Review

Clinicopathological features and surgical outcomes of cholangiolocellular carcinoma: a systematic review

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ABSTRACT

Background: Colangiolocellular carcinoma (CoCC) is a rare type of primary malignant liver tumor.

Patients and methods: We searched computed medical databases, ranging from 1959 to 2015, which described surgical resections of CoCCs. The clinicopathological data were evaluated for its association with hepatic CoCC, along with the prognosis for each patient and the surgical outcomes described in the case report.

Results: We obtained clinicopathological data for 75 patients (46 men and 29 women), with a mean age of 64 years (range, 15-84 years), who had undergone surgical resections for CoCCs. Although CoCCs have similar clinicopathological features to hepatocellular carcinomas and/or cholangiocarcinomas, the treatment strategies in patients with CoCCs are identical to those used to treat other primary neoplasms of the liver. The immunohistochemical features of CoCC also included testing positive for epithelial membrane antigen. The overall 1-, 3-, and 5-year survival rates after surgery, for 75 cases with available data, were 92.4%, 65.9%, and 60.8%, respectively.

Conclusions: To determine the best management strategy for this tumor and to improve the accuracy of prognosis for patients, we aim to continue to collect and analyze the epidemiological and pathological data for CoCCs.

Key words: Cholangiolocellular carcinoma, liver, surgery, outcome

INTRODUCTION

Cholangiolocellular carcinoma (CoCC) is a rare type of primary malignant liver tumor, which was first reported by Steiner and Higginson in 1959 (1). The incidence of CoCCs was reported to be 0.56% in patients with resected primary malignant liver tumors (2). The tumor is thought to be derived from hepatic stem cells, which exist in the canals of Hering (2-9). CoCCs have been previously classified as a type of intrahepatic cholangiocarcinoma (10,11). Currently, on the basis that combined hepatocellular-cholangiocarcinomas are derived from hepatic progenitor and/or stem cells (12), CoCC are classified, in the latest version of the World Health Organization (WHO) classification of the digestive system, as combined hepatocellular cholangiocarcinomas with stem cell features (13). In Japan, CoCCs are currently classified as independent primary malignant liver tumors along with the hepatocellular carcinoma, intrahepatic cholangiocarcinoma and combined hapetocellular-cholangiocarcinoma according to the Liver Cancer Study Group of Japan, which has outlined general rules for the clinical and pathological studies of primary liver cancers in 2008 (14). In survival, hepatocellular carcinoma show better prognosis compared to both combined hepatocellular-cholangiocarcinomas and intrahepatic cholangiocarcinoma after curative surgery. Furthermore, the postoperative survival of combined hepatocellular-cholangiocarcinoma without stem cell features is thought to be worse than those of pure hepatocellular carcinoma, and similar to those of intrahepatic cholangiocarcinoma (15). However, the prognosis of CoCCs remains still unclear with conflicting evidence on small series and number of patients. Therefore, long-term follow-up of larger cohorts of strictly categorized tumors is needed to adequately define the clinical and biological behavior of all the combined variants.

We conducted a retrospective analysis of the currently published CoCC cases, to determine their clinicopathological features and the potential surgical outcomes, including survival rates, for patients with this uncommon tumor.

METHODS

Eligibility criteria

The reporting of this systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement (16). Both English and Japanese observational studies and articles were eligible for inclusion. There were no limitations with regards to the date of publication of the included studies. Only articles for which the full-text versions could be retrieved were included. For a study to be suitable for the qualitative synthesis, it had to contain information on the patient's surgical treatment for CoCC. In addition, the study had to describe a defined follow-up period after the primary surgery, in which there had to be an assessment of the patient's outcome after the surgery. Any study, which did not meet the above-mentioned requirements, was not eligible for inclusion.

Literature search

A literature search was performed using the following terms: 'cholangiolocellular carcinoma' and 'liver'. Both MEDLINE and Igakuchuo-Zasshi (a database of Japanese articles) were searched for data on surgical resections of CoCCs, with their publication dates ranging from 1959 to 2015. Studies were included regardless of their publication status. Additional studies, included in the reference lists of the retrieved articles as well as relevant systematic

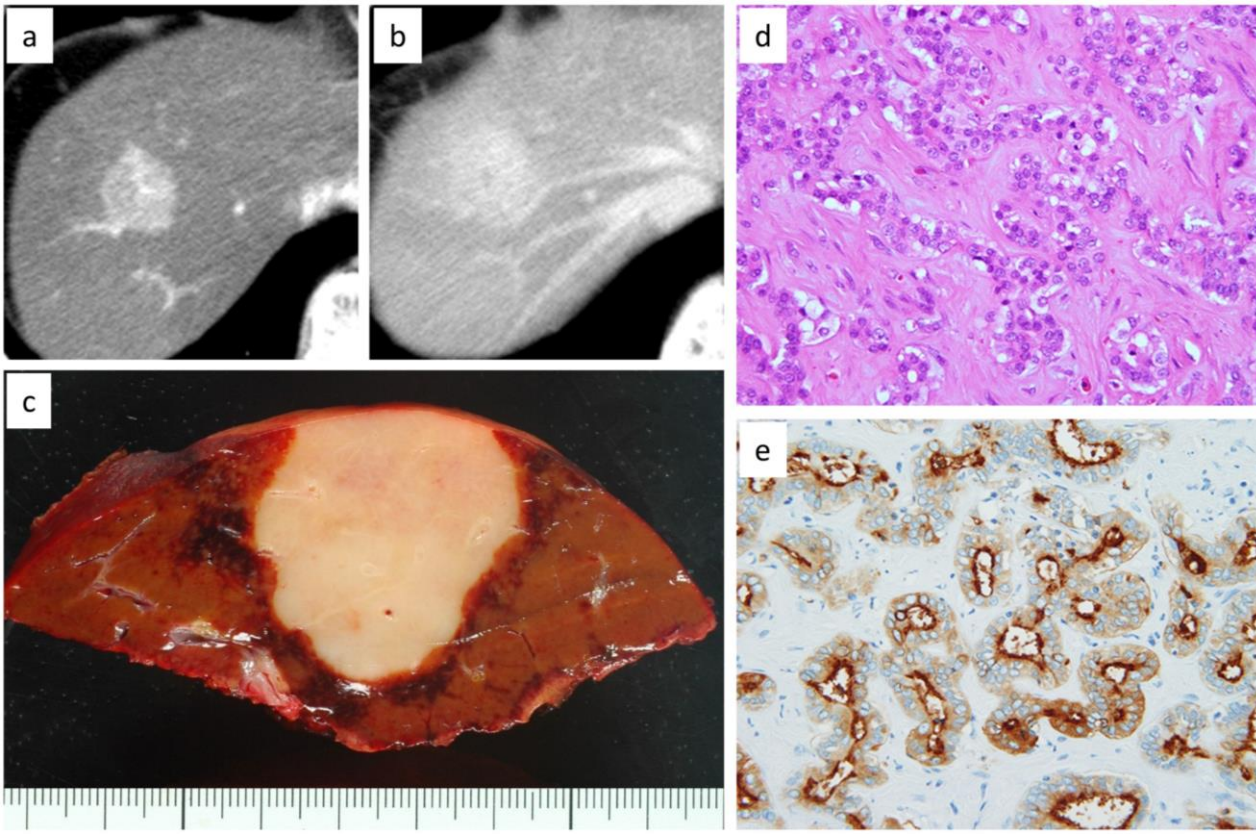

Figure 1. Typical clinicopathologic findings from our case presentation. (a) CT imaging showed high attenuating tumor with peripheral enhancement in early phase. Vessel penetratrion into the tumor showed in the early phase, no peripheral bile duct dilation. **(b)** The tumor had homogeneous enhancement on delayed phase whose margin of the tumor was not clear. **(c)** Macroscopically, the resected tumor was whitish color, solid, not encapsulated and had an irregular margin. **(d)** Histologic findings of the resected tumor showed small ductules similar to cholangioles proliferating in an anastomosing pattern with abundant fibrous stroma (HE, ×40). **(e)** Immunohistochemically, epithelial membrane antigen (EMA) was strongly positive in the membranous areas of the tubules. (EMA, ×40)

reviews, were also searched.

Data collocation and assessment

A standard data extraction form was developed for data collection. Information extracted from the included studies was systematically handled using a customized Microsoft Excel spreadsheet. Extraction variables consisted of the demographic baseline variables and the clinical characteristics of CoCCs cases described in the reports, including age, sex, tumor location, etiology of the hepatitis viral infection, tumor size, and survival times. We also analyzed the published data on the prognosis of each patient.

Study analysis

Survival rates were generated using the Kaplan-Meier method and compared by using the log-rank

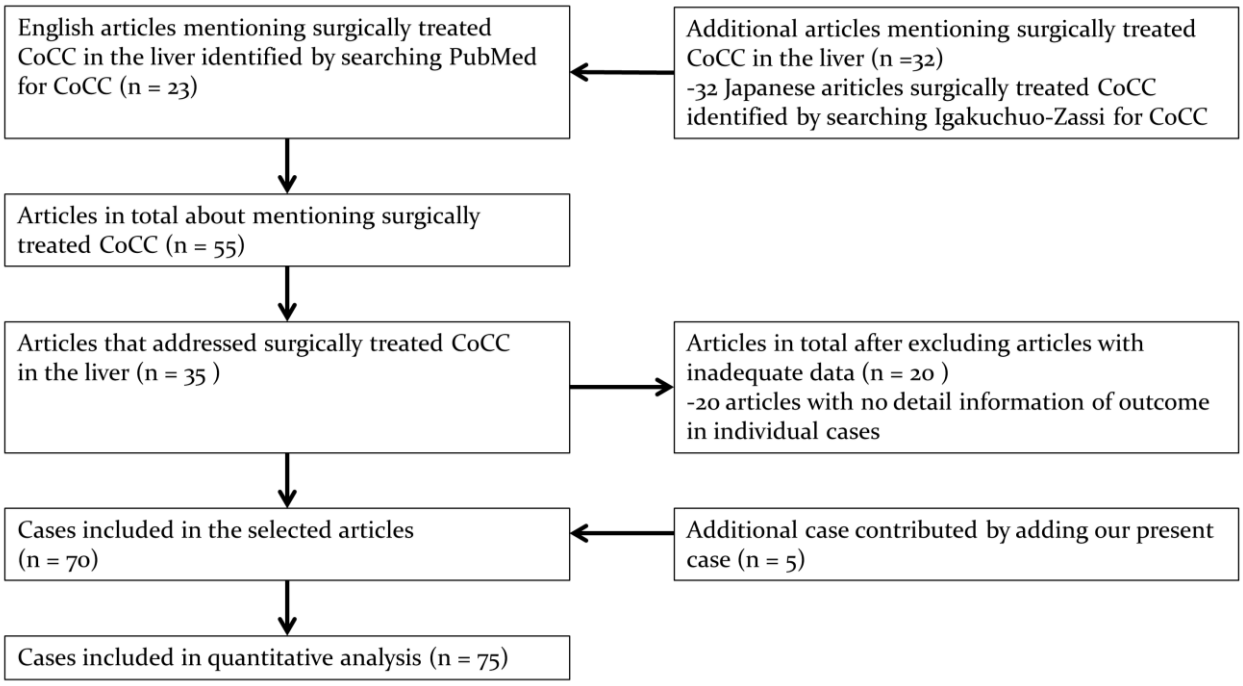

Figure 2. **PRISMA design showing selection of articles and patients cases for review.**

test. All analyses were performed using SPSS® (SPSS; Chicago, IL). Values are expressed as the mean ± standard deviation. *P* values <0.05 were considered statistically significant.

RESULTS

Typical clinicopathological findings from our case presentation

The radiological features of CoCCs have not been clarified because of their rarity and the inherent difficulties related to diagnosis. No specific features have been observed, except the lack of necrosis and a fibrous capsule and the presence of dual characteristics seen in both hepatocellular carcinomas and intrahapetic cholangiocarcinomas (2,5-7). However, imaging techniques have shown that CoCCs have some common features. For example, enhanced abdominal computed tomography (CT) imaging showed an enhancement of the tumor in the early phase (Fig. 1a), as well as homogeneous enhancement in the delayed phase, where the margin of the tumor was not clearly visible (Fig. 1b). Macroscopically, the resected tumor was whitish, solid, not encapsulated, and possessed an irregular margin (Fig. 1c). Histological findings obtained from the resected tumor showed small ductules, similar to proliferating cholangioles, in an anastomosing pattern along with abundant fibrous stroma (Fig. 1d). Immunohistochemically, the epithelial membrane antigen (EMA) was found to be strongly expressed in the membranous areas of the tubules. These findings are compatible with those obtained from other CoCC patients (Fig. 1e).

Literature review

We identified 23 articles in PubMed and 32 articles from other sources (Fig. 2) that contained suitable data for our study. Ultimately, 55 articles were

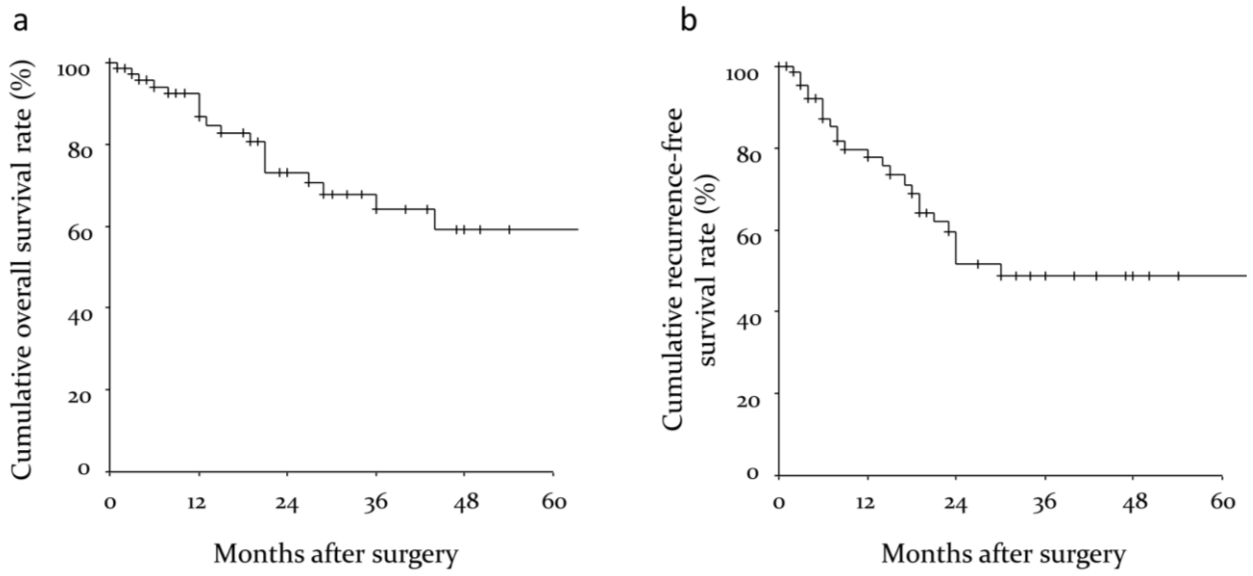

Figure 3. Overall survival and disease-free survival in patients with CoCC of the liver. Kaplan-Meier estimates of overall survival (a) and Kaplan-Meier estimates of disease-free survival rates (b).

included for our narrative synthesis and systematic review (1,2,17-70). We identified comprehensive data for 75 cases of curative surgical resection of CoCCs, which included 5 patients who we had previously treated in our clinic (Supplemental Table 1). The published diagnoses for all of the patients were true indications for surgical resection.

Clinicolpathological features of CoCCs

The clinicopathological characteristics of the examined CoCC cases are presented in Supplemental Table 1. Out of the 75 cases of CoCC, for which we found comprehensive data, 46 occurred in men and 29 occurred in women. The mean patient age was 64 years (range, 15 to 87 years). Based on the observed cases, CoCCs were not associated with any specific clinical syndromes. In 29 cases, the patients did not display any visible symptoms, while in the remaining 10 cases the patients were diagnosed whole displaying certain clinical symptoms. These symptoms were abdominal pain or discomfort in 8 patients, liver dysfunction in 1, and general fatigue in 1. Interestingly, among the CoCC patients, 33 (44.0%) were diagnosed with viral hepatitis. Out of the 75 patients, 11 were hepatitis B virus-positive, 19 were hepatitis C virus-positive, 3 were positive for both, and 31 patients were negative for both. Among the 37 patients who were preoperatively diagnosed with a solitary tumor, 8 were found to have multiple tumor nodules in their resected specimens. The mean resected CoCC size in the observed 75 patients was 4.9 ± 3.1 cm (range, 0.8-15.0 cm) (Supplemental Table 1). Hepatic regional lymph node metastases were underestimated in only one of the 33 (3.0%) patients without a preoperative metastatic lymph node, although, interestingly, Ariizumi et al. reported that the regional incidence of lymph node metastases was 14.0% in the dataset obtained from patients treated at a single institute (34). Vascular invasion was observed in 10 out of the 21 (47.6%) patients, based on the evaluation of the resected specimens.

Table 1. The subgroup analysis of patients with CoCCs

Characteristics	No. of patients	Survival rate in years			*P* value
		1	3	5	
Overall	75	92.4	65.9	60.8	
Age (years)					
< 65	37	87.1	69.9	59.7	0.961
≥ 65	38	97.1	70.9	63	
Gender					
Male	46	90.2	66.6	59.9	0.956
Female	29	95.7	67	67	
Symptom					
Absent	29	92.7	71	53.2	0.762
Present	10	100	66.7	66.7	
Hepatitis viral infection					
Negative	35	89.5	68.2	68.2	0.914
Positive	33	88.9	66	55	
Size of the tumor					
< 3 cm	20	94.7	86.1	86.1	0.072
≥ 3 cm	55	85.9	58	52.2	
No. of tumor					
Solitary	37	86.2	62.7	41.8	0.385
Multiple	8	85.7	85.7	85.7	
CEA (ng/mL)					
< 3	44	100	77.2	77.2	0.015
≥ 3	15	78	58.5	39	
CA19-9 (U/mL)					
< 50	45	97.1	78.6	78.6	0.004
≥ 50	18	74.9	49.2	24.6	
AFP (mAU/mL)					
< 20	55	100	69.5	69.5	0.001
≥ 20	11	88.9	0	0	

Survival outcomes and recurrence patterns in patients with CoCCs

Survival outcome data was available for only 75 CoCC cases, including the patients from our hospital. The mean follow-up term after curative surgery was 25.6 months (range, 0 to 140). Overall, the 1-, 3-, and

5-year survival rates after surgery were 92.4%, 65.9%, and 60.8%, respectively (Fig. 3a). Among the 75 patients, 59 (66.7%) showed no recurrence. The analysis of disease-free survival was based on 26 events among the 75 patients (33.3%). Disease-free survival rates at 1-, 3-, and 5-years were 77.7%, 48.9%, and 48.9%, respectively (Fig. 3b). The major sites of recurrence were the remnant liver (19 patients), lung (5 patients), bone (4 patients), and lymph node (2 patients). Among patients who experienced recurrence, the median time from surgery to recurrence was 13.0 months.

Subgroup analysis

By comparing the survival rates between the various subgroup identified by each predictive factor, the following factors were found to be significantly associated with poor outcomes after surgery: 1) elevated serum carcinoembryonic antigen (CEA) level (>3 ng/mL), 2) elevated serum carbohydrate antigen 19-9 (CA19-9) level (>50 U/mL), and 3) elevated serum alfa-fetoprotein (AFP) level (>20 mAU/mL). Based on the subgroup analysis of patients with CoCCs, factors such as age, sex, symptoms, etiology of viral hepatitis, tumor size, number of the tumors, and grade of vascular invasion, were not found to be significant prognostic factors (Table 1).

DISCUSSION

We conducted a retrospective analysis of 75 CoCC cases, with a focus on the clinicopathological features and surgical outcomes (35-70). This is the first report of CoCC on systematic review. CoCC is a rare type of malignant liver tumor. However, reports of CoCCs have been gradually increasing over the last decade, more likely due to its recognition by the WHO classification (13). Clinically, it is difficult to diagnose CoCCs, although modern imaging modalities can provide informative findings. Hepatocellular carcinomas and intrahepatic cholangiocarcinomas were both a part of the differential diagnosis for treating physicians. Contrast-enhanced CT analysis of CoCCs shows early enhancement in the arterial phase and enhancement contrast retention in the delayed phase. Peripheral biliary dilatation, intratumoral hemorrhage, and capsular retraction were not commonly observed. T1-weighted magnetic resonance imaging, the tumor showed hypointensity, whereas, on T2-weighted imaging, mixed intensity was observed (25,26,52,71). These findings were diagnostically significant for CoCC. However, as CoCCs, hepatocellular carcinomas, intrahepatic cholangiocarcinomas, and secondary metastatic liver tumors all have similar radiological features, CoCCs are indistinguishable from other hepatic tumors based on imaging modalities alone (25,26,52,71,72).

Similarly, CoCC diagnosis using radiological methods can be extremely difficult. It is hypothesized that this is due to the pathological characteristics of CoCC, which is composed of a mixture of small monotonous glands and antler-like anastomosing patterns, along with abundant hyalinized and/or edematous fibrous stroma that shows lymphocytic infiltration. Furthermore, CoCC tumor cells are cuboidal and smaller than normal hepatocytes, with scanty eosinophilic cytoplasm, round nuclei, and distinct nucleoli (2,5,16,71). Previous research on the topic has shown that positive staining for epithelial membrane antigen (EMA), located in the membranous site of the cancer duct, is a helpful marker for CoCC; however, this result does not necessarily support the final pathological findings associated with CoCCs

(2,5,12,73).

Based on our current medical knowledge, complete surgical resection remains the only viable curative treatment option for CoCC patients (34,46). The current overall 5-year survival rate, after curative surgical management, is 60.8% in patients with CoCCs. This result showed that the prognosis of CoCC can be predicted to be better than that of cholangiocellular carcinoma, less than hepatocellular carcinoma, and be similar to combined hepatocellular-cholangiocarcinoma. Although some of the cases that we examined included patients who had met the criteria for surgical treatments, for either hepatocellular carcinomas or intrahepatic cholnagiocarcinomas, at an advanced stage (74-78). Ariizumi et al. had previously demonstrated that the potential prognostic factors for CoCCs were the presence of regional lymph node metastases and intrahepatic metastases (34). Of course, based on this it could be hypothesized that the risk factors involved with CoCC recurrence are microvascular involvement and lymphatic permeation, as both intrahepatic metastases and lymph node metastases were found to be a poor prognostic factor. However, whether these multiple lesions are derived from microvascular metastases or from multicentric development, as seen in hepatocellular carcinoma and/or intrahepatic cholangiocarcinomas, remains unclear. Furthermore, it remains to be seen whether regional lymphadenectomy, for the purpose of CoCC treatment, is clinically beneficial.

Interestingly, in our current systematic review, the only potential prognostic factor observed in CoCC patients was the elevated level of certain serum tumor markers, such as CEA, CA19-9, and AFP. This lack of variable prognostic factors is present, as one would definitely assume that due to variance in the patients' background and the heterogeneous treatment strategies applied, a larger number of prognostic factors would be identifiable. Furthermore, our current research suggested that, although only 17 (37.8%) tumors remained at Stage I or II, CoCCs might be less aggressive, when compared with intrahepatic cholangiocarcinomas. In fact, the time to recurrence was longer in patients with CoCCs than in patients with intrahepatic cholangiocarcinomas (74-78). Therefore, we suggested that physicians should pay close attention to the detection of CoCCs at an early stage, especially in patients with hepatitis viral infections, as 48.5% of patients with CoCCs had previously suffered from a hepatitis viral infection.

This study was subject to certain inherent limitations and biases associated with the small retrospective study design. A major limitation of our study was the uncertainly at which our results could be extrapolated, as the current study included case report and published pathological results, without performing the immunohistochemical staining for EMA. Immunohistochemical staining for EMA was performed 24 patients out of 75 patients in our study. Another potential limitation is the lack of re-evaluation for the specimens by a dedicated pathologist. The establishment of a definite diagnosis for CoCC is inevitably pathological and therefore demands a professional who is highly specialized in liver disease. Because of their relatively recent discovery and extreme scarcity, the proper diagnosis of CoCCs is still challenging, even for high-volume liver pathologists. Therefore, to determine the best management strategy for CoCC and to improve the accuracy of prognosis, further collection and analysis of epidemiological and pathological data is necessary.

In conclusion, pre-operative diagnosis of

CoCCs would have been difficult, even with the various imaging modalities that are available. Currently, surgical treatment is the only curative management option for CoCCs. In patients with uncommon lesions in the liver, CoCCs should be considered a part of the differential diagnosis.

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Abbreviations:

AFP, alfa-fetoprotein

B, bile duct invasion

CA19-9, carbohydrate antigen 19-9

CEA, carcinoembryonic antigen

CK19, cytokeratin 19

CoCC, colangiolocellular carcinoma

CT, computed tomography

EMA, epithelial membrane antigen

HBV, hepatitis B viral infection

HCV, hepatitis C viral infection

HE, hematoxylin and eosin staining

PRISMA, the Preferred Reporting Items for Systematic Reviews and Meta-analyses

PIVKA-II, protein induced by Vitamin K absence or antagonists-II

S, segment

Vp, micro-portal vein invasion

Vv, micro-venous invasion

WNR, within normal range.

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Supplemental Table 1. The clinicopathological characteristics of the CoCC cases (online version)

Case	Author	Year	Age (yr)	Gender	Symptom	Etiology	CEA	CA19-9	AFP	PIVKA2	No. of tumor	Location	Size (cm)	Encapsulation	Thrombus	Vv	Vp	B	Ck19	Relapse site (months)	Outcome	Status
1	Hanawa[34]	1994	61	M	abdominal pain	-	2.6	WNR	5.8	WNR	solitary	S5	2.2	-	-					-	40	alive
2	Yamamoto[35]	1996	59	F	none	HCV	1.1	113	5		solitary	S5/8	9.0	-	-		+			Liver (17)	29	alive
3	Yoshida[36]	1999	64	F	none	HBV	1.1	13	213	13	solitary	S8	6.5	-	-	-	-		+	-	5	alive
4	Ide[37]	1999	63	M	none	HCV			30.3	WNR	multiple	S1	1.7	-	-	-	-	-	+	-	18	alive
5	Ohuchida[38]	2002	69	F	none	HCV	WNR	WNR	WNR	WNR	solitary	S7	2.5	-	-		+			-	43	alive
6	Ohtsuka[39]	2003	67	M	none	HBV	2.5	22	4.5	9	solitary	S4	5.5	-	-				+	Liver (15)	36	dead
7	Kaneda[40]	2003	23	M	abdonominal pain	HBV	WNR	WNR	6818.7		solitary	S5	7.5	-	-				+	Liver, Lung (3)	15	dead
8	Okuda[41]	2005	58	M					8				3.5							-	29	dead
9	Okada[42]	2005	75	M	none	HBV/HCV	WNR	7.53	WNR		solitary	S7	1.3	-	-				+	-	48	alive
10	Sanada[43]	2005	54	F	liver dysfunction	-	1.3	25.8	3.2		solitary	S8	8.0	-	-	-	-	-		-	3	alive
11	Matsuda[44]	2006	70	M	none	HCV	WNR	WNR	WNR	2155	multiple	S7	2.2	-	-					-	30	alive
12	Komuta[45]	2008	69	F		HCV	5.1	57	5				2.0							-	93	alive
13		2008	56	M									4.6							-	140	alive
14		2008	72	F		HBV							4.5							Liver (4)	12	dead
15		2008	55	M		HCV	1.3	15	7				3.0							-	118	alive
16		2008	62	M		-	11.8	405	2.5				3.7							-	54	alive
17		2008	56	M		-	9.3	69					2.0							-	82	alive
18		2008	69	M		-	2	26					7.5							Lung (21)	76	alive
19		2008	77	M		HCV	5.4	10.1	3				3.8							-	67	alive
20		2008	70	F		-			10				5.0							Liver (9)	21	dead
21		2008	49	F		-	4.2	33.3	18.7				11.0							Liver (18)	19	alive
22		2008	75	M		-	3.5	697	17.7				2.4							-	3	dead
23		2008	70	M		HCV	3.5	14	7.1				2.5							Bone (30)	32	alive
24		2008	73	M		HCV	1.8	94	10.3				2.0							Liver (12)	21	dead
25		2008	69	M		HBV/HCV	3	65	3.6				0.8							-	27	alive
26		2008	63	M		-	2.6	22	5				5.0							Lung (25)	27	alive
27		2008	59	M		-	1.2	134	10.4				2.3							-	15	alive
28		2008	60	F		-	2.5	11	1.9				6.5							Liver (8)	10	alive
29		2008	75	F		-	2.3	57	7.2				2.0							-	1	alive
30		2008	65	F					54.8				5.0							-	47	alive
31		2008	67	F			2	4					9.5							Liver (14)	19	dead
32		2008	56	M		HBV/HCV	1.9	2.1	9.5				4.6							-	4	alive
33		2008	70	F			1.7	143.3	3				7.0							-	23	alive
34		2008	70	F			0.9	8	2.5				5.0							-	12	alive
35		2008	60	M			1.6	570	8.2				4.2							-	2	alive
36		2008	52	M			1.5	14	8				3.2							-	27	dead
37		2008	57	F		-	3.7		1463				6.5							Liver (24)	28	alive
38		2008	54	F		-	1.2	12	2.1				14.6							-	2	alive
39		2008	62	F			1	12	5				10.5							-	8	alive
40		2008	74	M		-	0.6	21	15				4.1							-	1	alive
41	Kanamoto[46]	2008	71	F	none	HCV	1.4	9	6	10	solitary	S5	1.5	-					+	-	12	alive
42	Tamura[47]	2008	25	F	abdominal pain	-	WNR	WNR	WNR	WNR	solitary	S5678	15.0	-	-	-	-	-		-	48	alive
43	Hashizume[48]	2009	87	M	none	-	1.1	17.6	2.2		solitary	S6	3.0	-	-				+	-	12	alive
44	Ishigami[49]	2009	59	M	none	HBV	7	992			solitary	S7	5.0	-	-	-	-	-		Lung (24)	44	dead
45	Iwamuro[50]	2009	53	M	none	HBV	2.5	14.8	4		solitary	S7	1.5	-	-					Bone (19)	19	alive
46	Motosugi[51]	2009	70	F		-		WNR	WNR		solitary	S8	5.0	-						Lymph (6)	12	dead
47		2009	77	M		HCV		elevated	WNR		solitary	S8	3.5	-						-	30	alive
48		2009	54	F		-		WNR	WNR		solitary	S3	7.5	-						Liver (6)	6	dead
49		2009	54	M		HBV		WNR	elevated		solitary	S6	3.0	-						Liver (8)	8	dead
50		2009	76	F		HCV		elevated	elevated		solitary	S7	2.5	-						Bone (24)	24	alive
51		2009	70	M		-		WNR	WNR		solitary	S3/4	6.3	-						-	3	alive
52	Ohnishi[52]	2009	70	F	abdominal pain	-	2.6	15			solitary	S4/5	6.7	-	-	-	+	-	+	Liver (3)	5	alive
53	Okada[53]	2009	70	M	none	-			2305	99	solitary	S5	5.7	-	-				+	-	9	alive
54	Morihiro[54]	2009	77	M	none	HCV	14.8	82.3	9.1		solitary	S8	2.2	-						-	20	alive
55		2009	62	M	none		2	27.1	5.1		solitary	S4	5.0	-						-	1	dead
56	Hatanaka[55]	2010	59	M	none	HCV	1.8	64	8.6	7	multiple	S8	3.0	-	-	-	-	-	+	-	50	alive
57	Ikeda[56]	2010	64	M	none	HBV			39.7	202	multiple	S8	2.2	-	-					-	8	alive
58	Sasaki[57]	2010	62	M	none	HBV			172.8	864	multiple	S8	5.3		-		+			Liver (2)	4	dead
59	Kadono[58]	2011	45	F	epigastric discomfort	-	1	29.3	3.3	3	solitary	S4	7.5	-	-				+	-	12	alive
60	Handa [59]	2011	61	M	general fatigue	HCV	WNR	WNR	WNR	WNR	solitary	S7	4.0	-	-				+	-	8	alive
61	Sempoux[60]	2011	60	M	abdominal pain, Jaundice	HCV			1572		multiple	S6	3.0	-	-	-	+	+	+	-	3	alive
62	Toda[61]	2011	74	F	none	-	1.5	10.3			multiple	S7	7.1	-	-					Liver (19)	19	alive
63	Tajima[62]	2011	69	M	none	-	1.8	5	2.9	18	solitary	S6/7	8.0	-	-	-	+	-	+	-	19	alive
64	Koga[63]	2012	69	M	none	HBV	1.7	11.5	1.4	22	solitary	S5	4.1	-	-	-	-	-	+	-	0	alive
65	Lai[64]	2012	15	M	none	-	WNR	WNR	WNR		solitary	S5	0.8	-	-				+	-	6	alive
66	Nakayama [65]	2012	78	M	none	HCV	WNR	WNR	WNR	WNR	solitary	s8	8.0	-	-					-	3	alive
67	Kawashima[66]	2012	57	F	abdominal pain		1.7	WNR	WNR	13	solitary	S5	7.0	-	-	-	-	+		-	4	alive
68	Maeda[67]	2013	68	M	none	HCV	WNR	WNR	WNR		solitary	S4	3.0	-	-					Liver, Lymph (7)	13	dead
69	Kaizu[68]	2015	74	F	none	-	WNR	196	WNR	WNR	solitary	S2	6.8	-	+	+	+	+	+	-	32	alive
70	Ishii[69]	2015	59	M	abdominal pain	HBV	53.7	6752			solitary	S5/6/7/8	14.0	-	-	+	+	-	+	Liver (4)	4	alive
71	Our case	2016	77	M	none	-	7.8		4.8	26	multiple	S7/8	3.0	-	-	+	-	+	+	Liver (23)	64	dead
72		2016	67	M	none	-	6.8	24	6.8	29	solitary	S8	3.1	-	-	-	-	-	+	-	43	alive
73		2016	59	F	none	-	2.9	26.6	5.4	13	solitary	S2/3	5.7	-	-	-	-	-	+	-	36	alive
74		2016	72	M	none	HCV	3.5	7.3	5.7		solitary	S5	2.2	-	-	+	-	-	+	-	34	alive
75		2016	83	F	none	-	1.4	17.4	8.8	12	solitary	S8	4.5	-	-	+	-	-	+	Lung (6), Bone (9), Liver(17)	21	dead