomy. Hepatectomy, in addition to bile duct resection, has become a common procedure in the treatment of hilar cholangiocarcinoma. Considering that resection with positive ductal margin with carcinoma in situ still offers a significant benefit over that with invasive carcinoma, attempted curative resection would be justified.

Although current progress in the imaging of extrahepatic cholangiocarcinoma offers improved preoperative delin-

Table 5 Three-year survivors with positive ductal margins

Patient		Primary tumor site	Histologic grade	pT	pN	pM	TNM stage	Surgery	Ductal margin status	Site of recurrence	Outcome (month)
1	62/F	Hilar	G1	2	0	0	1b	R3H+TC+BDR	CIS	Local	36; DOD
2	64/M	Hilar	G2	3	0	0	2a	ERH+TC+BDR+PPPD	CIS	–	63; DOO
3	63/M	Hilar	G3	1	0	0	1a	BDR	Invasive	–	42; DOO
4	67/F	Nonhilar	G1	1	0	0	1a	PPPD	CIS	PER	45; DOD
5	69/M	Nonhilar	G3	1	0	0	1a	PPPD	CIS	–	69; NED
6	61/M	Hilar	G2	3	0	0	2a	R3H+TC+BDR	CIS	HEP, Lung, AW	41; DOD

pM pathologic distant metastasis classification; *F* female; *R3H* right hepatic trisegmentectomy; *TC* total caudate lobectomy; *BDR* resection of extrahepatic bile ducts; *CIS* carcinoma in situ; *DOD* died of disease; *M* male; *ERH* extended right hepatic lobectomy; *PPPD* pylorus preserving pancreatoduodenectomy; *DOO* died of other causes; *PER* peritoneal dissemination; *NED* alive with no evidence of disease; *HEP* liver metastasis; *AW* abdominal wall recurrence

eation of the main tumor mass, accurate staging of microscopic extension along the bile duct remains difficult. Instead, intraoperative histological diagnosis by means of frozen-section examination is usually used as a final confirmation of the status of the resection margin.

In conclusion, among patients undergoing surgical resection for extrahepatic cholangiocarcinoma, invasive carcinoma at the ductal resection margins appears to have a strong relation to local recurrence, and also to have a significant negative impact on survival, whereas residual carcinoma in situ does not. Discerning whether carcinoma in situ or invasive carcinoma is present is very important in clinical cases in which the resection margin at the ductal stump is positive by frozen-section pathological examination.

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