Table S1 Clinicopathological parameters of 43 pancreatic cancer cases analyzed by array-based comparative genomic hybridization.

Table S2 Numerical aberrations observed in 44 pancreatic adenocarcinoma cases examined by array-based comparative genomic hybridization.

Table S3 Loci lost frequently (>25% cases) in 44 pancreatic adenocarcinoma cases examined by array-based comparative genomic hybridization, arranged by region.

Table S4 Loci gained frequently (>25% cases) in 44 pancreatic adenocarcinoma cases examined by array-based comparative genomic hybridization, arranged by region.

Table S5 Association of sub-chromosomal numerical aberrations with selected clinicopathological parameters in pancreatic cancer.

Table S6 (A) Loci altered more frequently in moderately compared with well differentiated pancreatic adenocarcinomas. (B) Loci altered more frequently in poorly compared with moderately differentiated pancreatic adenocarcinomas.

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Surgical Outcomes of the Mass-Forming plus Periductal Infiltrating Types of Intrahepatic Cholangiocarcinoma: A Comparative Study with the Typical Mass-Forming Type of Intrahepatic Cholangiocarcinoma

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Abstract
Background The purpose of this study was to clarify the clinicopathologic characteristics and surgical outcomes of patients with the mass-forming (MF) plus periductal infiltrating (PI) type of intrahepatic cholangiocellular carcinoma (ICC).
Methods Between January 1, 1998, and December 31, 2004, a total of 94 patients with ICC underwent macroscopic curative resection, and the macroscopic type of the tumors was assessed prospectively. Among the 74 patients with the MF type ($n = 46$) and the MF plus PI type ($n = 28$) of ICC, multivariate analysis was conducted to identify the potential prognostic factors. The clinicopathologic data of the two groups were compared.
Results The results revealed two independent prognostic factors: presence/absence of intrahepatic metastasis and the macroscopic type of the tumor. ICCs categorized macroscopically as the MF plus PI type were significantly associated with jaundice ($p < 0.001$), bile duct invasion ($p < 0.001$), portal vein invasion ($p = 0.025$), lymph node involvement ($p = 0.017$), and positive surgical margin ($p = 0.038$).
Conclusion Identification of the macroscopic type of the tumor is useful for predicting survival after hepatectomy in patients with ICC. The MF plus PI type of ICC appears to have a more unfavorable prognosis, even after radical surgery, than the MF type of ICC.

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Intrahepatic cholangiocarcinoma (ICC) arising from the intrahepatic bile ducts has been reported to be a rare malignant tumor, accounting for approximately 5% to 10% of all primary liver cancers [1, 2]. However, an increase in the incidence and mortality of this cancer has been reported recently [3]. ICC is mainly recognized as a localized round tumor with a distinct border on the cut surface of the liver [2]. In 1997, the Liver Cancer Study Group of Japan (LCSGJ) proposed a new classification of ICC based on the macroscopic appearance of the tumors: the mass-forming (MF) type, periductal infiltrating (PI) type, intraductal growth type (IG), and mixed type containing more than one of the other three basic types [4].

The ICC has a tendency to spread diffusely along Glisson's sheath in a radial fashion from the original spherical tumor [5–7], and the MF plus PI type (MF-dominant type) is one of the most commonly encountered subtypes of ICC [8]. This tumor subtype occurs as a definitive mass in the liver, commonly causing infiltration along the portal pedicle and invasion of the wall of large vessels and bile ducts. It is usually detected only at an advanced stage [9]. There are only a few studies until now that have investigated the clinical significance of the macroscopic appearance of the tumor, with special reference to the MF plus PI subtype, as a prognostic indicator in patients with an ICC [10, 11].

We prospectively classified the 94 surgically resected cases at our hospital since 1998 on the basis of the gross appearance of the surgically resected tumors and examined the clinicopathologic characteristics and surgical outcomes of patients with the MF plus PI type of ICC compared with those of patients with the MF type of ICC.

Patients and methods

Between January 1, 1998 and December 31, 2004, a total of 94 patients with ICC underwent macroscopic curative resection at the Hepatobiliary and Pancreatic Surgery Division, National Cancer Center Hospital, Tokyo, Japan. ICC is defined as carcinoma arising from the second-order or more distal branches of the intrahepatic bile ducts. The criteria for resectability were the absence of (1) peritoneal dissemination, (2) bulky lymph node metastasis, (3) extensive invasion of the hepatoduodenal ligament, and (4) intrahepatic metastases in the remaining liver. Macroscopic curative resection was defined as the absence of apparent residual tumor in the operative field. The type of surgical procedure performed depended on both the tumor location and the mode of extension. In patients suspected to have lymph node involvement on the basis of preoperative imaging or intraoperative findings, lymph node dissection was performed around the hepatoduodenal ligament, posterior to the upper portion of the pancreatic head, and along the common hepatic artery.

The macroscopic typing of the resected tumor specimens was conducted prospectively and confirmed by microscopic examination according to the Classification of Primary Liver Cancer as: the mass-forming type (MF: characterized by the presence of a spherical mass with a distinct border in the liver parenchyma); the periductal-infiltrating type (PI: characterized by tumor infiltration along the bile duct, occasionally involving the surrounding blood vessels and/or hepatic parenchyma); or the intraductal growth type (IG: characterized by papillary and/or granular growth into the bile duct lumen, occasionally showing superficial extension). When more than one type of lesion was found, all of the types detected and the predominant type were recorded [4]. The distribution of the macroscopic tumor types in our cases was as follows: MF type, 47 (50%); MF plus PI type, 29 (31%); MF plus IG, 6 (6%); PI type, 8 (9%); IG type, 4 (4%). The 76 patients with the MF and MF plus PI type of ICC were the focus of the present study.

One hospital death (1%) was recorded in the group with the MF plus PI type of ICC and one patient with MF type of ICC was lost to follow-up. Patients were closely followed up every 3 months on an outpatient basis with measurement of the serum levels of carbohydrate antigen 19-9 (CA19-9) and carcinoembryonic antigen (CEA), chest radiography, and abdominal ultrasonography and/or computed tomography. The specific sites of the first tumor recurrence and the time until disease recurrence were recorded. Radiologic evidence of tumor recurrence was accepted as a criterion of recurrence even if the patient did not undergo a biopsy. When progression of the disease was confirmed by repeated imaging studies, the date of first detection of a suspicious radiologic finding was recorded as the date of the initial disease recurrence. The data of the hospital death case and the case lost to follow-up were excluded from the follow-up analysis. The median follow-up duration was 20 months (range 4–82 months).

Among the 74 patients, 14 potential prognostic factors, including the macroscopic type of the tumor, were investigated using the log-rank test. Pathologic factors associated with the tumor invasiveness, such as lymph node metastasis, portal vein (vp) or hepatic vein invasion (vv), bile duct invasion (b), and intrahepatic metastasis (im), were evaluated in relation to the tumor types. The tumors were further classified clinically into four groups as follows: (0, no tumor invasion of the portal vein, hepatic vein, or bile duct; 1, tumor invasion distal to the second branch of the portal vein or bile duct and/or invasion of a branch of the hepatic vein; 2, tumor invasion of the second branch of the portal vein or the bile duct, the major hepatic veins, and/or the short hepatic veins; 3, tumor invasion of the first branch of the portal vein or of the bile duct, tumor invasion of the inferior vena cava) according to the degree of "vp", "vv," and "b" [4]. A positive surgical margin was defined by histopathologic detection of tumor cells at the surgical margin.

The continuous variables were classified into two groups according to the median value of each factor. All the variables were dichotomized for the analysis. Survival estimates were calculated by the Kaplan-Meier method. Multivariate regression analysis was performed using the Cox proportional hazards model, and factors associated with $p < 0.10$ were entered into the final model adopted. Comparison between patients with the MF type and MF plus PI type of ICC was performed by univariate analysis in terms of 12 clinicopathologic factors using the chi-squared test with Yates' correction. All statistical analyses were performed using the Software Package for Social Sciences, version 11.5J for Windows® (SPSS, Chicago, IL, USA). A two-sided $p < 0.05$ was considered to denote statistical significance.

Results

A total of 76 patients with the two types of the tumors (MF type or MF plus PI type) had undergone various kinds of

Table 1 Macroscopic types and operative procedures

Hepatectomy and other operative procedures	MF type (n = 47)	MF plus PI type (n = 29)	p
Left lobectomy	16 (34%)	16 (55%)	0.001
Left trisegmentectomy	6 (13%)	3 (10%)	
Central bisegmentectomy	1 (2%)	1 (3%)	
Right lobectomy	12 (26%)	9 (32%)	
Right trisegmentectomy	2 (4%)	0	
Segmentectomy/limited resection	10 (21%)	0	
Caudate lobe resection	21 (67%)	23 (79%)	0.006
IVC resection	5 (11%)	3 (10%)	1.000
Arterial resection and reconstruction	0	3 (10%)	0.052
Portal vein resection and reconstruction	4 (9%)	6 (21%)	0.167
Extrahepatic bile duct resection	12 (26%)	26 (90%)	< 0.001
Lymph node dissection[a]	26 (55%)	26 (90%)	0.002

MF: mass-forming; PI: periductal infiltrating; IVC: inferior vena cava

[a] Lymph node dissection in the hepatoduodenal ligament, retroperitoneal region along the hepatic artery, and behind the pancreas

hepatectomy and additional operative procedures (Table 1). The mean age of the patients was 64 ± 10 years (median 66 years; range 34–84 years). There were 28 women (37%) and 48 men (63%). Segmentectomy or limited resection was the most frequently performed procedure in the patients with the MF type of ICC (p = 0.02). The frequency of combined resection of the caudate lobe (p = 0.006), extrahepatic bile duct resection (p < 0.001), and/or lymph node dissection (p = 0.002) was significantly higher in the patients with the MF plus PI type of ICC. The incidence of concomitant resections of the inferior vena cava, hepatic artery, and portal vein was similar in the two groups. One patient with the MF plus PI type of ICC who underwent left lobectomy with combined resection of the caudate lobe, extrahepatic bile duct resection, and lymph node dissection died of liver failure caused by multiple liver abscesses 142 days after the operation.

The possible risk factors for survival in the patients with the MF type (n = 46) and MF plus PI type (n = 28) of ICC were examined using the log-rank test (Table 2). The poor prognostic factors according to the univariate analysis were the presence of intrahepatic metastases (p = 0.0002), portal vein involvement (p = 0.0538), lymph node involvement (p = 0.0061), a positive surgical margin (p = 0.0030), and the MF plus PI type of ICC (p = 0.0442). Fig. 1 shows the results of the survival analysis in the 74 patients with the MF or MF plus PI type of ICC. Among the possible prognostic factors identified by the univariate analysis, the following factors were found to be independently associated with a poorer prognosis: the presence of intrahepatic metastases (p < 0.001) and the MF plus PI type of ICC (p = 0.014), with hazard ratios [95% confidence intervals (CI)] of 3.560 (1.847–6.862) and 2.237 (1.175–4.259), respectively.

A comparison of the clinicopathologic factors in the patients with the MF and MF plus PI types of ICC is shown in Table 3. Significant differences were recognized between the two groups in terms of the presenting symptoms (p = 0.026) and the frequency of jaundice (p < 0.001), portal vein invasion (p = 0.025), bile duct invasion (p < 0.001), lymph node involvement (p = 0.017), and positive surgical margin (p = 0.038). Both groups had similar rates of intrahepatic metastasis and hepatic vein invasion. Patients with the MF plus PI type of ICC had a smaller mean tumor size than those with the MF type of ICC, but the difference was not statistically significant (p = 0.098).

The sites of initial recurrence were compared between the two groups (Table 4). The most frequent site of recurrence was the liver in patients with the MF type of ICC (16/35, 45.7%) and local recurrence (hepatic resection margin or bilioenteric anastomosis) was the most frequently encountered site of the initial recurrence in the patients with the MF plus PI type of ICC (9/26, 34.6%). Thus, local recurrence was more frequent in patients with the MF plus PI type of ICC (p = 0.0044).

Discussion

Based on a study of cases collected from the member institutes of the committee of the LCSGJ, Yamasaki [12] reported a prevalence rate of the MF type (including the predominant MF type) of ICC of 78.6% among all cases of ICC (136/173). In the present study, the MF type (50%, 47/94) and the MF plus PI type (31%, 29/94) accounted for 81% (79/94) of all the patients with ICC. The IG type of ICC has been recognized as a distinct entity with a more

Table 2 Possible clinical and pathologic risk factors for survival

Factors	No. of patients	(%)	Survival rate (%)			Median survival	*p*
			1 Year	3 Years	5 Years	(months)	
Overall	74		69.5	35.5	31.1	24	
Age (median 66 years)							
>66	33	45	67.5	32.6	26.1	31	0.4105
≤66	41	55	72.0	37.4	37.4	22	
Sex							
Male	46	62	65.9	45.6	34.2	31	0.5067
Female	28	38	75.0	23.4	23.4	23	
Jaundice							
Absent	63	85	72.1	34.3	30.1	23	0.7171
Present	11	15	54.6	40.9	(−)	24	
Ca 19-9 (median 220 IU/ml)							
<220	37	51	75.7	46.9	37.5	25	0.1121
≥220	35	49	61.6	23.1	23.1	21	
CEA (median 3.0 mg/dl)							
<3.1	38	51	78.5	41.1	41.1	25	0.1121
≥3.1	36	49	60.0	26.9	–	22	
Size (median 5.0 cm)							
<5.0	36	49	79.0	46.2	30.8	25	0.2725
≥5.0	38	51	59.0	28.9	28.9	20	
Intrahepatic metastases							
Absent	48	65	88.3	44.1	44.1	31	0.0002
Present	26	35	41.9	12.6	–	10	
Portal vein involvement							
vp0-1	47	64	74.0	41.0	41.0	31	0.0538
vp2-3	27	36	61.1	25.1	12.6	17	
Hepatic vein involvement							
vv0-1	53	72	69.8	35.8	35.8	25	0.3629
vv2-3	21	28	69.1	32.0	–	22	
Bile duct invasion							
B0-1	37	50	77.8	44.2	38.7	31	0.0877
B2-3	37	50	61.0	21.9	–	22	
Histologic differentiation							
Well	16	22	81.3	42.9	34.3	24	0.6101
Mod./poor	58	78	66.0	32.3	32.3	22	
Lymph node involvement							
Absent	40	54	71.9	46.2	46.2	32	0.0061
Present	34	46	63.6	10.2	–	21	
Surgical margin							
Negative	51	67	71.9	47.0	47	0 32	0.0030
Positive	23	33	63.6	10.2	–	20	
Macroscopic type							
Mass-forming type	46	62	73.2	45.5	39.8	32	0.0442
Mass-forming plus periductal infiltration type	28	38	63.0	16.0	–	22	

favorable prognosis than that of the other types of ICC [13]. However, the clinical significance of the MF plus PI type of ICC as a prognostic indicator remains unclear. Yamamoto et al. [10] noted that patients with the MF plus PI type of ICC had a dismal prognosis owing to the high incidence of noncurative resection and lymph node

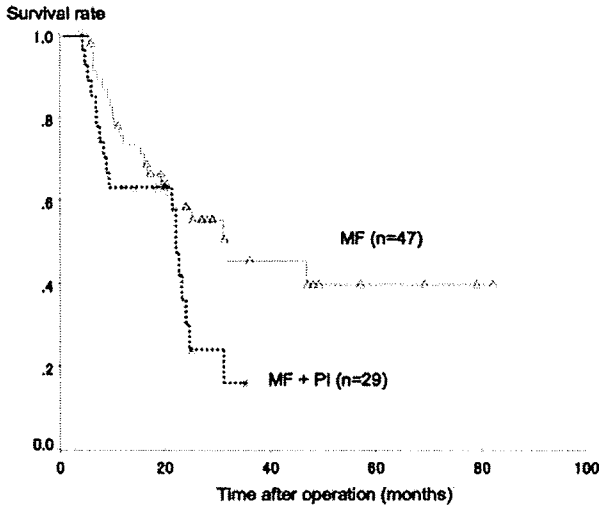

Fig. 1 Cumulative survival curve after surgery for cases of intrahepatic cholangiocarcinoma according to the gross appearance of the tumor. MF: mass-forming; PI: periductal infiltrating. $p < 0.0442$ (log-rank test)

metastases. On the other hand, Ohtsuka et al [11] reported that there was no significant difference in the survival rate between patients with this aforementioned type and other types of ICC. The results of the multivariate analysis in the present study suggested the MF plus PI type of ICC was associated with a poorer survival than the MF type of ICC. No definitive conclusion can be drawn from the limited number of cases from a single center, so cooperative multicenter trials that are powered adequately are necessary. However, the macroscopic classification might be useful for planning the surgical procedure and predicting the survival after hepatectomy in patients with the MF plus PI type of ICC because the recent advances in imaging techniques allow determination of the macroscopic type of ICC preoperatively [8].

One of the major speculations to explain the worse outcome of the MF plus PI type of ICC is that it represents a more advanced stage of the MF ICC [7]. The present study also showed that the MF plus PI type was more frequently associated with portal vein invasion and lymph node metastases, suggesting that it might represent a more advanced stage of tumor than the MF type of ICC. However, the tumor size and incidence of intrahepatic metastases, which are important components in defining the primary tumor stage, were not statistically different between the MF type and MF plus PI type of tumor. Two different modes of spread are generally recognized in patients with ICCs: lymph node metastasis spreading via lymphatics along Glisson's sheath and intrahepatic metastasis spreading via the portal venous system to the liver [9]. The stronger association of the MF plus PI type ICC with the former might be the primary reason for its more aggressive biologic nature.

Table 3 Relation between the macroscopic classification and other clinicopathologic factors

Factors	MF type ($n = 46$)	MF plus PI type ($n = 28$)	p
Age (median 66 years)			
>66	22 (48%)	11 (39%)	0.630
≤66	24 (52%)	17 (61%)	
Sex			
Male	26 (57%)	20 (71%)	0.226
Female	20 (43%)	8 (29%)	
Symptoms			
Absent	35 (76%)	14 (50%)	0.026
Present	11 (24%)	14 (50%)	
Jaundice			
Absent	46 (100%)	17 (60%)	<0.001
Present	0	11	
CA 19-9 (median 220 IU/ml)			
>220	17 (39%)	18 (64%)	0.052
≤220	27 (61%)	10 (36%)	
Size (median 5.0 cm)			
>5.0	26 (57%)	10 (36%)	0.098
≤5.0	20 (43%)	18 (64%)	
Intrahepatic metastases			
Absent	29 (63%)	19 (68%)	0.803
Present	17 (37%)	9 (32%)	
Portal vein invasion			
vp0-1	34 (74%)	13 (46%)	0.025
vp2-3	12 (26%)	15 (54%)	
Hepatic vein invasion			
vv0-1	36 (78%)	17 (61%)	0.119
vv2-3	10 (22%)	11 (39%)	
Bile duct invasion			
B0-1	35 (76%)	2 (7%)	<0.001
B2-3	11 (24%)	26 (93%)	
Lymph node involvement			
Absent	30 (65%)	10 (36%)	0.017
Present	16	18	
Liver cirrhosis or hepatitis			
Absent	40 (87%)	27 (96%)	0.347
Present	6 (13%)	1 (4%)	
Surgical margin			
Negative	36 (78%)	15 (54%)	0.038
Positive	10 (22%)	13 (46%)	

The MF plus PI type of ICC usually behaves just like a perihilar bile duct carcinoma, requiring aggressive surgical management [9, 10, 14–16]. Lang et al. [16] emphasized the necessity of extended hepatectomy with complete tumor removal as the only treatment strategy that can yield

Table 4 Initial recurrence sites

Macroscopic type	MF type (n = 46)	MF plus PI type (n = 28)
Recurrence	35 (76.1%)	26 (92.9%)
Solitary recurrence	28 (80.0%)	20 (76.9%)
Local recurrence*	0	9 (34.6%)
Liver	16 (45.7%)	6 (23.1%)
Lymph nodes	8 (22.9%)	1 (3.8%)
Peritoneum	1 (2.9%)	2 (7.7%)
Pleural	0	1 (3.8%)
Lung	2 (5.7%)	0
Bone	1 (2.9%)	0
Skin	0	1 (3.8%)
Multiple recurrences	7 (20.0%)	6 (23.1%)
Liver and lymph nodes	3 (6.5%)	2 (7.7%)
Lung and lymph nodes	0	1 (3.8%)
Local recurrence and liver	1 (2.9%)	1 (3.8%)
Local recurrence and lymph nodes	0	1 (3.8%)
Skin, bone, and liver	1 (2.9%)	1 (3.8%)
Lung, liver, and lymph nodes	2 (5.7%)	0

*p = 0.0044

prolonged survival in these cases. However, patients with the MF plus PI type of ICC still had a higher incidence of a positive surgical margin compared with that in the patients with the MF type in the current study. Yamamoto et al. [10] also reported that microscopic curative resection was achieved in only 3 (17%) of 18 patients with the MF plus PI type of ICC. Thus, another major cause for the poor prognosis might be the difficulty of achieving microscopic curative resection even with extended surgical procedures in patients with the MF plus PI type of ICC.

The results of analysis of the recurrence patterns revealed that local recurrence was higher in patients with the MF plus PI type compared to those in patients with the MF type of ICC. Recently, several studies have demonstrated that the use of adjuvant radiotherapy improved the survival of patients with hilar cholangiocarcinoma with a positive microscopic surgical margin [17–19]. Additional local therapy as well as systemic chemotherapy might be indispensable in this patient group. However, the efficacy of intraoperative or adjuvant radiotherapy in patients with ICCs has been scarcely investigated. The accumulation of sufficient numbers of resected cases is extremely difficult owing to the rarity of the disease. Therefore, it is important for studies to be sponsored by large cooperative groups and for patients to be stratified and analyzed by stage and adequate power to show a difference.

Previous reports have suggested that the presence of lymph node metastases may be one of the most unfavorable prognostic factors in cases of ICC [14, 20, 21]. Lymphatic metastases may be more commonly encountered in patients with the MF plus PI type of ICC. The role of regional lymphadenectomy remains controversial [20, 22, 23], although it might be applied as a standard operative procedure in patients with the MF plus PI type of ICC because these patients usually have normal liver function without chronic hepatitis or cirrhosis [23]. The incidence of lymph node recurrence was found to be similar between patients with the MF type and the MF plus PI type of ICC in the current study.

Although extended hepatectomy, extrahepatic bile duct resection, and lymph node dissection were performed in patients with the MF plus PI type of ICC, these patients still had a poorer surgical outcome compared with that of patients with the MF type of ICC. Therefore, with the currently employed criteria for patient selection for surgery, it is still difficult to achieve complete tumor resection, and additional radiotherapy and/or systemic chemotherapy should be considered in the event of local or hepatic recurrence after surgical treatment in patients with the MF plus PI type of ICC.

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資料は準備いたします。

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Prognosis of Perihilar Cholangiocarcinoma: Hilar Bile Duct Cancer versus Intrahepatic Cholangiocarcinoma Involving the Hepatic Hilus

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Background: Clinically hepatobiliary resection is indicated for both hilar bile duct cancer (BDC) and intrahepatic cholangiocarcinoma involving the hepatic hilus (CCC). The aim of this study was to compare the long-term outcome of BDC and CCC.

Methods: Between 1990 and 2004, we surgically treated 158 consecutive patients with perihilar cholangiocarcinoma. The clinicopathological data on all of the patients were analyzed retrospectively.

Results: The overall 3-year survival rate, 5-year survival rate, and median survival time for BDC patients were 48.4%, 38.4 %, and 33.7 months, respectively, and 35.8%, 24.5 %, and 22.7 months, respectively, in CCC patients ($P = .033$).

On multivariate analysis, three independent factors were related to longer survival in BDC patients: achieved in curative resection with cancer free margin (R0) ($P = .024$, odds ratio 1.862), well differentiated or papillary adenocarcinoma ($P = .011$, odds ratio 2.135), and absence of lymph node metastasis ($P < .001$, odds ratio 3.314). Five factors were related to longer survival in CCC patients: absence of intrahepatic daughter nodules ($P < .001$, odds ratio 2.318), CEA level ≤2.9 ng/mL ($P = .005$, odds ratio 2.606), no red blood cell transfusion requirement ($P = .016$, odds ratio 2.614), absence or slight degree of lymphatic system invasion ($P < .001$, odds ratio 4.577), and negative margin of the proximal bile duct ($P = .003$, odds ratio 7.398).

Conclusions: BDC and CCC appear to have different prognoses after hepatobiliary resection. Therefore, differentiating between these two categories must impact the prediction of postoperative survival in patients with perihilar cholangiocarcinoma.

Key Words: Hilar bile duct cancer—Intrahepatic cholangiocarcinoma—Hepatobiliary resection.

Hilar cholangiocarcinoma remains a challenging disease, and the prognosis is often dismal, even after aggressive surgery including hepatobiliary resection with caudate lobectomy.[1] Previous reports have included a limited number of resected cases, and reports of large, single-center studies are not common.[2–13]

Based on the anatomical origin of the tumor, hilar cholangiocarcinoma and perihilar cholangiocarcinoma are potentially divisible into two categories: hilar bile duct cancer (BDC) and intrahepatic cholangiocarcinoma involving the hepatic hilus (CCC). BDC originates in the epithelium of the common hepatic, right or left hepatic duct, whereas CCC

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originates in the intrahepatic bile duct or bile ductules.

In the clinical setting, curative resection for both BDC and CCC involves hepatobiliary resection with regional lymphadenectomy. Many previous studies have treated BDC and CCC as the same entity; thus, the clinicopathological differences between BDC and CCC remain unclear, and the clinical usefulness of differentiating between these two groups has not been elucidated.

We have distinguished between BDC and CCC based on pathology and have collected the clinicopathological data since the 1980s. Thus, a review of these patients' data is crucial for determining future strategies.

The aims of this study were to review the long-term outcome of major hepatobiliary resections done over the last 15 years for BDC and CCC using a similar treatment strategy in a single center and to characterize the prognostic factors affecting the long-term outcome for each group to clarify the differences between groups.

PATIENTS AND METHODS

Between January 1, 1990 and December 31, 2004, 225 patients were admitted to our department with a tentative diagnosis of perihilar cholangiocarcinoma. The following patients were excluded: patients who did not undergo laparotomy because of highly advanced disease or poor hepatic functional reserve during the preoperative workup, those in whom resection was not possible due to locally advanced status or dissemination, patients who had a hilar bile duct resection or a minor hepatectomy, and patients with gallbladder cancer or benign biliary stricture based on postoperative pathology. Thus 158 patients, consisting of 99 patients (62.7%) with hilar bile duct cancer (BDC) and 59 patients (37.3%) with intrahepatic cholangiocarcinoma involving the hepatic hilus (CCC), treated with major hepatobiliary resection were enrolled in this study (Table 1). The patient population consisted of 52 women and 106 men, with a median age of 65 years (range, 33–83 years).

The medical records that had been collected, including the hospital charts, operation records, and pathology reports, were analyzed retrospectively.

Our standard management strategies and surgical procedures have been described previously.[14] Briefly, after a preoperative imaging diagnosis of tumor extension was made, biliary drainage was done to ensure that the patient recovered from cholestatic liver damage, if necessary. To induce compensatory hypertrophy of the future remnant liver, preoperative portal vein embolization (PVE)[15,16] for the liver segment to be resected was done if the estimated resection volume exceeded 50–55% of the whole liver; 71 patients (44.9%) underwent PVE.

All patients underwent major hepatobiliary resection with a hepatectomy involving two or more sectors and systematic lymphadenectomy of the nodes located at the hepatoduodenal ligament, the upper part of the retropancreatic nodes, and the celiac nodes, as well as skeletonization of the hepatic hilus. Operative mortality included both death within 30 days of surgery and all in-hospital death. Morbidity included all postoperative complications that affected the outcome or lengthened the hospital stay. The surgical procedures are summarized in Table 2.

Histopathological Evaluation, Pathological Diagnosis, and Staging

First, the extrahepatic bile duct was incised longitudinally from the distal to the proximal margin. The anatomical orientation of the individual vessels and the surgical margins of the resected specimen were assessed macroscopically. The en bloc dissected lymph nodes were classified according to the anatomical location. Both the proximal and distal margins of the bile duct were routinely evaluated using intraoperative frozen section.

The resected specimen was fixed in 10% formalin, after that multiple, 5-mm thick, thin slice sections of the resected specimen were prepared in alignment with the computed tomography (CT) plane. In every section, the biliary anatomy was identified in relation to the vasculature. Then, sagittal, thin slice sections every 3 to 5 mm were added to precisely determine tumor extension around the hepatic hilum. Distal tumor extension was clarified based on the serial perpendicular sections to the longitudinal axis of the distal bile duct. In every case, histological tumor extension was investigated in 20 to 40 sections, and lymph node involvement was independently evaluated.

The criteria used to discriminate between BDC and CCC depended primarily on the location of the main tumor, as is schematically shown in Fig. 1. BDC was defined as a tumor originating in the upper common, right or left hepatic duct. Representative cases of BDC and CCC on the slice section of resected specimen are illustrated in Fig. 2. To evaluate the origin or the dominant spatial location of the tumor, hematoxylin-eosin staining was routinely used; elastica stain was additionally used to delineate the elastic

TABLE 1. *Patient characteristics and preoperative variables*

Variable	BDC (n = 99)	CCC (n = 59)	P value
Age (years)	64, [33–83]	66 [34–82]	
Gender (men / women)	69/30	37/22	
Preoperative biliary drainage (performed)	77 (78%)	16 (27%)	<.001
ICGR15 (%)	8.4 [0.8–48.1]	7.1 [0.2–63.2]	
CEA (ng/mL)	2.5 [0.7–22.1]	2.9 [0.8–560]	
CA19-9 (U/mL)	101 [1–14,750]	306 [1–256,800]	.006

[range].
ICGR15 indicates indocyanine green retention value at 15 minutes; CEA, carcinoembrionic antigen; CA19-9, carbohydrate antigen 19-9.

TABLE 2. *Surgical procedures and operative variables*

	BDC (n = 99)	CCC (n = 59)	P value
Type of hepatectomy			
Left hepatectomy	42 (42%)	29 (49%)	
Left trisectionectomy	5 (5)	9 (15)	
Central bisectionectomy	1 (1)	1 (2)	
Right hepatectomy	49 (49)	18 (31)	
Right trisectionectomy	2 (2)	2 (3)	
with PD	10 (10)	0	.012
with PV	18 (18)	14 (24)	
with PVE	53 (54)	18 (31)	.005
Right-sided hepatectomy	51 (52)	20 (34)	.033
Operation time (minutes)	655 [302–1125]	616 [372–950]	.051
Intraoperative blood loss (g)	1670 [446–5087]	1574 [445–7530]	
Red blood cell transfusion performed	34 (34)	26 (44)	
Postoperative morbidity	51 (52)	32 (54)	
In-hospital mortality	0 (0)	2 (3)	.066

[range]
PD, pancreatoduodenectomy; PV, resection and reconstruction of the portal vein; PVE, portal vein embolization prior to the resectional surgery.
Percentages are described in parentheses.

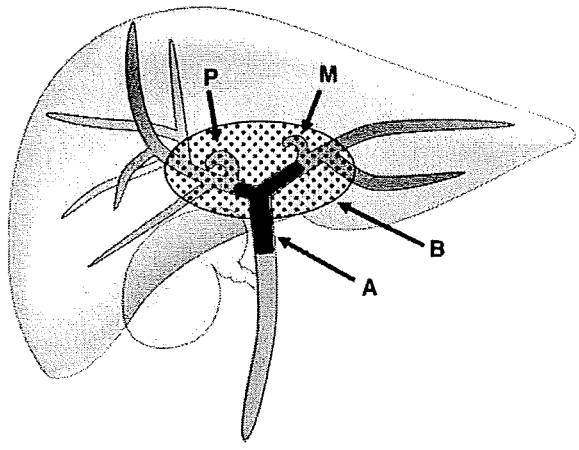

FIG. 1. Tumor origin for differentiating hilar bile duct cancer (BDC) and intrahepatic cholangiocarcinoma involving the hepatic hilus (CCC). Histopathologically, tumors thought to be originated in the black pasted area (**A**) were defined as BDC, and also tumors thought to be originated in the area with dot spots (**B**) were defined as CCC. P, right posterior sectional branch of the bile duct; M, left medial sectional branch of the bile duct.

fibers of the hepatic hilum and the intrahepatic Glisson's capsule in difficult cases of differentiating BDC from CCC. Namely, we can estimate special tumor domination whether inside or outside of hilar plate by the aid of elastica stain.

Macroscopically, the BDC tumors were classified as being polypoid and nodular or infiltrating. The CCC tumors were classified by the pathologists as being mass forming or non mass forming (periductal infiltrating or intraductal growth) type[17] on the plane of the thin slice section.

Pathological TNM classification was determined according to the criteria of the International Union Against Cancer (UICC) (sixth edition),[18] using the chapter dealing with extrahepatic bile duct cancer for BDC and that dealing with liver cancer for CCC. During the study period, the histopathological diagnoses were recorded and accumulated, then reviewed by the pathologists for this paper.

Follow-Up

All patients were followed at our outpatient clinic, where chest x-rays, abdominal ultrasound, CT, and the measurement of CEA and CA19-9 levels was done every 3–6 months after surgery. In principle, postoperative

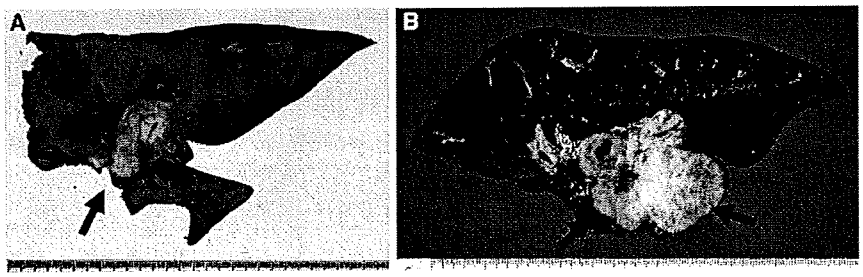

FIG. 2. Representative case of hilar bile duct cancer (A) and intrahepatic cholangiocarcinoma involving the hepatic hilus (B) on the slice section of resected specimen. Arrows indicate tumor.

adjuvant therapy such as chemotherapy, radiotherapy, or chemoradiotherapy was not adopted until tumor recurrence was definitively diagnosed.

Statistical Analysis

The results are expressed as median values, with the respective ranges indicated within square brackets. The relationship between the postoperative morbidity and the dichotomous variables was evaluated by chi-square analysis or Fisher's test, whichever was appropriate. The statistical significance of continuous variables was determined using the Mann-Whitney test. Patient survival was calculated using the Kaplan-Meier method, including deaths from all causes. Univariate comparisons of the survival curves were performed using the log-rank test. Multivariate regression analysis (backward elimination method) was performed using the Cox proportional hazards model,[19] and variables associated with $P < .10$ were entered into the final model. Results were considered significant when the P values were less than .05. The statistical analyses were performed using a statistical analysis software package (SPSS 11.5, SPSS Inc. Chicago, IL).

RESULTS

The patients' overall 1-, 3-, and 5-year survival rates were 81.0%, 43.7%, and 33.4%, respectively. The median survival was 28.4 (4.1–187.1) months, and the median follow-up time was 25.2 (4.1–187.1) months. Ninety-seven patients died of tumor recurrence, and two patients died without evidence of tumor recurrence. The remaining 59 patients are currently alive; 12 have recurrence, and 47 have no sign of recurrence at the time of writing.

The patient characteristics and preoperative variables are summarized in Table 1. The six clinicopathological variables were compared. Preoperative biliary drainage was performed significantly more frequently in BDC patients ($P < .001$). Serum CA19-9 levels were significantly higher in CCC patients ($P = .006$). There were no significant differences in other variables between BDC and CCC patients. There were no in-hospital deaths in the BDC group, but two patients with CCC died in hospital (CCC mortality rate, 3.4%; overall mortality rate, 1.3%). Eighty-three patients (52.5%) developed postoperative morbidity. There were no statistically significant differences in mortality or morbidity between the two groups (Table 2).

The overall 1-, 3-, 5-year survival rates and median survival time of BDC patients were 87.9%, 48.4%, 38.4 %, and 33.7 months, respectively. The overall 1-, 3-, 5-year survival rates and median survival time of CCC patients were 69.5%, 35.8%, 24.5 %, and 22.7 months, respectively. There was a significant difference in the overall survival between BDC and CCC patients ($P = .033$) (Fig. 3). Figures 4**A** and 4**B** show the survival curves of BDC and CCC patients by UICC staging. Significant differences were noted between stages I and II ($P = .0023$), stages I and III ($P = .0453$), and stages I and IV ($P = .0006$) in BDC patients (Fig. 4**A**). Significant differences were also noted between stages I and IV ($P = .0039$), stages II and IV ($P = .0112$), and stages III and IV ($P = .0285$) in CCC patients (Fig. 4**B**). For any given stage, there was no significant difference in survival between BDC and CCC patients: stage I ($P = .5016$), II ($P = .3316$), III ($P = .9584$), and IV ($P = .1387$).

The surgical procedures and operative variables are summarized in Table 2. Hepatopancreatoduodenectomy (HPD)[20] ($P = .012$), PVE ($P = .005$), and right-sided hepatectomy ($P = .033$) were performed significantly more frequently in BDC patients. There were no other significant differences in the surgical procedures or operative variables between the BDC and CCC patients.

The 11 histopathological variables were compared (Table 3). Well differentiated or papillary adenocarcinoma ($P = .034$) and positive proximal ($P = .046$)

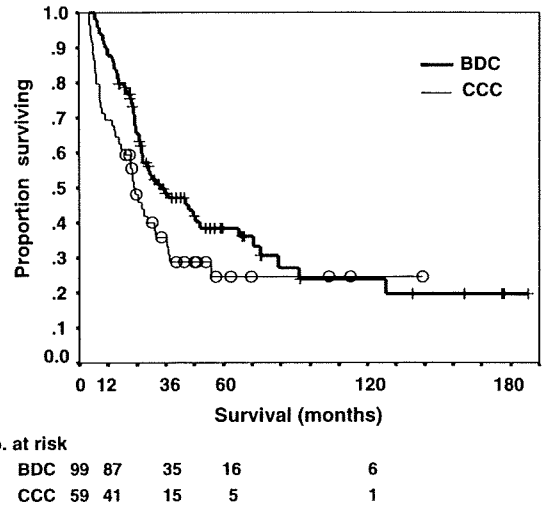

FIG. 3. The survival curves for hilar bile duct cancer (BDC) patients and intrahepatic cholangiocarcinoma involving the hepatic hilus (CCC) patients. The overall 1-, 3-, 5-year survival rates, and median survival time of BDC patients were 87.9%, 48.4%, 38.4 %, and 33.7 months, respectively. The overall 1-, 3-, 5-year survival rates, and median survival time of CCC patients were 69.5%, 35.8%, 24.5 %, and 22.7 months, respectively. There was a significant difference in the overall survival between BDC and CCC patients (P = .0333).

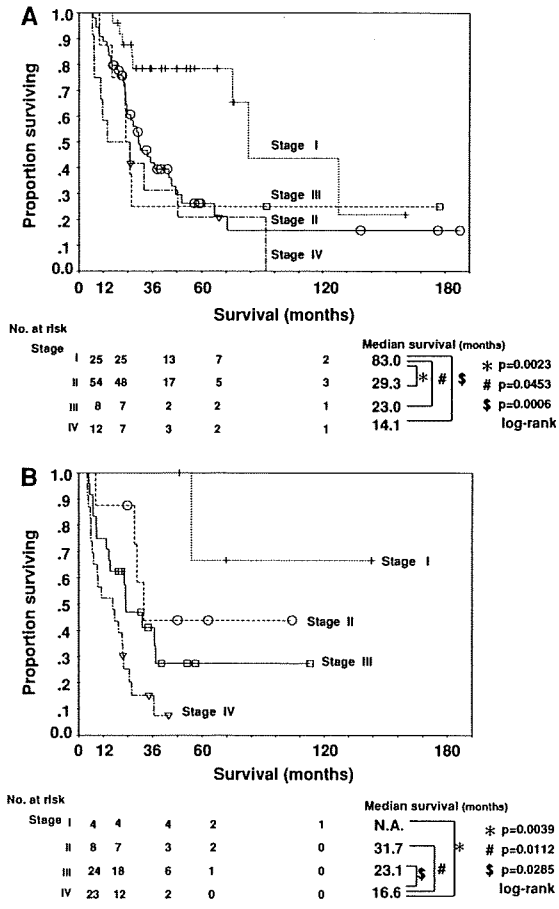

FIG. 4 Survival curves. (A) BDC patients by UICC pathological stage. Significant differences were noted between stages I and II (P = .0023), stages I and III (P = .0453), and stages I and IV (P = .0006). (B) The survival curves of CCC patients by UICC pathological stage. Significant differences were noted between stages I and IV (P = .0039), stages II and IV (P = .0112), and stages III and IV (P = .0285).

or distal (P = .028) bile duct margins were significantly more frequent in BDC patients. On the other hand, resected major portal vein invasion (P = .001) and moderate to severe venous invasion (P = .004) were significantly more frequent in CCC patients. There were no significant differences between BDC and CCC patients in the remaining six histopathological variables.

The 9 clinical and 11 histopathological risk factors possibly related to survival in BDC patients were analyzed by the log-rank test (Table 4). Male gender (P = .040), preoperative biliary drainage (P = .005), and an ICG R15 over 10% (P = .030) were significant clinical risk factors in BDC patients. Histologic differentiation (P = .010), depth of tumor invasion (P = .005), lymph node involvement (P < .001), resected major portal vein invasion (P = .009), venous invasion (P = .039), and nervous system invasion (P = .004) were significant histopathological risk factors in BDC patients.

The 8 clinical and 12 histopathological risk factors possibly related to survival in CCC patients were analyzed by the log-rank test (Table 5). Serum CA 19-9 (P = .006), CEA level (P = .002), and red blood cell transfusion requirement (P < .001) were significant clinical risk factors in CCC patients. Macroscopic tumor type (P = .004), resected major portal vein invasion (P = .011), T-category (P = .001), lymph node involvement (P = .016), lymphatic system invasion (P = .014), venous invasion (P = .017), nervous system invasion (P = .036), presence of intrahepatic daughter nodules (P = .003), and cancer-positive proximal bile duct margin (P = .003) were significant histopathological risk factors in CCC patients.

Multivariate analysis using the Cox proportional hazard model identified the curative resection with cancer-free margin (R0) (P = .024, odds ratio 1.862), the histologic type (well differentiated or papillary adenocarcinoma) (P = .011, odds ratio 2.135), and the absence of lymph node involvement (P < .001, odds ratio 3.314) as independent factors that contributed to

TABLE 3. *Histopathological variables*

Variable		BDC (n = 99)	CCC (n = 59)	P value
Histologic differentiation	Well, papillary	36 (36%)	12 (20%)	.034
T-category	1, 2	40 (40)	26 (44)	
Lymph node metastasis	Present	47 (47)	36 (61)	
Invasion of the resected major portal vein	Present	26 (26)	31 (53)	.001
Invasion of the lymphatic system	Absent or slight	62 (63)	29 (49)	
Invasion of the venous system	Absent or slight	65 (66)	25 (42)	.004
Invasion of the nervous system	Absent or slight	32 (32)	18 (31)	
Histological stage	I, II	79 (80)	12 (20)	< .001
Proximal ductal margin	Positive	29 (29)	9 (15)	.046
Distal ductal margin	Positive	17 (17)	3 (5)	.028
Dissected periductal margin	Positive	13 (13)	10 (17)	
R0 resection	Achieved	58 (59)	43 (73)	

Percentage are described in parentheses.

prolonged survival in BDC patients. On the other hand, the absence of intrahepatic daughter nodules (P < .001, odds ratio 2.318), preoperative serum CEA level of 2.9 ng/mL or less (P = .005, odds ratio 2.606), red blood cell transfusion requirement (P = .016, odds ratio 2.614), absence or slight degree of lymphatic system invasion (P < .001, odds ratio 4.577), and cancer-negative proximal bile duct margin (P = .003, odds ratio 7.398) were identified as independent factors that contributed to prolonged survival in CCC patients (Table 6).

DISCUSSION

The clinical impact of differentiating between BDC and CCC has not been clarified. In this setting, our present study is the first large, single-center series that has addressed the prognostic factors for BDC and CCC separately. Nakeeb et al.[21] evaluated the surgical outcome of cholangiocarcinoma divided into three categories: intrahepatic, perihilar, and distal cholang iocarcinoma. Their classification appears to be reasonable with respect to the choice of surgical procedure: hepatectomy for intrahepatic cholangiocarcinoma, hepatobiliary resection for perihilar cholangiocarcinoma, and the Whipple procedure for distal cholangiocarcinoma. Although perihilar cholangiocarcinoma can be divided into BDC and CCC based on the anatomical origin of the tumor, a substantial number of reports have described the surgical outcome of hilar cholangiocarcinoma, which have likely included CCC patients. We previously reported the safety and short-term outcome of major hepatobiliary resection for perihilar cholangiocarcinoma.[14] In the present study, we performed a prognostic analysis of perihilar cholangiocarcinoma patients treated with major hepatobiliary resection to delineate the characteristics of long-term survivors and to assess the impact of differentiating between BDC and CCC.

The overall survival of BDC patients was significantly better than that of CCC patients (Fig. 1, P = .033). This difference is potentially caused by a different distribution of the pathological stages in this study; CCC patients had a higher proportion of stage III or IV disease (74.6%) than BDC patients (25.3%, P < .001). In fact, there was no significant difference in the overall survival between BDC and CCC patients with the same stage. However, the validity of using the UICC staging system based on the TNM classification of extrahepatic bile duct cancer for BDC and liver cancer for CCC to compare the two groups might be questioned. Many of the possible risk factors that were analyzed are similar for both BDC and CCC, though on univariate analysis, only a few factors were significant predictors for both. On multivariate analysis, no significant independent prognostic factors were common for both BDC and CCC. Thus, BDC and CCC appear to show independent biological behaviors. Therefore, differentiating between BDC and CCC would have an impact on our ability to predict postoperative survival based on their independent prognostic factors.

BDC is typically associated with thickness or irregularity of the bile duct wall with or without involvement of adjacent liver parenchyma or portal structures. CCC is frequently associated with tumor bulk with or without invasion to Glisson's capsule on imaging studies; both BDC and CCC may show intraductal tumor extension.[17] Tumor bulk might be related to the higher CEA and CA19-9 levels seen in CCC than in BDC. Nevertheless, precise preoperative differentiation between BDC and CCC using various diagnostic imaging studies or clinical manifestation is

TABLE 4. *Possible clinical and pathological risk factors for survival in BDC (univariate analysis)*

Factors	No. of patients	Survival rate (%) 3-year	5-year	Median survival (months)	*P* value
Overall	99	48.4	38.4	33.7	
Age (median: 64 years)					
≤64	50	56.7	41.6	47.6	
>64	49	39.6	35.6	29.3	
Gender					.040
Male	69	43.6	31	30.1	
Female	30	58.8	53.9	72.7	
Biliary drainage					.005
Not performed	22	80.7	68.7	72.7	
Performed	77	38.5	28.8	26.7	
ICG R15 (normal range; ≤10%)					.030
≤10	62	54.4	45.8	47.6	
>10	37	38.2	26.4	26.5	
CA19-9 (median: 101 U/mL)					
≤101	50	48.3	38.0	33.7	
>101	49	48.7	39.6	35.5	
CEA (median: 2.5 ng/mL)					
≤2.5	53	41.5	27.8	26.7	
>2.5	46	55.8	51.9	66.4	
With PD					
Yes	10	41.1	41.1	32	
No	89	49.1	38.3	35.5	
With VR					
Yes	24	41.9	35.9	28.3	
No	75	50.4	39.1	37.2	
Red blood cell transfusion					
Performed	34	39.2	31.4	28.3	
Not performed	65	54	43	44.3	
Macroscopic type of the tumor					
Polypoid	9	63.5	47.6	45.5	
Nodular or infiltrative	90	47.0	37.7	32.0	
Histologic differentiation					
Well or papillary	36	60.0	56.3	83.0	.010
Others	63	42.0	25.9	26.5	
Depth of tumor invasion					
Mucosal, fibromuscle layer	8	100.0	100.0	N.A.	.005
Subserosal or more	91	43.8	33.7	29.3	
T category					
1, 2	40	59.6	59.6	83.0	
3, 4	59	41.1	25.0	29.1	
Lymph node involvement					<.001
Negative	52	67.3	58.4	75.2	
Positive	47	27.7	15.9	23.1	
Invasion of the resected portal vein					.009
Absent	73	55.7	51.1	66.4	
Present	26	30.8	13.2	23.5	
Invasion of the lymphatic system					
Absent or slight	62	54.4	46.6	45.5	
Moderate to marked	37	38.8	25.9	29.3	
Invasion of the venous system					.039
Absent or slight	65	57.4	46.0	47.6	
Moderate to marked	34	31.2	23.4	25.2	
Invasion of the nervous system					.004
Absent or slight	32	70.5	60.6	127.7	
Moderate to marked	67	38.2	28.3	26.0	
Proximal ductal margin					
Negative	70	54.1	41.1	45.5	
Positive	29	32.6	32.6	25.2	
R0 resection					
Achieved	58	57.2	44.4	45.5	
Not achieved	41	35.1	30.1	29.9	

ICGR15 indicates indocyanine green retention value at 15 minutes; CA19-9, carbohydrate antigen 19-9; CEA, carcinoembrionic antigen; PD, pancreatoduodenectomy; VR, vascular (hepatic artery, portal vein or inferior vena cava) resection and reconstruction; N.A., not available.