의학석사 학위논문

WHO 2010 분류에 따른 간세포암-담관암 혼합 암종의 절제후 예후 분석

Analysis of post-resection prognosis of combined hepatocellular carcinoma-cholangiocarcinoma according to the 2010 WHO classification

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이 논문을 의학박사 학위 논문으로 제출함

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Abstract

Background: Combined hepatocellular carcinoma and cholangiocarcinoma (cHCC-CC) has wide histologic diversity. This study investigated the effects of cHCC-CC histology, according to the 2010 World Health Organization (WHO) classification, on patient prognosis.

Methods: The medical records of patients who underwent surgical resection for cHCC-CC at Asan Medical Center between July 2012 and June 2019 were retrospectively evaluated.

Results: During the study period, 168 patients, 122 (72.6%) men and 46 (27.4%) women, of mean age 56.6±10.7 years, underwent surgical resection for cHCC-CC, including 159 (94.6%) who underwent R0 resection. Mean tumor diameter was 4.4±2.8 cm, and 161 patients (95.8%) had solitary tumors. Histologically, 86 (51.2%) patients had classical type, and 82 (48.8%) had tumors with stem cell (SC) features, including 33 (19.6%) with intermediate-cell and 23 (13.7%) each with typical SC and cholangiolocellular features; three (1.8%) tumors were unclassifiable. Except for patient age, clinicopathological features did not differ according to the 2010 WHO classification. At 1, 3, and 5 years, tumor recurrence rates were 31.9%, 49.6%, and 58.1%, respectively, and patient survival rates were 91.0%, 70.2%, and 60.3%, respectively. Univariate analysis showed that tumor size >5 cm, microscopic and macroscopic vascular invasion, lymph node metastasis, 8th AJCC tumor stage, and 2010 WHO classification were significantly prognostic. Multivariate analysis showed that 8th AJCC tumor stage and 2010 WHO histologic classification were independently prognostic for tumor recurrence and patient survival. There were no significant prognostic differences among the three SC subtypes.

Conclusions: Post-resection outcomes are better in patients with SC-type than with classical-type cHCC-CC.

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Introduction

Combined hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma (ICC) is an uncommon type of primary liver cancer, first described as a distinct disease entity in 1903. This tumor was first classified in 1949 [1] and again in 1985 [2]. The third classification, by the World Health Organization (WHO) in 2010, categorized this tumor according to its origin from hepatic progenitor cells (HPCs) [3]. Thus, combined HCC and CC (cHCC-CC) can be classified into two main histological forms, the classical type and subtypes with stem cell (SC) features.

We have previously evaluated the association between pathological characteristics and post-resection prognosis of patients with cHCC-CC according to the 2010 WHO classification [4]. Because of the low incidence of cHCC-CC and the relatively recent adoption of the 2010 WHO classification, only a few studies to date have evaluated the pathology-based prognosis of these patients following hepatic resection (HR) [3-7]. The present study investigated the clinical and pathological features, as determined by the 2010 WHO classification, and the post-resection outcomes of patients with cHCC-CC who underwent HR.

Patients and Methods

Patients

The liver cancer database of Asan Medical Center was searched to identify patients with cHCC-CC who were diagnosed according to the 2010 WHO classification from July 2012 to June 2019. Of the 6,504 patients who underwent HR for HCC and

intrahepatic cholangiocarcinoma (ICC) in our institution during the study period [8], 179 (2.8%) underwent HR for cHCC-CC. Patients who had HCC and cHCC-CC concurrently, and those who underwent R2 resection, were excluded. Finally, 168 patients were selected for this study; all were followed up until July 2020 through a review of institutional medical records and with the assistance of the National Health Insurance Service. The study protocol was approved by the Institutional Review Board at Asan Medical Center (IRB no. 2019-1347), which waived the requirement for informed consent due to the retrospective nature of this study. This study was performed in accordance with the ethical guidelines of the World Medical Association Declaration of Helsinki 2013.

Histologic diagnosis according to the 2010 WHO classification

Tumors were categorized as the classical type and as subtypes with SC features based on the 2010 WHO classification [3]. Tumors with SC features were subclassified as typical, intermediate-cell, and cholangiolocellular subtypes. The typical subtype was defined as tumors with a nest of mature hepatocytes surrounded by peripheral clusters of small cells exhibiting morphological and immunohistochemical characteristics of progenitor cells; the intermediate-cell subtype was defined as tumors containing cells with features intermediate between hepatocytes and cholangiocytes, with immunohistochemical markers of both arranged in trabeculae, solid nests, or strands. The cholangiolocellular subtype was defined as tumors composed of cells morphologically mimicking cholangioles

arranged in a tubular anastomosing pattern within a dense, sclerotic stroma and expressing progenitor/SC markers.

Tumors were classified into subtypes based on the results of immunohistochemical staining for HepPar1, CD10, CD34, cytokeratin 7, cytokeratin 19, carcinoembryonic antigen (CEA), alpha-fetoprotein (AFP), nuclear cell adhesion molecule (NCAM1/CD56), epithelial cell adhesion molecule (EpCAM), reticulin, KIT (CD117), and others [3]. A small number of tumors with SC features could not be immunohistochemically characterized into one of these three subtypes and were therefore defined as being of unclassifiable subtype.

Tumor staging according to the 8th edition of the American Joint Committee on Cancer (AJCC) staging system

All cHCC-CCs were staged according to the 8th edition of the AJCC staging system for ICC because this staging system was found to be equally valid for ICCs, cHCC-CCs, and primary endocrine tumors of the liver [9]. T1 stage is defined as a solitary tumor without vascular invasion (T1a ≤5 cm and T1b >5 cm); T2 stage includes solitary tumors with vascular invasion or multiple tumors; T3 stage is defined as penetration of the visceral peritoneum; and T4 stage is defined as direct invasion of extrahepatic structures.

Statistical analysis

Continuous variables were analyzed by Student's *t*-tests or analysis of variance

(ANOVA), depending on their distribution. Categorical variables were compared by the chi-square test or Fisher's exact test. Survival curves were estimated by the Kaplan–Meier method and compared by the log-rank test. Cox proportional hazard regression analysis was used to calculate hazard ratios and 95% confidence intervals. All statistical analyses were performed using SPSS version 22 (IBM, New York, NY), with p-values <0.05 regarded as statistically significant.

Results

Clinicopathological features

The clinical features of the 168 patients pathologically diagnosed with cHCC-CC are summarized in **Table 1**. These patients included 122 (72.6%) men and 46 (27.4%) women, of mean age 56.6 ± 10.7 years (range: 30–81 years). Most patients had been preoperatively diagnosed with HCC, with 19 (11.3%) initially undergoing transcatheter arterial chemoembolization (TACE) and one (0.6%) undergoing radiofrequency ablation.

Of these 168 patients, 159 (94.6%) underwent R0 resection and nine (5.4%) underwent R1 resection. The extents of HR were anatomical resection in 144 (85.7%) and non-anatomical resection including subsegmentectomy and partial hepatectomy in 24 (14.3%). Laparoscopic HR and concurrent bile duct resection were performed in 17 (10.1%) and 4 (2.4%), respectively (**Table 2**).

The pathological findings of these patients are summarized in **Table 1.** Mean tumor diameter was 4.4±2.8 cm, and 161 (95.8%) patients had solitary tumors.

Histologically, 86 (51.2%) patients had classical-type cHCC-CCs, whereas 82 (48.8%) had tumors with SC features, including 23 (13.7%) with typical subtype, 33 (19.6%) with intermediate-cell subtype, 23 (13.7%) with cholangiolocellular subtype, and three (1.8%) with unclassifiable type. Except for age, there were no statistically significant differences in clinical and pathological features in patients assorted by the 2010 WHO classification (**Table 1**).

Post-resection prognosis

None of these 168 patients died of perioperative complications. During a mean follow-up period of 43.8 ± 24.8 months (range: 3–95 months), 90 (53.6%) patients had recurrent tumors.

The preferred initial treatments for these recurrent lesions were TACE (n = 31) and radiofrequency ablation (n = 10) and systemic chemotherapy (n = 10) for intrahepatic recurrence; and systemic chemotherapy for intra- and extrahepatic recurrence (n = 7), pulmonary metastasis (n = 5) and intraperitoneal extrahepatic metastasis (n = 7). No specific recurrence treatment was provided to 13 patients because of poor general condition and rapid tumor progression (**Table 3**).

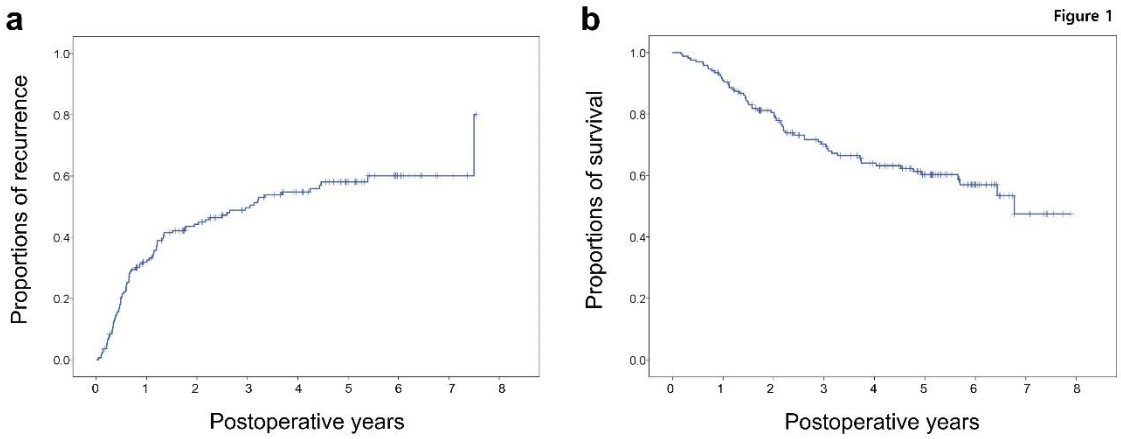

Figure 1. Kaplan–Meier analysis of (**a**) tumor recurrence and (**b**) overall survival of all 168 patients with combined hepatocellular carcinoma-cholangiocarcinoma.

The cumulative 1-, 3-, and 5-year tumor recurrence rates in these patients were 31.9%, 49.6%, and 58.1%, respectively, whereas their 1-, 3-, and 5-year overall patient survival rates were 91.0%, 70.2%, and 60.3%, respectively (**Fig. 1**).

According to the 8th AJCC staging system, 68 (40.5%) patients had stage IA, 25 (14.9%) had stage IB, 62 (36.9%) had stage II, four (2.4%) had stage IIIA, and nine (5.4%) had stage IIIB tumors. Tumor recurrence and patient survival rates showed definite prognostic contrasts according to 8th AJCC tumor stages (all $p < 0.001$) (**Fig. 2**).

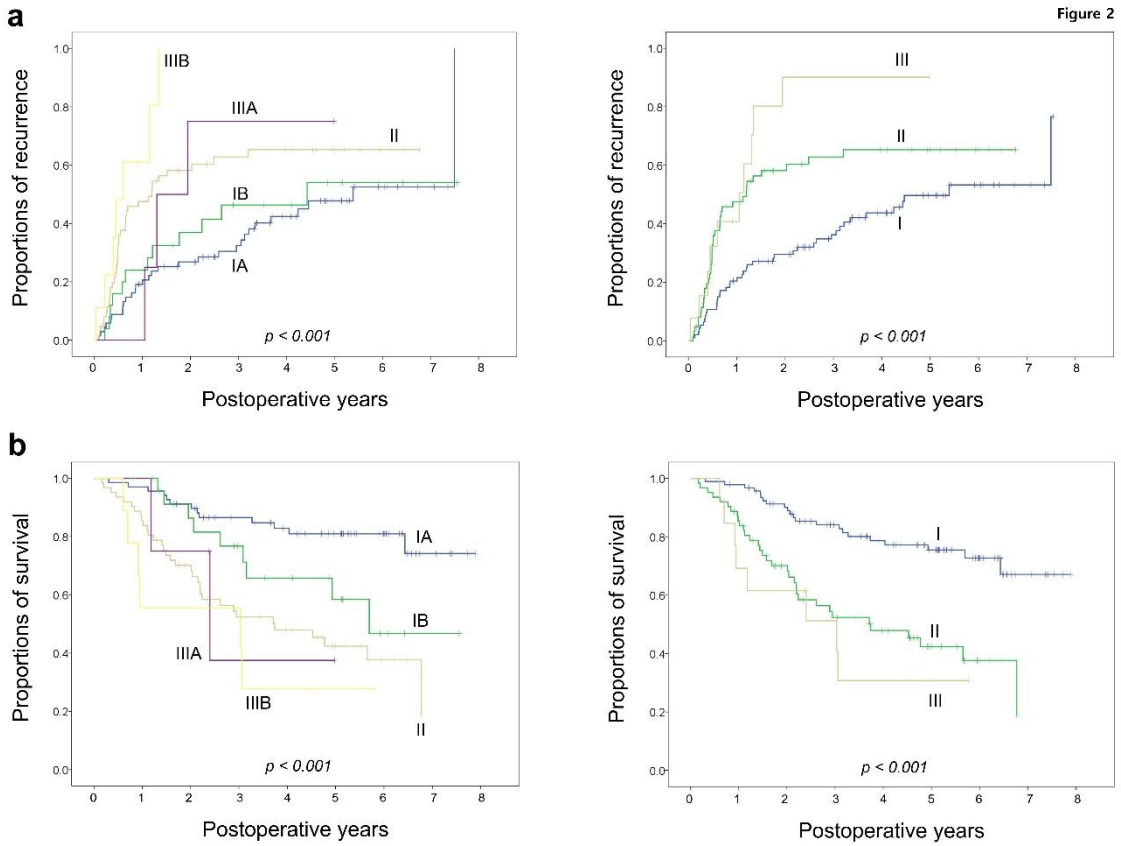

Figure 2. Kaplan–Meier analysis of (**a**) tumor recurrence and (**b**) overall survival of patients classified according to the 8th AJCC tumor staging system

Risk factor analysis for post-resection prognosis

Univariate analyses revealed that significant risk factors for both tumor recurrence and overall patient survival included tumor size >5 cm, microscopic and macroscopic vascular invasion, lymph node metastasis, 8th AJCC tumor stage, and 2010 WHO histologic classification (**Table 4**). Because tumor size >5 cm, microscopic and macroscopic vascular invasion, and lymph node metastasis are essential components

of the 8th AJCC tumor staging system, these risk factors can be simplified as the 8th AJCC tumor stage and 2010 WHO histologic classification. Multivariate analysis showed that these two factors were also independent prognostic factors for tumor recurrence and overall patient survival (**Table 5**).

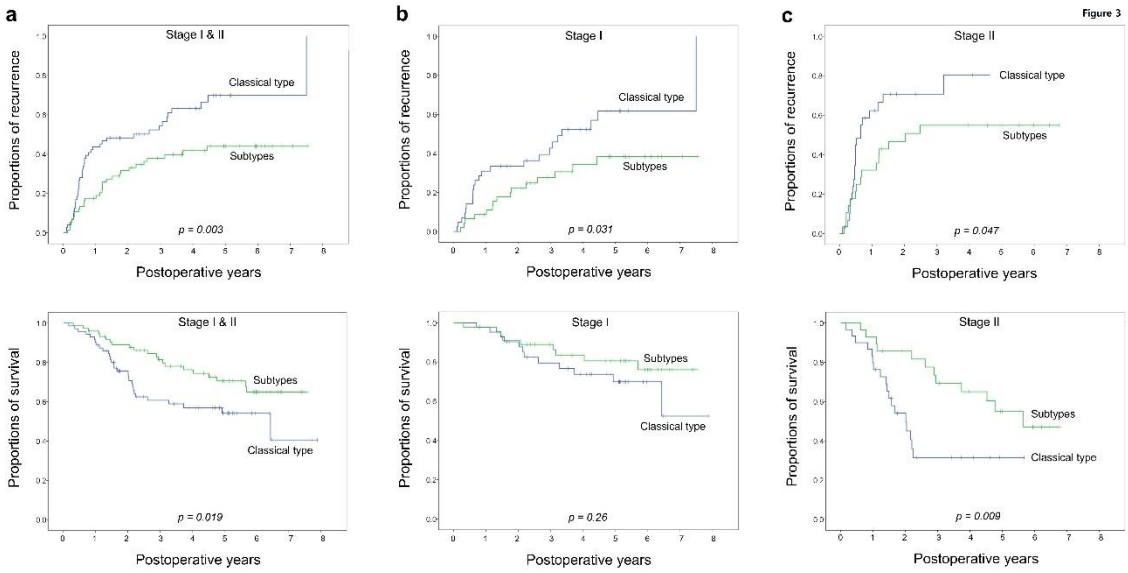

Figure 3. Kaplan–Meier analysis of tumor recurrence and overall survival in patients who underwent R0 resection for classical-type cHCC-CC and subtypes with stem cell features according to the 2010 WHO classification. (**a**) AJCC tumor stages I and II, (**b**) AJCC tumor stage I, (**c**) AJCC tumor stage II.

Prognostic analysis according to the 2010 WHO classification

To avoid the confounding effects from less frequent findings, patients with 8th AJCC stage III tumors and unclassifiable subtype, and those who underwent R1 resection,

were excluded. Analysis of the 146 patients with 8th AJCC stages I and II cHCC-CCs showed that tumor recurrence rate was significantly higher (p = 0.003) and overall survival significantly lower (p = 0.019) in patients with classical-type cHCC-CCs than in those with tumors with SC feature subtypes (**Fig. 3**). Furthermore, analysis of the 74 patients with 8th AJCC stages I and II cHCC-CCs with SC features showed no significant differences among these three histologic subtypes in tumor recurrence rate (p = 0.33) and patient survival (p = 0.97) (**Fig. 4**).

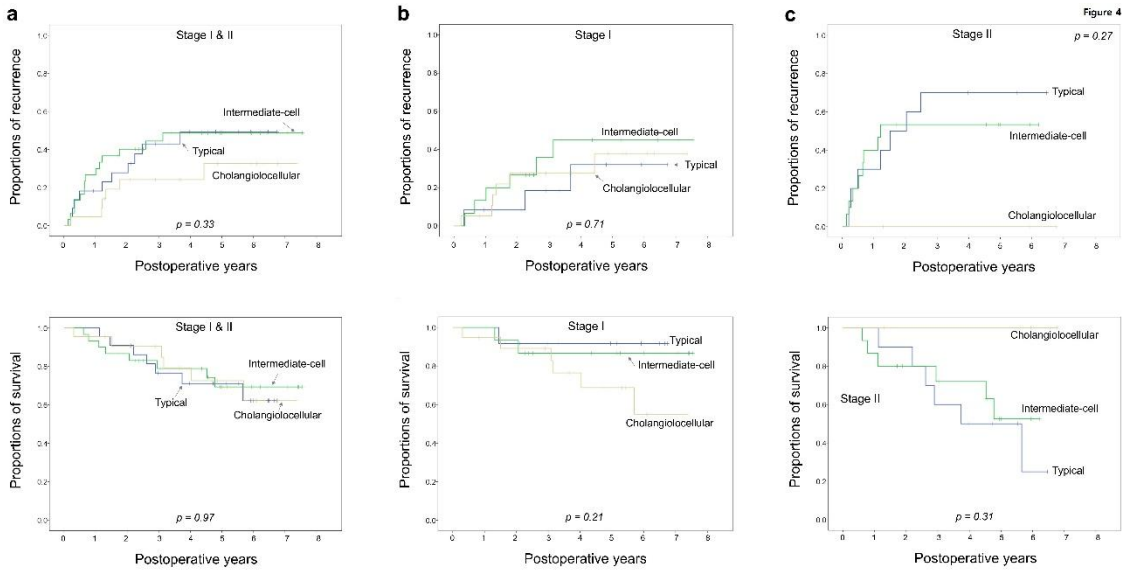

Figure 4. Kaplan–Meier analysis tumor recurrence and overall survival in patients who underwent R0 resection for the three subtypes of cHCC-CC with stem cell features, as determined by the 2010 WHO classification. **a**) AJCC tumor stages I and II, (**b**) AJCC tumor stage I, (**c**) AJCC tumor stage II.

Discussion

cHCC-CCs are rare tumors, comprising approximately 2.6% of primary liver malignancies in the present study. This incidence was lower than the 5.8% reported in our previous study [4], but was generally consistent with rates ranging from 0.8% to 14.3% of primary liver malignancies in other patient populations [10-12]. A population-level analysis in the United States found that between 1988 and 2009, 52,825 patients had HCC, 7181 had ICC, and 465 had cHCC-CC, making the proportion of those with cHCC-CC 0.8% [13].

Advances in molecular biology have led to the development of the cancer SC theory of solid neoplasms. Primary liver cancers, including HCC, ICC, and cHCC-CC, are thought to originate from HPCs. HPCs are liver-specific adult SCs that are activated when mature hepatocytes and/or cholangiocytes are damaged. Advances in HPC research have provided insight into the development of cHCC-CCs [14-16]. These tumors are to derive from bipotent HPCs, which are intermediate SCs capable of undergoing bidirectional differentiation into hepatocytes or bile duct epithelial cells [17-20]. Microdissection of cHCC-CCs and DNA extraction showed that both the hepatocellular and cholangiocellular components of these tumors share identical allelic losses, suggesting their monoclonal origin [21]. Gene expression profiling, however, showed that biliary committed cells were precursors of cholangiolocellular type, and biphenotypic progenitor-like cells were precursors of the classical type and other SC subtypes of cHCC-CCs, suggesting that these tumors may derive from more than one cell type [22].

The 2010 WHO classification divides cHCC-CCs into two types, the classical type and subtypes with SC features [3]. The classical type, which contains areas typical of both HCC and ICC, was observed in 51.2% of our patients. These tumors are thought to develop from independent and separate HCCs and ICCs. HCCs develop first and transform into ICC or vice versa. Alternatively, malignant changes may occur first in HPCs, followed by their differentiation into HCC and ICC to variable degrees.

Although cHCC-CCs with SC features were initially reported to be rare [6], they are actually relatively common, with 48.8% of patients in the present study having this tumor type, including 13.7% with the typical subtype. The intermediate-cell subtype, observed in 19.6% of patients, corresponds to liver carcinoma of the intermediate (hepatocyte-cholangiocyte) phenotype [23]. Cholangiolocellular carcinoma was classified as a subtype of ICC in previous WHO classifications, but, in 2010, it was classified as a cholangiolocellular subtype of cHCC-CC with SC features [24]. Although considered a rare malignant liver tumor, 13.7% of the patients in this study had cholangiolocellular carcinoma [24]. In addition, tumors in 1.8% of our patients could not be classified. These findings indicate that the classification of various subtypes of cHCC-CC patients with SC features is still challenging and requires further validation [6].

At the time the 2010 WHO classification was introduced, prognosis of patients was thought to be worse in patients with SC features than in patients with HCC. However, the prognosis of patients with cHCC-CC and SC features had not

been determined, as findings were based on conflicting evidence from studies that included relatively few patients [3]. Several small-volume studies have assessed the prognosis of patients with cHCC-CC classified according to the 2010 WHO guidelines. Although one Japanese study reported that patients with subtypes with SC features had poorer survival outcomes than patients with classical type [5], another found no significant differences in survival outcomes between these patients with classical type and subtypes with SC features [6]. Moreover, retrospective classification of 63 cHCC-CC specimens, all of which were reported to contain all three SC subtypes in various degrees and combinations, according to the 2010 WHO classification, found that four (6.3%) could be classified as the classical type, and three (4.8%), 28 (44.4%) and 27 (42.9%) as having typical, intermediate-cell and cholangiolocellular subtypes of cHCC-CCs with SC features, respectively [7]. The proportions of these subtypes varied widely in these three Japanese studies. Our previous study of post-resection prognosis in 100 patients with cHCC-CC found that the presence of SC features was closely associated with favorable tumor biology [4]. However, we found that histologic type according to the 2010 WHO classification was not an independent prognostic factor in that study, primarily because of the relatively small sample number and the short follow-up period.

The results of present study clearly demonstrated that the histological types of cHCC-CC according to the 2010 WHO classification and tumor staging were independently prognostic of tumor recurrence and overall patient survival. Patients having subtypes with SC features showed better prognosis than those with classical-

type cHCC-CC, but there were no differences among patients with the three subtypes with SC features. To our knowledge, the present study is the largest cohort study of patients who were prospectively diagnosed with cHCC-CC according to the 2010 WHO classification. Our previous comparison of prognosis in patients with cHCC-CC and a propensity score-matched group of patients with ICC showed that post-resection tumor recurrence and patient survival were similar in patients with classical-type cHCC-CC and ICC [4], whereas survival outcomes were improved in patients having cHCC-CC subtypes with SC features [5, 25]. These results suggested that classical-type cHCC-CC and ICC may share similarly aggressive tumor biology, but that subtypes with SC features may have a less aggressive tumor biology.

The recurrence rate of cHCC-CC after HR was high. Methods used to treat recurrent lesions include liver-directed therapy, such as TACE and systemic chemotherapy. TACE is frequently used to treat recurrent cHCC-CC lesions, but its therapeutic effect is unclear because of the histological heterogeneity of cHCC-CCs, with these tumors being more fibrotic and less vascular than HCCs [26]. Studies of the efficacy of TACE in patients with primary unresectable and recurrent cHCC-CCs in our institution found that treatment response and prognosis were highly related to tumor vascularity [27, 28]. The role of systemic chemotherapy for unresectable and recurrent cHCC-CCs remains unclear, although it has been associated with unfavorable outcomes. For example, a multicenter study involving 36 patients evaluating several first-line treatments, including gemcitabine/cisplatin, fluorouracil/cisplatin, and sorafenib, showed that overall survival was poorer in

patients who received sorafenib monotherapy than in those treated with platinum-containing regimens [29].

Liver transplantation (LT) has been performed in a small number of patients with cHCC-CC. Our previous study of LT in 32 patients with cHCC-CC, including 24 diagnosed with HCC before LT and 12 with a concurrent HCC mass in the explant liver, found that post-transplant tumor recurrence and overall patient survival rates were 15.6% and 84.4%, respectively, at 1 year, and 32.2% and 65.8%, respectively, at 5 years [30]. Five-year tumor recurrence and overall survival rates in patients with very early stage cHCC-CC (1 or 2 tumors ≤2.0 cm) were 13.3% and 93.3%, respectively. These findings suggested that pathologically confirmed cHCC-CC is usually not an eligible indication of LT because very early stage cHCC-CC is often misdiagnosed as HCC before HR or LT. However, in the present study, one patient who had two small recurrent lesions after HR for a solitary 3.2 cm-sized cHCC-CC of intermediate-cell subtype underwent salvage living donor LT. A lung metastasis occurring 10 months after LT was removed by pulmonary metastasectomy. This patient has been undergoing systemic chemotherapy for over 1 year due to multiple extrahepatic metastases.

This study had several limitations, including its retrospective design, and inclusion of patients at a single center in a hepatitis B virus-endemic area. Multi-regional, multicenter collective studies are needed to validate the prognostic influence of cHCC-CC subtypes with SC features.

In conclusion, cHCC-CC is a neoplasm with wide histologic diversity, indicating a strong association with HPCs. Patients classified as having cHCC-CC subtypes with SC features have better post-resection outcomes than those classified as having classical-type cHCC-CC, suggesting a close relationship between post-resection outcomes and histological types according to the 2010 WHO classification.

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Table 1. Clinicopathological features of the 168 patients with combined hepatocellular carcinoma-cholangiocarcinoma according to the 2010 WHO classification

	All	Classical type (A)	Subtypes with stem cell features					p-value
			Typical (B)	Intermediate -cell (C)	Cholangiolocellular (D)	Unclassifiable (E)	B + C + D + E	A vs. (B + C + D + E)
No. of patients	168 (100%)	86 (51.2%)	23 (13.7%)	33 (19.6%)	23 (13.7%)	3 (1.8%)	82 (48.8%)	
Age (years)	56.6±10.7	56.1±11.4	54.0±7.8	55.4±9.9	60.6±10.3	71.0±10.0	57.1±10.0	0.57
Sex (male / female)	122 / 46	68 / 17	17 / 7	19 / 14	16 / 7	2 / 1	53 / 29	0.026
Background liver disease								0.23*
Hepatitis B virus infection	98	53	15	20	9	1	45	
Hepatitis C virus infection	6	4	1	0	1	0	2	
Others	64	29	7	13	13	2	35	
Serum AFP								0.15
Mean (ng/mL)	4181.2± 35936.4	116.3± 315.4	28617.7± 93489.9	285.9± 648.8	16.2±40.8	3.7±2.5	8517.2± 51483.3	
Median (ng/mL)	8.2	9.2	57.0	11.9	2.0	3.5	8.0	
Serum PIVKA-II								0.92
Mean (mAU/mL)	2330.0± 3756.4	994.1± 3396.7	1324.3± 4567.9	1370.5± 5093.6	290.3± 1067.7	144.5±176.1	1058.2± 4177.7	
Median (mAU/mL)	30.0	40.0	27.0	29.0	24.0	152.0	27.0	
Serum CA 19-9								0.20
Mean (ng/mL)	29.4±69.4	38.1±80.7	11.3±7.8	35.9±85.1	9.4±7.2	15.5±15.7	21.2±56.3	
Median (ng/mL)	12.0	14.0	9.0	13.0	7.0	14.0	9.0	
ICG-R15 (%)	11.5±5.7	12.3±6.6	11.9±4.6	11.0±4.9	9.3±4.4	14.0±2.3	10.9±4.7	0.14

Preoperative locoregional treatment (n)	20	12	3	3	2	0	8	0.40
Anatomical resection (n)	144	73	17	30	22	2	71	0.75
R0 resection (n)	159	79	1	32	23	3	80	0.17
Tumor size (cm)								0.71
Mean	4.4±2.8	4.5±2.9	4.2±2.8	4.1±1.9	4.3±2.0	8.1±7.8	4.3±2.6	
Median	3.5	3.4	3.0	3.6	4.1	5.0	3.5	
≤5 cm (n)	114	57	15	25	15	2	57	
>5 cm (n)	54	29	8	8	8	1	25	
Tumor number (n)								0.53
Single	161	82	23	30	23	3	79	
Multiple	7	4	0	3	0	0	3	
Microscopic vascular invasion (n)	68	39	11	13	3	2	29	0.19
Macroscopic vascular invasion (n)	18	11	3	2	2	0	7	0.37
Lymph node metastasis (n)	9	6	0	2	1	0	3	0.27
8th AJCC tumor stage (n)								0.42**
IA	68	36	8	11	12	1	32	
IB	25	9	4	5	7	0	16	
II	62	33	10	15	3	1	29	
IIIA	4	2	1	0	0	1	2	
IIIB	9	6	0	2	1	0	3	

Abbreviations: AFP, alpha-fetoprotein; PIVKA-II, proteins induced by vitamin K antagonist or absence-II; CA 19-9, carbohydrate antigen 19-9; ICG-R15, indocyanine green retention test at 15 minutes; MELD, model for end-stage liver disease; AJCC, American Joint Committee on Cancer.

*Viral hepatis vs. others.

**Stage I vs. other advanced stages.

Table 2. Extents of hepatic resection

Types of resection		No. of patients
Anatomical resection (n)		144 (85.7%)
	Right hepatectomy ± caudate resection	26
	Left hepatectomy ± caudate resection	29
	Right anterior sectionectomy	27
	Right posterior sectionectomy	26
	Central bisectionectomy	12
	Left lateral sectionectomy	16
	Left medial sectionectomy	3
	Caudate lobectomy	2
	Right trisectionectomy	3
Non-anatomical resection (n)	Partial hepatectomy*	24 (14.3%)
Concurrent bile duct resection (n)		4 (2.4%)
Laparoscopic resection (n)		17 (10.1%)

*Including subsegmentectomy and non-anatomical partial hepatectomy.

Table 3. Initial treatments for the first recurrence in 90 patients with post-resection tumor recurrence

Site of first recurrence		No. of patients
Intrahepatic recurrence		62 (68.9%)
	TACE	31
	RFA	10
	Repeat resection	5
	Liver transplantation	1
	Chemotherapy	10
	No specific treatment	5
Intra- and extrahepatic recurrence*		12 (13.3%)
	TACE	1
	Chemotherapy	7
	No specific treatment	4
Pulmonary metastasis		5 (5.6%)
	Chemotherapy	5
Intraperitoneal extrahepatic metastasis		11 (12.2%)
	Chemotherapy	7
	No specific treatment	4

Abbreviations: TACE, transcatheter arterial chemoembolization; RFA, radiofrequency ablation.

*Including lung and intraperitoneal metastases.

Chemotherapy regimens included gemcitabine, 5-fluorouracil, sorafenib, and other agents.

Table 4. Univariate analyses of factors associated with tumor recurrence and patient survival

	No. of patients	Tumor recurrence		Overall patient survival	
		5-year recurrence rate (%)	p-value	5-year survival rate (%)	p-value
Sex			0.41		0.61
Male	122	60.2		59.2	
Female	46	51.2		63.5	
Background liver disease			0.38		0.33
Viral hepatitis	104	56.0		66.2	
Others	64	59.3		50.0	
Serum AFP			0.64		0.31
≤7 ng/mL	69	64.8		62.4	
>7 ng/mL	86	56.6		56.6	
Serum PIVKA-II			0.15		0.34
≤40 mAU/mL	91	59.0		63.4	
>40 mAU/mL	55	67.6		55.3	
Serum CA 19-9			0.20		0.095
≤37 ng/mL	100	62.9		55.8	
>37 ng/mL	11	72.7		36.4	
Anatomical resection	144		0.71		0.46
Yes	144	57.7		58.2	
No	24	67.4		72.4	
Surgical curability			0.16		0.18
R0 resection	159	57.7		61.6	
R1 resection	9	66.7		38.9	
Tumor size			0.006		<0.001
≤5cm	114	51.4		70.6	
>5 cm	54	71.6		37.6	
Tumor number			0.13		0.13
Single	161	57.6		61.3	
Multiple	7	71.4		38.1	

Microscopic vascular invasion			<0.001		<0.001
Absent	100	49.8		73.7	
Present	68	71.0		39.3	
Macroscopic vascular invasion			0.012		<0.001
Absent	150	56.1		65.0	
Present	18	76.3		15.2	
Lymph node metastasis			0.001		0.012
Absent	159	56.3		62.2	
Present	9	100		27.8	
8th AJCC tumor stage			<0.001		<0.001
I	93	49.7		75.5	
II–III	75	69.3		40.7	
2010 WHO classification			0.003		0.010
Classical type	86	68.1		51.8	
Subtypes with stem cell features	82	47.9		68.9	

Abbreviations: AFP, alpha-fetoprotein; PIVKA-II, proteins induced by vitamin K antagonist or absence-II; CA 19-9, carbohydrate antigen 19-9; AJCC, American Joint Committee on Cancer.

Table 5. Multivariate analyses of factors associated with tumor recurrence and patient survival

	Tumor recurrence			Overall patient survival		
	Hazard ratio	p-value	95% CI	Hazard ratio	p-value	95% CI
8th AJCC stage		<0.001			<0.001	
Stage I	1					
Stages II and III	2.23		1.46–3.41	3.61		2.13–6.13
2010 WHO classification		0.002			0.003	
Subtypes with stem cell features	1			1		
Classical type	1.97		1.29–3.02	2.17		1.29–3.64

95% CI, 95% confidence interval.

국문 요약

혼합 간세포암-간내담도암은 다양한 조직학적 특성을 지니고 있다. 이에 2010 년 세계 보건기구 (WHO)의 분류에 따른 조직학적 특성에 따라 절제술후 예후 분석을 시행 하였다.

이번연구에서는 2012 년 7 월 부터 2019 년 6 월까지 아산병원에서 절제술을 시행한 168 명의 환자의 의무기록을 후향적으로 조사하여 연구 하였으며 상기 기간동안 168 명의 환자를 확인 하였다. 조직학적으로 86 명(51.2%) 이 classical type 이었고 82 명(48.8%) 이 stem cell 특징을 가지고 있었다.

단변량 분석을 통해 종양의 크기가 >5 cm 이상, microscopic and macroscopic vascular invasion, lymph node metastasis, 8th AJCC tumor stage, 2010 WHO 분류가 환자의 예후에 영향을 미치는 인자였으며 다변량 분석상 8th AJCC tumor stage 와 2010 WHO 분류의 두가지 요소가 종양의 재발과 환자의 생존율에 영향을 끼치는 인자 였다.

추가로 2010 년 세계 보건기구 (WHO)의 분류에 따른 조직학적 특성에 따라 절제술후 예후 분석시 classical type 보다 stem cell 특징이 관찰된 환자군에서 더욱 양호한 수술후 예후가 관찰되었다.

이러한 결과는 혼합 간세포암-간내담도암 환자에 있어 외과적 절제 후 환자의 예후는 2010 년 WHO 의 조직학적 분류에 따라 stem cell type 이 예후가 더 양호함을 시사 하였다.