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Comparison of the Clinicopathological Features in Small Bile Duct and Bile Ductular Type Intrahepatic Cholangiocarcinoma

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Abstract. *Background: The classification of intrahepatic cholangiocarcinomas (ICCs) has been reported in several studies, however, it remains controversial. Materials and Methods: Between January 2003 and December 2015, 94 patients underwent hepatectomy for ICC. The ICCs of 63 of these patients were classified as predominantly small bile duct type or bile ductular type ICC and were included in this analysis. Results: Thirty-seven patients (58.7%) were classified into the small bile duct ICC group, and 26 (41.3%) into the bile ductular ICC group. A multivariate analysis identified intrahepatic metastasis [hazard ratio (HR)=2.53, p=0.011], small bile duct ICC (HR=2.05, p=0.046) and portal vein invasion (HR 2.05, p=0.047) as independent prognostic factors for poorer survival. Conclusion: It is important to correctly distinguish between small bile duct and bile ductular ICC types because these two types clearly have different clinicopathological and prognostic features.*

Intrahepatic cholangiocarcinoma (ICC) is anatomically divided into the perihilar type, which generally evolves from the intrahepatic large bile duct, and the peripheral type, which generally evolves from the small bile duct. The large bile ducts are grossly visible and consist of the first to third branches of right or left hepatic bile ducts. The small bile ducts are microscopically recognizable and consist of septal and interlobular bile ducts. The interlobular bile ducts are connected to bile ductules (1). The nature of the tumors is reported to be different between the perihilar type and the peripheral type (2). The peripheral type is associated with the presence of chronic hepatitis virus infection and liver cirrhosis (3, 4), whereas patients with the perihilar type sometimes show biliary intraepithelial neoplasia and often develop lymph node metastasis and have a poorer prognosis (5). The different origins of ICC in the biliary duct may be related to different routes of cholangiocarcinogenesis and mechanisms of disease progression (2, 4).

Regarding histopathological features, Nakanuma *et al.* divided ICCs into the conventional type, bile ductular type, and rare variants (6, 7). The conventional type is pathologically further divided into the small bile duct type (peripheral type) and large bile duct type (perihilar type). On the other hand, the small bile duct type and bile ductular type were anatomically categorized to the peripheral ICC, in contrast to the large bile duct type, which was anatomically categorized to the perihilar type (2) (Figure 1).

The small bile duct type was considered to have the nature of conventional ICC, such as tubular and micropapillary carcinoma with desmoplastic variation and this may have different features from the bile ductular type characterized by bile ductular features with slit-like lumen. However, the differentiation of the clinicopathological features between small bile duct and bile ductular type ICC, which were anatomically categorized as the same peripheral type, has not been well defined.

We reported that hypervascular ICC has a less invasive nature and is associated with the presence of bile ductular type ICC (4, 5, 8). In the present study, we focused on the differentiation of the clinicopathological features and prognosis of small bile duct type and bile ductular type ICC.

Materials and Methods

Patients. Between January 2003 and December 2015, 94 patients underwent hepatectomy for primary ICC at the Division of Hepato-Biliary-Pancreatic Surgery, Shizuoka Cancer Center, Shizuoka, Japan. Among these 94 patients, 77 with predominantly mass-forming (MF) type disease were divided into conventional ductal carcinoma (small bile duct type and large bile duct type), bile

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ductular type, intraductal neoplasm and rare variants, which Nakanuma *et al*. proposed as the classifications of ICCs (7). Among these patients, 63 whose tumors were classified as predominantly small bile duct type or bile ductular type ICC were studied in the analysis. The Shizuoka Cancer Center Institutional Review Board approved the retrospective collection and the analysis of the data in this study (approval number 29-J16-29-1-3).

Surgical procedures. When the tumor involved the perihilar bile duct, hemihepatectomy or trisectionectomy with *en bloc* resection of the caudate lobe and extrahepatic bile duct with regional lymph node dissection was performed. Hemihepatectomy or more extended resection was defined as major hepatectomy, and hepatic resection, which was limited to fewer than two sections was defined as minor hepatectomy. The tumour-node-metastasis stage was defined based on the eighth edition of the American Joint Committee on Cancer/International Union Against Cancer staging system (9).

Pathological examination. All of the resected specimens were fixed in 10% neutral buffered formalin, embedded in paraffin, and subjected to hematoxylin and eosin, periodic acid Schiff after diastase digestion, Elastica van Gieson, and Azan–Mallory staining. Immunohistochemical staining of S100 calcium-binding protein P (S100P) and neural cell adhesion molecule (NCAM) was also performed on paraffin-embedded sections. Primary antibodies used in this study were rabbit monoclonal anti-S100P (1:100 dilution; Abcam, Cambridge, MA, USA) and mouse monoclonal anti-NCAM (1:100 dilution; Leica, Newcastle Upon Tyne, UK). After deparaffinization by xylene and rehydration with ethanol, antigen retrieval was performed by boiling in citrate buffer (pH 6.0) at 121˚C for 10 min and the sections were treated with 0.3% hydrogen peroxide in methanol at room temperature for 20 min to inactivate the endogenous peroxidase. The sections were incubated at room temperature for 30 min with a primary antibody. The EnVision+ system (DAKO, Glostrup, Denmark) was used for secondary antibody detection and color development with diaminobenzidine tetrahydrochloride at room temperature for 30 min.

The expression levels of NCAM and S100P were subjectively graded as negative, focal (1-10%) and moderate to strong (≥11%). That of S100P was classified into the following two groups according to the distribution of positive cells in the tumor: negative group (<10%) and positive group (≥10%).

The pathological diagnosis and morphological classification were made using hematoxylin and eosin-stained sections; immunohistochemistry was performed adjunctively. All resected specimens were reviewed by two pathologists (YN and YK), who investigated the macroscopic type of the neoplasms based on the Classification of Primary Liver Cancer (Liver Cancer Study Group of Japan) (10) and classified pathologically into conventional ductal carcinoma (small bile duct type and large bile duct type), bile ductular type ICC, intraductal neoplasm and rare variants. Grossly, small bile duct type ICC is of the MF type. Regarding histological features, variable sized tubular or acinar adenocarcinoma with variable desmoplastic and inflammatory reactions exhibits nodular growth and invades the parenchyma with a replacing or compressive pattern. Large bile duct type ICC grossly belongs to the periductal infiltrating (PI) type and PI with MF type. Cancerous large bile duct exhibits luminal spread of carcinoma with papillary, micropapillary and flat configurations along the affected lumen, and variable invasion of carcinoma cells with a tubular, acinar or micropapillary configuration into the duct wall and surrounding parenchyma. On the other hand, bile ductular type ICC grossly belongs to the MF type, with histological features including that the adenocarcinoma cells exhibit well-differentiated, cord-like or ductular structures with a slit-like lumen and arborization. The size of carcinoma cells is usually small in comparison to conventional ICC (6, 7) (Figure 2).

Follow-up after surgery. A physical examination and blood tests, including tumor markers, were performed every 3-6 months after surgery. Computed tomography was performed at least twice per year for the first 5 years.

Statistical analysis. Continuous data are expressed as the median (range), unless otherwise specified. The Mann–Whitney *U*-test was used for the analysis of continuous variables and Fisher's exact probability test for the analysis of categorical variables. Survival time was determined from the time of surgery to the time of the last follow-up examination. Postoperative survival was calculated using the Kaplan–Meier method, and differences in the survival curves were compared using the log-rank test. Prognostic factors for survival were identified using a multivariate Cox proportional hazards model. All tests were two-sided, and *p*-values of less than 0.05 were considered to indicate statistical significance. All statistical calculations were performed using a freely available software program (EZR version 1.36) (11).

Results

The study population included 63 patients [male, n=24; female, n=39; median age (range)=68 (46-83) years; median tumor size (range)=53 (11-150) mm]. Major hepatectomy was performed in 44 cases (69.8%), and lymph node dissection was performed in 45 cases (71.4%). The cumulative 5-year overall survival and median survival time were 37.8% and 35.2 months, respectively.

The 63 patients were classified into 37 with predominantly small bile duct type (small bile duct group), and 26 patients with predominantly bile ductular type (bile ductular group). The small bile duct group included patients with foci of coexisting bile ductular type ICC (n=5), coexisting large bile duct type ICC (n=3), and coexisting micropapillary components (n=4). The bile ductular group included patients with foci of coexisting small bile duct type ICC (n=6) and a patient with foci of other types of ICC (n=1).

The preoperative and operative parameters of the 37 patients in the small bile duct group and the 26 patients in the bile ductular group are summarized in Table I. There were no significant differences in the preoperative and operative parameters of the two groups, including hepatic virus infection status, tumor markers, rate of major hepatectomy, vessel resection and bile duct resection.

The pathological features of the 63 patients were summarized in Table II. There were no significant differences in tumor size, macroscopic type, rate of perineural invasion or the rate of NCAM positivity between the two groups. The rate of S100P positivity, and the rates

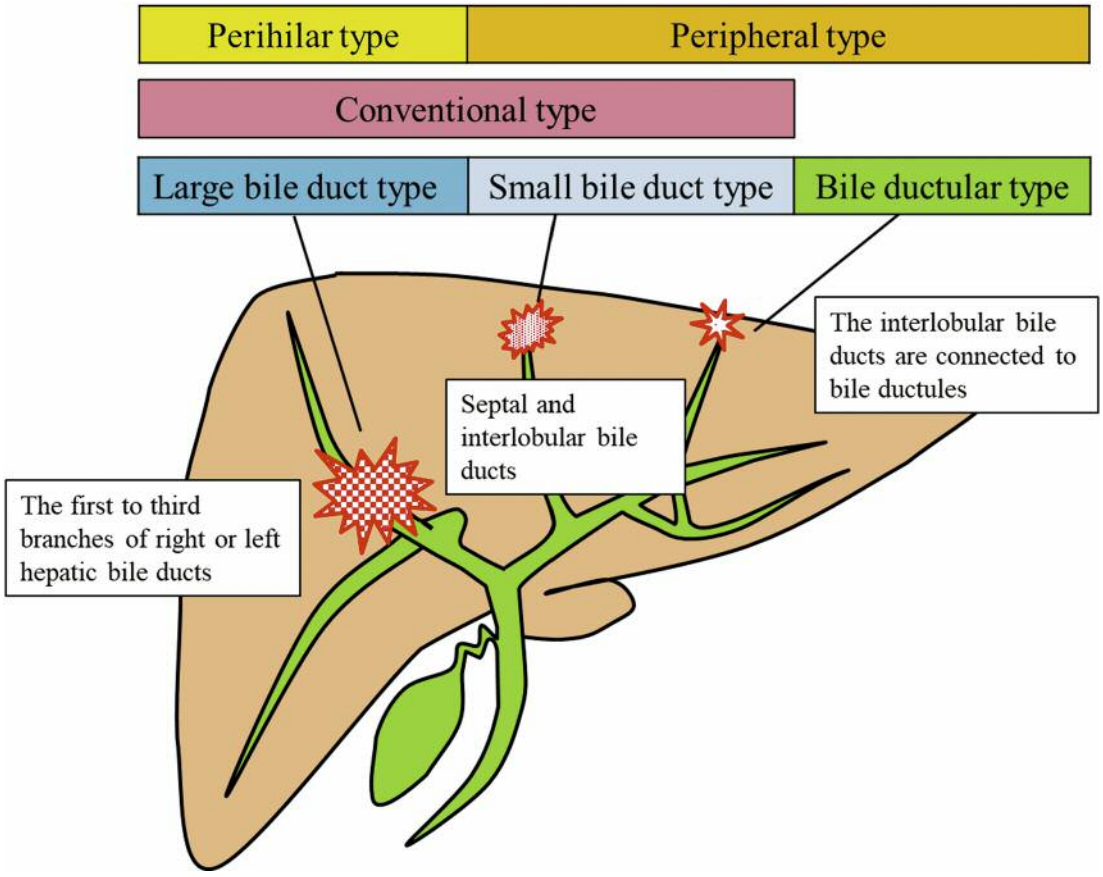

Figure 1. *Anatomical and pathological classification of intrahepatic cholangiocarcinoma.*

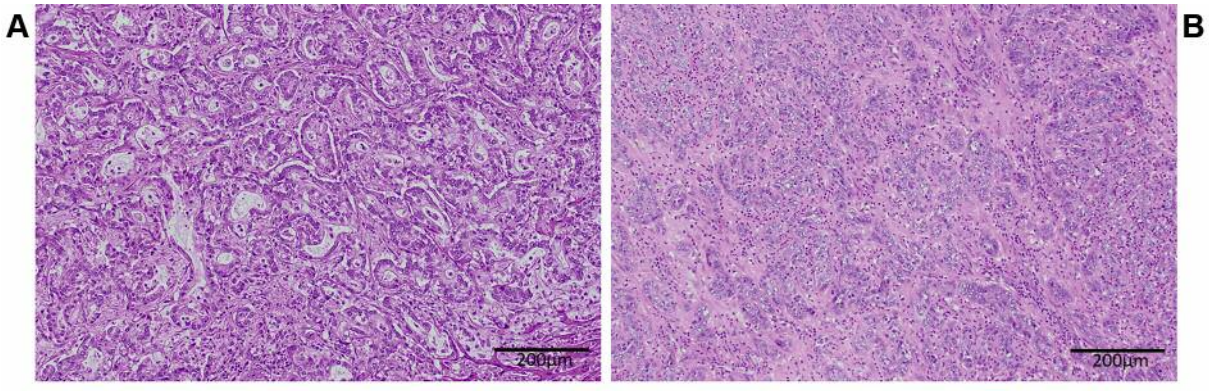

Figure 2. *A: Small bile duct type intrahepatic cholangiocarcinoma (ICC). B: Bile ductular type ICC (hematoxylin-eosin staining).*

of lymphatic invasion, vascular invasion and mucin secretion in the small bile duct group were significantly higher than those in the bile ductular group. The rate of background fibrosis in the small bile duct group was significantly lower than those in the bile ductular group. Survival after surgery was significantly better in the 26 patients of the bile ductular group than the 37 patients of the small bile duct group (48.2% *vs*. 31.0% at 5 years, p=0.018) (Figure 3A). Disease

Table I. *Clinical features of intrahepatic cholangiocarcinoma.*

Characteristic		Small bile duct group n=37)	Bile ductular group n=26)	*p*-Value
Age, years	Median (range)	66 (51-81)	69.5 (46-83)	0.929
Gender, n (%)	Male	14 (37.8)	10 (38.5)	>0.99
Hepatitis B surface antigen, n (%)	Positive	5 (13.5)	5 (19.2)	0.728
Hepatitis C antibody, n (%)	Positive	2 (5.4)	2 (7.7)	>0.99
BMI, kg/m^2	Median (range)	20.9 (14.6-29.6)	20.4 (13.7-26.0)	0.078
CEA, ng/ml	Median (range)	3.7 (1.2-640)	2.4 (0.6-42.4)	0.150
CA19-9, U/ml	Median (range)	62.0 (2.0-190,714)	39.5 (8.0-12,010)	0.391
Diabetes mellitus, n (%)	Yes	10 (27.0)	5 (19.2)	0.558
Operation time, min	Median (range)	495 (124-984)	451 (76-744)	0.522
Type of hepatectomy, n (%)	Major	27 (73.0)	17 (65.4)	0.558
Lymph node dissection, n (%)	Yes	29 (78.4)	16 (61.5)	0.167
Bile duct resection, n (%)	Yes	17 (46.0)	10 (38.5)	0.612
Hepatic artery resection, n (%)	Yes	3 (8.1)	0 (0)	0.261
Portal vein resection, n (%)	Yes	3 (8.1)	2 (7.7)	>0.99

BMI: Body mass index; CEA: carcinoembryonic antigen; CA19-9: carbohydrate antigen 19-9.

Table II. *Clinicopathological features of intrahepatic cholangiocarcinoma.*

Characteristic		Small bile duct group n=37)	Bile ductular group n=26)	*p*-Value
Tumor size, mm	Median (range)	55 (21-150)	52 (11-110)	0.763
Operative margin	Positive	4 (10.8)	1 (3.8)	0.394
Macroscopic findings, n (%)	MF or MF+IG	28 (75.7)	24 (92.3)	0.105
Intrahepatic metastases, n (%)	Yes	11 (29.7)	9 (34.6)	0.785
Lymph node metastases, n (%)	Yes	12 (32.4)	4 (15.4)	0.152
Lymphatic invasion, n (%)	Yes	20 (54.1)	5 (19.2)	0.003
Hepatic arterial invasion, n (%)	Yes	2 (5.4)	0 (0)	0.507
Portal vein invasion, n (%)	Yes	17 (45.9)	5 (19.2)	0.035
Hepatic vein invasion, n (%)	Yes	17 (45.9)	1 (3.8)	<0.001
Background fibrosis, n (%)	Yes	5 (13.5)	11 (42.3)	0.017
Mucin secretion, n (%)*	Excessive	20 (60.6)	6 (24.0)	0.008
NCAM immunostaining, n (%)*	Yes	14 (37.8)	14 (56.0)	0.427
S100P, n (%)*	Yes	19 (57.6)	4 (15.4)	0.002

MF: Mass-forming; IG: intraductal growth; NCAM: neural cell adhesion molecule; S100P: S100 calcium-binding protein P. *Analyzed in 58 patients.

free survival in the bile ductular group was also significantly better than that in the small bile duct group (48.8% *vs.* 31.2% at 5 years, p=0.043) (Figure 3B). Survival analyses were performed to identify prognostic factors for the 63 patients (Table III). A multivariate analysis identified intrahepatic metastasis [hazard ratio (HR)=2.53, p=0.011)], small bile duct group ICC (HR=2.05, p=0.046) and portal vein invasion (HR=2.05, p=0.047) as independent prognostic factors for survival after surgery.

Discussion

ICCs have been classified by the analysis of clinicopathological, immunohistochemical, and molecular features in several recent reports (6, 7, 12-14). Komuta *et al.* classified ICCs as mucin-producing ICC, cholangiocellular carcinoma and mixed ICC, according to the combination of and predominance of the hepatocyte differentiation area, the ductular area and mucin producing CC (13). Aishima *et al.* classified ICCs into two types: perihilar large duct-type ICC, and peripheral small duct-type ICC, arising from small bile duct type ICC or ductular type ICC (14). Additionally, in contrast to the classifications of Nakanuma and Komuta, they reported that peripheral small duct type ICC was similar to small bile duct type ICC, bile ductular type ICC, mixed ICC and CLC. Hayashi *et al.* classified ICCs into type 1 and type 2, based on the combination of mucin productivity and immunophenotype (S100P, N-cadherin and NCAM) (12).

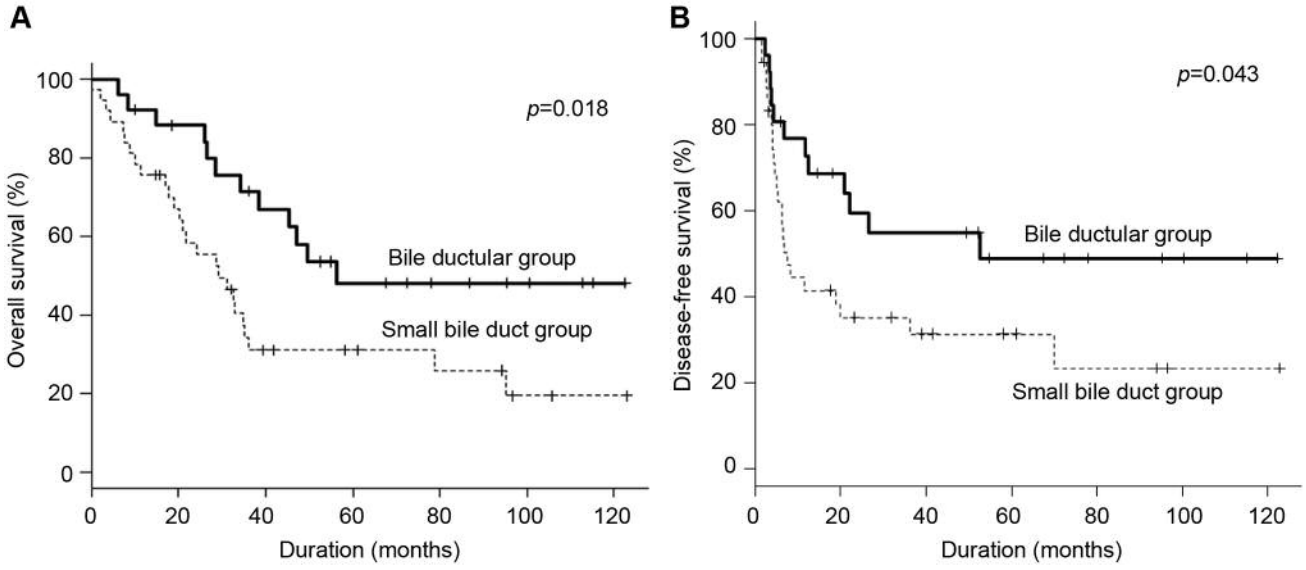

Figure 3. *Kaplan–Meier curves for overall (A) and disease-free (B) survival of the small bile duct and bile ductular groups.*

Applying Nakanuma's classification to these cases, type 2 corresponded to a fraction of the small bile duct type and bile ductular type cases.

Taken together, ICCs were anatomically classified into perihilar type ICC and peripheral type ICC (1). Moreover, peripheral type ICC includes two types: small bile duct type, which was thought to arise from septal or intralobular bile ducts, and bile ductular type, which was thought to arise from the bile ductules or proliferating reactive bile ductules. Although previous studies have used various rules to classify ICCs, the differences between small bile duct type and bile ductular type have not been well characterized. In the present study, these two types of ICC had different clinicopathological features, and overall survival for the small bile duct group was significantly worse than that for the bile ductular group. Lymphatic invasion, portal vein invasion and hepatic vein invasion were observed in the small bile duct group significantly more frequently than in the bile ductular group. Considering these features of anatomically peripheral ICC, the nature of small bile duct type tumors, which were generally classified as conventional ICC, was obviously different from that of bile ductular type tumors. Thus, it is important to correctly distinguish small bile duct type ICC and bile ductular type ICC because these two types obviously have different features. As far as we are aware, this is the first report to compare the survival of small bile duct type ICC to bile ductular type ICC.

Tsai *et al*. showed that the immunohistochemical expression of S100P identified a subset of peripheral ICC that probably originated from the larger bile duct, and that this subset of peripheral ICCs shared common morphological and molecular features with perihilar and extrahepatic cholangiocarcinoma (15). Although the present analysis only included small bile duct and bile ductular types, the overexpression of S100P was observed in a total of 23 patients (55.8%): 19 (57.5%) in the small bile duct group, and four (16%) in the bile ductular group. The rate of S100P positivity in the small bile duct group was significantly higher than that in the bile ductular group. S100P is a marker of large bile duct type ICC. The results suggest that small bile duct type ICC might have the features of conventional types of ICC, which are different from bile ductular type ICC. Thus, S100P staining will help in classifying anatomically peripheral ICC into small bile duct type and bile ductular type.

On the other hand, NCAM, a marker of hepatic progenitor cells, is characteristically detected on the cell membranes and cytoplasm of bile ductular type cells (7). In the present study, 14 patients (56.0%) in the bile ductular group were positive for NCAM; however, the rate of NCAM positivity did not differ between the two groups. In this study, a large number of patients had overlapping subtypes of ICC. Actually, this group included cases of mixed-type ICC (*e.g.* the coexistence of small bile duct type ICC and another type of ICC). The overlapping subtypes in ICCs may be one of the reasons for the lack of a significant differences in the rate of NCAM positivity between the two groups.

The present study is associated with several limitations, including its retrospective nature, the small number of patients, and the fact that it was performed at a single center. The number of patients with ICC, especially bile ductular type ICC, was limited. Further examinations, including histological, immunohistochemical and molecular analyses, should be performed at multiple centers.

Table III. *Univariate and multivariate survival analyses for intrahepatic cholangiocarcinoma.*

				Univariate	Multivariate	
	n	OS (%)	MST (months)	*p*-Value	HR (95% CI)	*p*-Value
Age						
≤70 Years	36	46.9	56.2	0.129		
>70 Years	27	26.0	32.7			
Tumor size						
≤50 mm	27	41.8	38.3	0.527		
>50 mm	36	34.7	34.9			
Intrahepatic metastases						
Present	20	6.7	28.3	0.001	2.53 (1.23-5.21)	0.011
Absent	43	51.7	78.7		1	
Morphology						
Small bile duct group	37	31.0	29.1	0.018	2.05 (1.01-4.17)	0.046
Bile ductular group	26	48.2	56.2		1	
Lymph node metastases						
Present	16	12.5	23.0	0.002	1.55 (0.73-3.28)	0.255
Absent	47	47.1	56.2		1	
Arterial invasion						
Present	2	NA	34.4	0.544		
Absent	61	39.3	35.1			
Portal vein invasion						
Present	22	15.4	25.9	<0.001	2.05 (1.01-4.15)	0.047
Absent	41	48.0	56.2		1	
Hepatic vein invasion						
Present	18	26.7	29.1	0.084		
Absent	45	42.5	46.9			

OS: Cumulative 5-year overall survival; MST: median survival time; HR: hazard ratio; CI: confidence interval.

Conclusion

Clinicopathological and prognostic differences were observed between small bile duct type ICC and bile ductular type ICC. The classification of peripheral ICC into these subtypes was clinically feasible.

Conflicts of Interest

The Authors declare no financial or any other type of support.

Authors' Contributions

Designed studies: MY, YY, and TS; Performed assays: MY, YY, YK, ST and YN; Analyzed data: MY and YY; Wrote article: MY and YY; Reviewed article: All Authors.

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