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Effects of microvascular invasion on clinical outcomes after resection with curative intent for cholangiocarcinoma

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Abstract

Surgery is the only curative treatment for cholangiocarcinoma, but even after surgery, survival rates are unsatisfactory. Recently, several reports have suggested microvascular invasion (MiVi) is associated with poor postoperative prognosis in hepatocellular carcinoma (HCC). We considered that MiVi might be associated with poor clinical outcomes in patients with surgically resectable cholangiocarcinoma.

The records of 91 patients who underwent resection with curative intent for cholangiocarcinoma at Inha University Hospital from 2007 to 2017 were comprehensively reviewed for clinicopathological characteristics, DFS, and overall survival (OS) relations between these factors and the presence of MiVi.

Forty-nine of the 91 study subjects had MiVi and 42 did not. Median overall survivals were 492 days in the MiVi group and 1008 days in the noMiVi group and median DFSs were 367 days and 760 days, respectively. Cumulative survival ratio and recurrence incidence rates were significantly different in the 2 groups ($P = .012$). Multivariable analysis showed the presence of MiVi was an independent risk factor of OS (hazard ratio [HR] 3.34; 95% confidence interval [CI], 1.40–7.97; $P = .007$).

Cholangiocarcinoma is known to have a poor prognosis. When microvascular invasion remains after surgery it is associated with poor clinical outcomes.

Abbreviations: DFS = disease-free survival, HCC = hepatocellular carcinoma, ICC = intrahepatic cholangiocarcinoma, MaVi = macrovascular invasion, MiVi = microvascular invasion, OS = overall survival.

Keywords: cholangiocarcinoma, curative intended surgery, microvascular invasion, prognosis, prognostic factor

1. Introduction

Cholangiocarcinoma is classified by anatomical location as perihilar, distal extrahepatic, and intrahepatic tumor of bile ducts. Approximately, half of cholangiocarcinoma patients present with the perihilar type, and 40% and 10% with the distal extrahepatic and intrahepatic types, respectively. Surgical treatment is the preferred option for all types, but fewer than one-third of patients are resectable at diagnosis.[1] Reported 5-year survival rates of the perihilar, distal extrahepatic, and intrahepatic types are 11% to 41%, 27% to 37%, and 22% to 44%, respectively.[2] Surgical extent depends on the tumor site and anatomical involvement. Major hepatectomy is needed for perihilar cholangiocarcinoma and pancreaticoduodenectomy is performed for complete resection of distal cholangiocarcinoma.[3] Intrahepatic cholangiocarcinoma (ICC) is treated by segmentectomy or hepatic lobectomy depending on tumor size and location.[4]

Known prognostic factors after surgery include local clearance (R0 no residual tumor or R1 microscopic residual tumor), lymph node metastasis, primary tumor size, and vascular invasion.[5,6] Reported 5-year survivals after R0 resection are perihilar (30%), distal extrahepatic (27%), and intrahepatic (63%). However, negative tumor margins are achieved in <30% of patients,[7] and the high incidence of recurrence after surgery is a major concern. Cholangiocarcinoma differs from hepatocellular carcinoma (HCC). HCC is rarely associated with lymphatic invasion, whereas cholangiocarcinoma commonly spreads through the lymphatic system, which is a major prognostic factor after surgery. Some authors have recommended lymphadenectomy during ICC resection, but data supporting its prophylactic effect are insufficient.[8] Primary tumor size-associated prognostic differences are reflected by the 8th UICC/AJCC TNM staging system, which is based on a tumor size cut-off of 5 cm. Vascular invasion represents an advanced phase of cancer progression and involves macrovascular and microvascular invasion. Prognostic

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differences are mentioned in the TNM staging system, but the definitions of the terms used are somewhat unclear.[9] macrovascular invasion (MaVi) is defined as tumor invasion of a major vessel as determined by macroscopic examination or radiological imaging, but microvascular is not clearly defined, although some features such as the presence of tumor emboli in a portal radicle vein, a large capsule vessel, or a vascular space lined by endothelial cells have been mentioned.[10] Microvascular invasion (MiVi) has been reported to predict poorer outcomes among patients with HCC after resection or liver transplantation.[11,12] Based on consideration of the pathogenesis of angioinvasion, we hypothesized MiVi probably affects clinical outcomes among cholangiocarcinoma patients that undergo curative resection.

2. Patients and methods

2.1. Patients

Patients with symptomatic or accidentally discovered laboratory/imaging abnormalities underwent further evaluation. Cholangiocarcinoma are basically included chest and abdominal CT, laboratory tests which including liver function test and tumor marker (CA 19–9, CEA). Some people need to further work up such as esophagoduodenoscopy, EUS, endoscopic retrograde cholangiopancreaticography (ERCP), and magnetic resonance imaging (MRI). Depending on the location of the lesion and the extent of involvement, surgical resection could consider primary treatment. If resection is impossible or metastatic, chemotherapy and radiation therapy are considered.

A retrospective review of all medical records including imaging, pathologic reports, and laboratory results was performed between 2007 and 2017. A total of 128 patients were diagnosed and underwent surgery with curative intent for cholangiocarcinoma at the Inha University School of Medicine. All patients were pathologically confirmed, but only patients that achieved curative resection (R0 or R1 resection) were included in the study. The patient exclusion criteria applied were as follows: receipt of palliative surgery or open/closed surgery due to an advanced stage, death due to a postoperative complication (eg, hepatic failure or infection), HCC as determined by postoperative biopsy, or a double primary cancer. Patient underwent surgical treatment based on staging according to standard medical guidelines. Of the 128 patients, 91 met these criteria in this study. This study is a retrospective analytical study using medical records. The consent was exempted from the consent of the subjects because the risk to the subjects was very low, and no personally identifiable information was collected. The study protocol was approved under the approval of the institutional review board of Inha university hospital. (Approval No 2019-11-031)

2.2. Data collection

Preoperative evaluation included imaging (ultrasonography, computed tomography [CT], ERCP, magnetic resonance cholangio-pancreatography, and positron emission tomography-CT) to evaluate primary tumor extension. All resected tumors were evaluated for size, number, histologic type, differentiation, adjacent organ invasion, and margin vascular, perineural invasion, and lymph node statuses. MaVi was defined as the presence of vessel invasion by gross examination and MiVi as tumor invasion of hepatic veins, the portal system or lymphatic ducts visible only by microscopy.[12] Surgical resection margins were classified by a pathologist as R0 resection (defined as the complete absence of cancer cells as determined microscopically) or R1 resection (defined as a microscopically positive margin).

After discharge, all patients underwent regular laboratory tests, which including CA 19-9 and hepatic function tests, and routine imaging by CT and/or MRI. Recurrence was diagnosed based on suspicious imaging findings or histological confirmation.

Surgical re-resection, chemotherapy, radiotherapy, and chemoradiation were considered when a positive resection margin or recurrence after surgery was detected based on considerations of tumor burden and general patient condition.

Overall survival (OS) was defined time between date of diagnosis to death, and disease-free survival (DFS) was defined as time between date of diagnosis and tumor recurrence.

2.3. Statistical analysis

The student *t* test was to determine the significances of differences between the MiVi and non-MiVi groups. Survival curves were constructed using the Kaplan-Meyer method, and survival curve differences were analyzed using the univariate log-rank test. Multivariate analysis was conducted using a Cox proportional hazards model to identify factors associated with OS or DFS. To confirm the proportional risk assumption, all significant factors determined by univariate analysis putting one risk factor into the Cox proportional risk model, and then entered into a multivariate analysis using the Cox proportional hazard regression model. Factors found to be related to OS and DFS with p values between 0.05 and 0.2 were entered into the multivariate analysis. Hazard ratios and 95% confidence intervals were estimated, and statistical significance was accepted for P values $< .05$. The analysis was performed using SPSS version 19.0 (IBM SPSS Inc, Chicago, IL)

3. Results

3.1. Baseline characteristics

One hundred and twenty-eight patients underwent curative surgery for cholangiocarcinoma from 2007 to 2017 at the authors' institute. Patients were confirmed not have: retropancreatic or paraceliac nodal metastases or distant liver metastases, invasion of the main hepatic artery, extrahepatic adjacent organ invasion, or disseminated disease before surgery by preoperative imaging.[13] Thirty-seven patients were excluded for the following reasons: 12 were switched to a palliative operation, 8 underwent open/closure, 9 succumbed to a postoperative complication, and 8 were excluded based on pathologic findings (4 were diagnosed with HCC, 1 patient had colon cancer and liver metastasis, 1 patient had double primary cancer, and 2 patients had no pathologic report) (Fig. 1).

Accordingly, 91 patients who underwent curative-intent resection for cholangiocarcinoma constituted the study cohort. Forty-nine (53.8%) had MiVi (53.8%). Average study subject age was 62 years and males accounted for 63%~64%. No significant intergroup difference was observed between blood liver functions or tumor marker (CA 19-9, alpha fetoprotein) levels. However, pathological characteristics after surgery differed significantly. The percentage of moderate to poorly differentiated cancers was higher in the MiVi group (NoMiVi: WD 35.7%, MD 42.8%, PD 11.9%/ MiVi: WD 10.2%, MD 40.8%, PD 42.8%) ($P = .002$), the R0 resection rate was lower in the MiVi group (NoMivi 42.9%, MiVi 10.2%, $P < .001$), and the lymphatic invasion rate was higher (NoMiVi 4.7%, MiVi 63.2%, $P < .001$). Tumors were also more

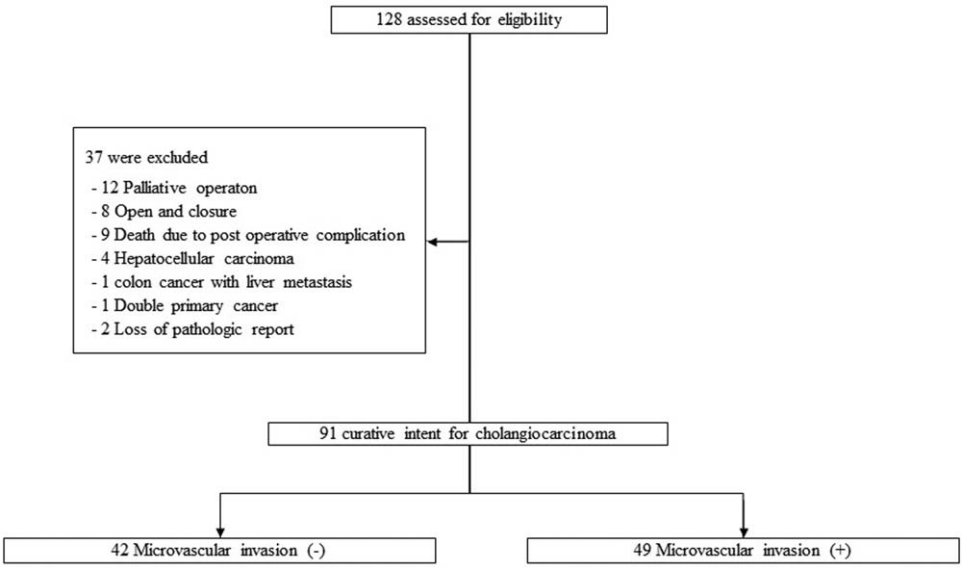

Figure 1. The diagram of the study depicting patient selection and enrollment.

invasive in the MiVi group ($P<.001$), and for this reason, a greater percentage of patients received adjuvant chemotherapy (NoMiVi 59.5%, MiVi 83.7%, $P=.006$) and radiotherapy (NoMiVi 26.2%, MiVi 46.9%, $P=.015$) after surgery. Furthermore, mean DFS and OS were significantly shorter in the MiVi group (DFS: NoMiVi 760 days, MiVi 367 days/OS: NoMiVi 1008 days, MiVi 492 days) (Table 1).

3.2. DFS and OS of patients

A comparison of cumulative incidences of death and recurrence survival curves showed MiVi was associated with significantly poorer prognoses (Fig. 2A and B, $P=.012$).

Univariate analysis showed lymphatic invasion and MiVi significantly influenced OS and DFS, but multivariable analysis

Table 1

Baseline characteristics.

	No vascular invasion (n=42)	Microvascular invasion (n=49)	*P*
Age, y	62.3 (55–66)	62.1 (58–65)	.92
Male sex	64.2% (n=27)	63.2% (n=31)	.89
CA 19–9, U/mL	166.5 (45.5–337.2)	228.1 (80.7–534.9)	.47
AFP, ng/mL	3.5	1444.6	.34
AST, U/L	134.2 (74–155)	135.1 (72–149)	.97
ALT, U/L	20.6 (55–167)	20.4 (90–186)	.84
ALP, U/L	489.9 (283–677)	746.6 (140–1114)	.13
Histologic type			.01
Adenocarcinoma			
Well-differentiated	35.7% (n=15)	10.2% (n=5)	
Moderately differentiated	42.8% (n=18)	40.8% (n=20)	
Poor differentiated	11.9% (n=5)	42.8% (n=21)	
Others	9.5% (n=4)	6.1% (n=3)	
R0 resection	42.9% (n=18)	10.2% (n=5)	<.01
Lymphatic invasion	4.7% (n=2)	63.2% (n=31)	<.01
Perineural invasion	47.6% (n=20)	48.9% (n=24)	.92
AJCC T stage			<.01
T1	50% (n=21)	4.08% (n=2)	
T2	33.3% (n=14)	59.2% (n=29)	
T3	9.5% (n=4)	28.6% (n=14)	
T4	4.7% (n=2)	8.1% (n=4)	
Missing	2.3% (n=1)		
Total bilirubin	3.4 (1.3–8.4)	4.6 (1.8–5.5)	.24
Adjuvant chemotherapy	59.5% (n=25)	83.7% (n=41)	.01
Adjuvant radiotherapy	26.2% (n=11)	46.9% (n=23)	.01
DFS, days	760.4 (460–1060)	367.9 (212–523)	.02
OS, days	1008.0 (607–1408)	492.4 (371–613)	.03

AFP=alpha fetoprotein, AJCC=American Joint Committee on Cancer, ALP=alkaline phosphatase, ALT=alanine aminotransferase, AST=aspartate aminotransferase, CA=cancer, DFS=disease free survival, n=number, OS=overall survival, P=probability, R=residual tumor, T=tumor.

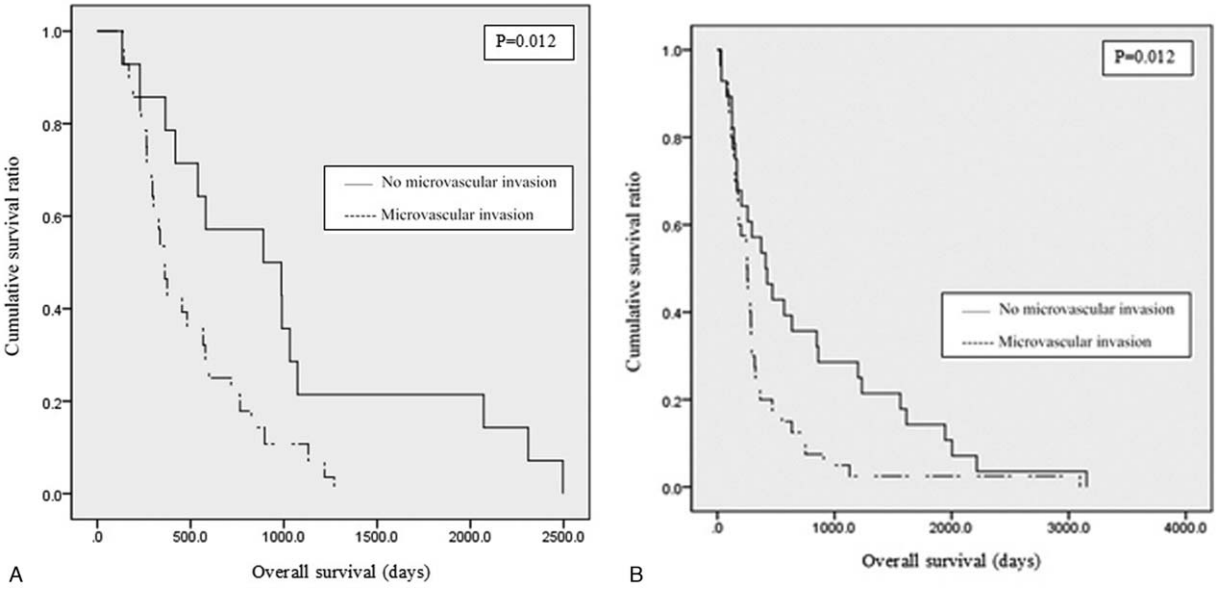

Figure 2. Kaplan-Meier curve comparing overall survival (A) and disease-free survival (B) of microvascular invasion in patients who underwent surgery with curative intent for cholangiocarcinoma.

showed only MiVi significantly and independently predicted OS ($P = .007$) (Tables 2 and 3).

3.3. Follow up results

During the 11-year study period, 41 patients died, 6 were referred for hospice care, and 25 patients were lost to follow-up. Nineteen patients remained alive at the time of writing. Twelve patients survived for >5 years after diagnosis. Cholangiocarcinoma locations were: 6 intrahepatic, 5 extrahepatic, and 1 perihilar area; and degrees of tissue differentiation were: 6 well-differentiated, 4 moderately differentiated, and 2 poorly differentiated. Postoperative resection margins were R0 in 8 and R1 in 4. Only 1 patient with MiVi survived for >5 years (Table 4). Three of the 12 patients that survived for >5 years experienced recurrence. A 69-year-old man[4] currently under hospice care had peritoneal seeding at time of relapse. A 68-year-old woman[9] underwent re-operation (pylorus-preserving pancreaticoduodenectomy) due to recurrence and did not develop further recurrence over 2 years and 4 months of subsequent follow-up. The other was 69-year old female patient[10] that underwent Rt. Hepatic lobectomy and adjuvant chemotherapy. Recurrence occurred 907 days after surgery and was treated by additional surgery and biliary stent insertion. Of the 12 patients, a 64-year-old woman[11] with the poorest prognosis had stage IIIA disease with portal vein invasion at diagnosis. She underwent hepaticojejunostomy with cholecystectomy and portal vein resection followed by adjuvant chemoradiotherapy, and no recurrence was subsequently observed (Table 4).

4. Discussion

Surgical treatment is the preferred curative treatment option for cholangiocarcinoma, but recurrence and mortality rates are high after surgery. The T classification of the 8th AJCC (American Joint Committee on Cancer) guideline, divides cholangiocarcinoma by tumor size and number and by the presence or absence of vascular invasion, but unfortunately vascular invasion is not well defined. Usually, vascular invasion includes MaVi and MiVi, and MaVi can be detected using various imaging procedures before treatment, for example, as a tumor thrombus in a major portal or hepatic vein, whereas MiVi must be detected by

Table 2

Prognostic factors for the overall survival of the whole cohort.

	Univariate analysis		Multivariate analysis	
Variable	***P***	**HR (95% CI)**	***P***	**HR (95% CI)**
R0 resection	.12	2.16 (0.8–5.8)		
Metastatic LN	.11	1.72 (0.8–3.3)		
Lymphatic invasion	.03	2.03 (1.05–3.95)	.86	0.91 (0.42–2.06)
Microvascular invasion	.002	3.19 (1.55–6.55)	.007	3.34 (1.40–7.97)
Perineural invasion	.332	0.74 (0.40–1.36)		
Stage	.100	1.28 (0.95–1.72)		
CA 19–9	.062	1.00 (1.00–1.01)		
RTx	.618	1.169 (0.63–2.16)		
CTx	.82	0.89 (0.32–2.51)		

CA = cancer, CI = confidence interval, CTx = chemotherapy, HR = hazard ratio, LN = lymph node, *P* = probability, R = residual tumor, RTx = radiotherapy.

Table 3

Prognostic factors for the disease-free survival of the whole cohort.

	Univariate analysis		Multivariate analysis	
Variable	***P***	**HR (95% CI)**	***P***	**HR (95% CI)**
R0 resection	.18	1.49 (0.82–2.73)		
Metastatic LN	.39	0.81 (0.50–1.31)		
Lymphatic invasion	.11	1.49 (0.90–2.44)		
Microvascular invasion	.01	1.91 (1.14–3.19)	0.53	1.21 (0.67–2.18)
Perineural invasion	.20	0.72 (0.45–1.89)	0.01	1.66 (1.18–2.34)
Stage	<.01	1.76 (1.31–2.36)	<0.01	Stage 1 2.89 2 8.62 3 28.75
CA 19–9	.62	1.00 (1.00–1.01)		
RTx	.75	0.92 (0.57–1.50)		
CTx	.28	1.40 (0.75–2.65)		

CA = cancer, CI = confidence interval, CTx = chemotherapy, HR = hazard ratio, LN = lymph node, *P* = probability, R = residual tumor, RTx = radiotherapy.

microscopy. Furthermore, the NCCN (National Comprehensice Cancer Network) guidelines do not provide recommendations for the classification of microvascular invasion or provide guidance for additional adjuvant chemotherapy. In HCC, MiVi has been well associated with poor outcomes after surgical resection and liver transplantation, and it has been proposed tumor cells spread intrahepatic dissemination through the portal circulation.[12] Shao et al and Jonas et al compared the pathologic findings of patients with ICC and HCC that underwent surgical exploration. In HCC patients the appearance of vessels at a muscular wall and MiVi at a tumor distance of >1 cm were found to significantly and adversely affect prognosis. However, in ICC only a MiVi to tumor distance of >1 cm was shown to be prognostic. The authors suggested these differences are due to the different invasion and metastasis pathways of HCC and ICC.[12,14]

The present study shows that MiVi was associated with poor histological differentiation, low R0 resection rates, more lymph node invasion, and advanced stage disease (Table 1). These findings suggest the presence of MiVi reflects the progression of advanced cancer and are consistent with the findings of a previous study, in which tumor size, MiVi, poor tumor grade, and poor tumor differentiation were independently associated with what in cholangiocarcinoma.[15] These associations mean that greater understanding of cholangiocarcinoma is needed at the pathophysiological level.

In the present study, perineural invasion was not a significant prognostic factor not only in OS but also DFS. Perineural invasion was defined as the presence of cancer cells extending along perineural spaces. Some have suggested perineural invasion is a prognostic factor in ICC and extrahepatic cholangiocarcinoma.[16,17] Anatomically, the biliary system is closely located to the peripheral nerve plexus and the celiac plexus, and this proximity may facilitate peripheral nerve invasion by biliary tumors. Murakawa et al suggested that rich autonomic nerve supply to the biliary system might also facilitate perineural invasion.[18] However, Kim et al showed that in cases where adequate dissection was performed, perineural invasion appeared to have no influence on survival[19] which was in accordance with our result. The reason for these conflicting results is that cholangiocarcinoma associated morbidities are relatively low compared to the individual diversity, which makes the topic difficult to analyze given the potential influences of a multitude of factors. Because little has been achieved in terms of improving the prognosis of cholangiocarcinoma, many studies have been initiated to identify risk factors, and some authors have suggested nomograms be used to predict survival.[20] We suggest meta-analysis and large-scale studies be conducted to identify the risk factors involved.

In the present study, cholangiocarcinoma at all locations was included, and this may have introduced bias into our prognostic assessment of the impact of microvascular invasion. Cholangiocarcinomas differ in terms of epidemiology, origin, etiology, and

Table 4

Survival over the 5 years after curative intent surgery for cholangiocarcinoma.

	Cancer location	Differentiation	Resection	Micro-invasion	Stage	Recur	DFS, days	OS, days
55/F[1]	Intrahepatic	MD	R0	No	IA	No		2038
48/F[2]	Intrahepatic	MD	R0	No	II	No		2127
54/M[3]	Perihilar	WD	R1	No	IA	No		2267
69/M[4]	Intrahepatic	WD	R0	No	IA	Yes	1944	2150
51/F[5]	Intrahepatic	MD	R0	No	IA	No		2396
64/M[6]	Intrahepatic	MD	R0	No	IA	No		2542
65/M[7]	Extrahepatic	WD	R0	No	IB	No		4405
68/M[8]	Intrahepatic	WD	R0	No	IA	No		2004
68/F[9]	Extrahepatic	WD	R1	No	II	Yes	1615	2707
69/F[10]	Extrahepatic	PD	R1	Yes	II	Yes	907	2689
64/F[11]	Extrahepatic	PD	R1	No	IIIA	No		3293
75/M[12]	Extrahepatic	WD	R0	No	IA	No		1886

DFS = disease-free survival, F = female, M = male, MD = moderately differentiated, PD = poorly differentiated, R = residual tumor, WD = well-differentiated.

pathogenesis,[21] and ICC is histologically consists of biliary epithelial and hepatic progenitor cells that are distinct from other types of cholangiocarcinoma.

In some studies conducted on animal models, it has been proposed ICC results from the transdifferentiation and neoplastic conversion of normal hepatocytes into malignant cholangiocytes.[22] In contrast, distal extrahepatic and perihilar cholangiocarcinoma arise from biliary epithelium and peribiliary glands.[23] Due to these pathophysiological differences, the metastasis mechanisms of bile duct cancer and HCC and of bile duct cancer in different locations probably differ. Zhang et al suggested ICC is a more aggressive type of cholangiocarcinoma that is associated with poorer outcomes after curative resection than peripheral ICC or Klatskin tumor.[24] However, Ercolani et al reported that in patients with comparable pathologic characteristics and stages, the outcomes of all 3 tumors at similar locations were indistinguishable. The authors concluded cholangiocarcinomas with different sites of origin have different tendencies to invade bordering structures.[25] Many opinions have been expressed on the prognostic impacts of cholangiocarcinoma location, but the mechanism responsible for locational effects on metastasis is unknown. For prognostic assessment of MiVi, it would be more objective to compare only patients with ICC who underwent R0 resection. Hu et al reported that MiVi affects the prognosis of ICC patients after resection with curative intent in a retrospective study that included 1089 patients in 11 countries, and concluded MiVi is a significant risk factor of DFS, which is consistent with our results. However, this study also had limitations that included patients with R1 resection.[26]

The present study has a number of limitations that warrant consideration. First, the sample size was too small to allow rigorous analysis of potential prognostic factors. Second, the study is inherently limited by its retrospective nature, and by a lack of data on additional factors such as genetic factors. Also, there would be many compounding factors that are able to affect in the interpretation of our results because this study was not randomized controlled study. Therefore, to verify our study, a large number, prospective and randomized study is required.

In conclusion, cholangiocarcinoma is known to have a poor prognosis even after surgery with curative intent. About half our study subjects had MiVi after surgery, and as the present study shows, its presence was associated with poor clinical outcomes, and we recommend adjuvant systemic chemotherapy for the patients who achieve R0 resection but having the MiVi. Further studies are required to identify the risk factors and to issue guidelines for the adjuvant treatment of cholangiocarcinoma.

Author contributions

Conceptualization: Jin-Seok Park.
Supervision: Seok Jung, Don Haeng Lee.
Writing – original draft: Bo-Hye Song, Boram Cha.
Writing – review & editing: Boram Cha, Jin-Seok Park.

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