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Clinicopathological Features and Prognosis in Patients with Cholangiolocellular Carcinoma and Hepatocellular Carcinoma

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Abstract

Cholangiolocellular Carcinoma (CLC) is a subtype of intrahepatic Cholangiocarcinoma (ICC). The study aimed to examine CLC and Hepatocellular Carcinoma (HCC) and to provide reliable proof for selecting reasonable diagnosis and treatment for CLC patients. The characteristics of two liver malignancies were analyzed from the clinicopathological features and survival outcomes. Our research revealed that number of patients with Elevated Alpha-Fetoprotein (AFP) (p=0.0002), Hepatitis B Virus (HBV)/Hepatitis C Virus (HCV) infection (p<0.0001), single tumor (p=0.0075), and liver fibrosis or cirrhosis (p=0.0043) were significantly lower in the CLC group than in the HCC group. The tumor size in the CLC group was significantly larger than that of the HCC group (p=0.02). The proportion of poorly or undifferentiated tumors (p=0.0003) and the number of neural invasions (p<0.0001) were significantly higher in the CLC group than in the HCC group (p=0.0003). In addition, the overall median survival rate (p=0.0032) and the disease-free survival rate were significantly lower in CLC patients than in HCC patients (p=0.0015). Furthermore multivariate analysis revealed the types and the differentiation of tumor and neural invasion can be regarded as significant independent prognostic factors for CLC and HCC patients' overall survival. In conclusion, CLC has the dual clinicopathological features of HCC and conventional Intrahepatic Cholangiocarcinoma (cICC). The prognosis of CLC was poorer than that of HCC. It is necessary to further explore the intrinsic pathological mechanism of CLC and develop targeted diagnosis and treatment strategies for it.

Keywords: Liver; Malignancy; Clinical; Pathological; Prognosis

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Introduction

According to histological characteristics, primary liver cancer can be divided into Hepatocellular Carcinoma (HCC), Intrahepatic Cholangiocarcinoma (ICC), and combined hepatocellular and Cholangiocarcinoma (CHC) [1]. CHC has been classified into ICC base on the 8th edition American Joint Committee on Cancer/Union for International Cancer Control (AJCC/UICC) Cancer Staging Manual.

With the increasing understanding of liver tumors, HCC and ICC have different tumor growth patterns and biological behaviors. Their treatment is different [2-4]. At present, radical surgical resection is still the only curable means for liver cancer. The current surgical procedure of HCC can be considered as radical as long as the lesion margin is negative [5]. For patients with no suspected hepatic lymph node metastasis, regional lymph node dissections may not be routinely performed [6,7]. ICC, one of the primary liver malignancies, is derived from intrahepatic secondary bile duct epithelial cells. Its curable treatment is the same as HCC, which is radical surgical resection [8]. However, the surgical procedure of ICC is controversial [9]. Some scholars suggest that extensive hepatectomy combined with regional lymph node dissection should be performed while others

argued that lymph nodes should not be dissected routinely as long as the margin is negative [7,10,11]. Recent studies have reported that traditional ICC is further divided into two subtypes according to the histological characteristics, named Cholangiolocellular Carcinoma (CLC) and conventional Intrahepatic Cholangiocarcinoma (cICC), finding that the prognosis of CLC patients is better than that of cICC patients. In addition, the clinical and pathological features of the two types of tumors, treatment, and prognosis are different [12-14]. Subsequent studies have shown that CLC and HCC share common stem cells and may have similarities in tumor biology [15,16]. This study retrospectively analyzed the data of CLC and HCC. We aim to explore the clinicopathological characteristics and prognosis between them and provide reliable proof for selecting reasonable diagnosis and treatment for CLC patients.

Material and Methods

Patients and specimens

This study retrospectively analyzed 81 patients with HCC and 19 patients with CLC which were confirmed by postoperative pathological examination after surgery from 2006 to 2015. The inclusion criteria were as follows: (1) Tumor was surgically removed; (2) Postoperative pathology confirmed as HCC, ICC, or CLC; (3) Surgical margin was R0 or R1.

The exclusion criteria were as follows: (1) Non-hepatoma or non-intrahepatic cholangiocarcinoma or multiple tumors concurrently with hepatocellular carcinoma and intrahepatic cholangiocarcinoma; (2) Exploratory surgery, palliative surgery, liver transplantation or biopsy only; (3) Incomplete clinicopathological data; (4) Death during hospitalization or follow-up due to non-tumor death factors; (5) Cases of lost follow-up.

Consents for surgical resection and clinical study were obtained before the operation.

Collection of clinical and pathological data

(1) Patients' medical records were retrospectively analyzed. Clinical and pathological information was tabulated, including the sex, age, virological markers, tumor markers, hepatic function indicators, etc. Tumor TNM staging was performed using the 8th edition of the AJCC Cancer Staging Manual. Pathological changes, such as inflammation, and cirrhosis, were reviewed microscopically and analyzed according to the Batts-Ludwig stages of inflammation and fibrosis.

(2) Distinction of tumor types: Surgical resection specimens were dissected and made into pathological sections with H&E staining. The type of tumor was identified as microscopically.

1) A total of 81 cases were identified as HCC;

2) Screening of CLC: CLC originates from the ductules/canals of Hering. Its proportion of small bile ducts accounts for more than 80% and without mucin secretion. cICC does not originate from the ductules/canals of Hering. The proportion of small bile ducts is less than 80% or with mucin secretion. Nineteen cases of CLC were selected for the research object.

3) The characteristics and survival rate of HCC and CLC were analyzed by comparing the clinicopathological data.

Follow-up

Survival time refers to the time from surgical resection to death or the last follow-up.

Statistical analysis

Normal and non-normal distribution data of continuous variables were expressed as "mean ± standard deviation" and "median (range)" respectively. Analysis of variance or Kruskal Wallis rank-sum test was used to compare the differences between all groups. Chi-square or Fisher's exact test was used for ratio comparison. Kaplan-Meier method and log-rank test were used to evaluate the postoperative survival rate. When $p<0.05$, the difference was statistically significant. We used GraphPad Prism (version 6.0; GraphPad Software, San Diego, California, US) for statistical analysis.

Results

Patient characteristics

Among the 81 HCC patients, 59 were males, and 22 were females. The age ranged from 30 to 76 years old with a median age of 56 years. Among the 19 CLC patients, 11 were males, and 8 were females. The age ranged from 34 to 79 years old with a median age of 63 years. The number of patients with abnormal levels of AFP (p=0.0002) and TBA (p=0.01) was significantly lower in the CLC group than in the HCC group. The infection rate of HBV/HCV in the HCC group was significantly higher than that in the CLC group (p<0.0001). The other results were not statistically significant. The results are shown in Table 1.

Tumor characteristics

The pathological data of two liver malignancies showed that the tumor size of CLC was significantly larger than that of HCC (p=0.02). Besides, compared with the HCC group, multiple nodules are more common in the CLC group (p=0.0075). In addition, the proportion of poor or undifferentiated tumors was significantly higher in the CLC group than in the HCC group (p=0.0003). The number of neural invasions was significantly higher in the CLC group than in the HCC group (p<0.0001). Furthermore, the number of patients with liver fibrosis or cirrhosis was significantly lower in the CLC group than in the HCC group (p=0.0043). Patients with lymph node metastasis, Microvascular Invasion (MVI), and TNM staging did not differ between groups (Table 2). The pathological examination is shown in Figure 1.

Prognostic factors

All 100 patients have completed follow-up interviews, 9 died and 10 were alive in CLC while 16 died and 65 were alive in HCC. Overall median survival was 19 months (range: 0.3 to 60) and disease-free median survival was 9 months (range: 0.3 to 60) in CLC. Overall median survival was 26 months (range: 3 to 117) and disease-free median survival was 18 months (range: 1 to 117) in HCC. The overall median survival rate (19 months) of CLC patients was significantly worse than that of HCC patients (26 months) (p=0.0032). DFS (9 months) of CLC patients was also significantly worse than that of HCC patients (18 months) (p=0.0015). Results are shown in Figure 2.

Based on the univariate analysis data, the risk factors for a poorer liver cancer prognosis included the tumor types, the differentiation of tumor, and neural invasion. Multivariate analysis showed that the tumor types, the differentiation of tumor, and neural invasion were significant independent risk factors for a poorer prognosis (Table 3).

Discussion

In this research, we retrospected 100 cases of liver cancer

Table 1: Patient characteristics.

	n	CLC	HCC	*p* value
Total number	100	19	81	
Age, years; median		63	56	
(range)		(34-79)	(30-76)	0.333
Gender				0.266
Male		11 (58%)	59 (73%)	
Female		8 (42%)	22 (27%)	
HBV/HCV infection				**<0.0001**
HBsAg/HCV, positive		5 (26%)	68 (84%)	
HBsAg/HCV, negative		14 (74%)	13 (16%)	
AFP>10 ng/ml				**0.0002**
AFP, positive		3 (16%)	53 (65%)	
AFP, negative		16 (84%)	28 (35%)	
CA19-9>39.9 U/ml				0.3248
CA19-9, positive		5 (26%)	13 (16%)	
CA19-9, negative		14 (74)	68 (84%)	
TB>20.5 umol/L				0.897
TB, positive		4 (21%)	16 (20%)	
TB, negative		15 (79%)	65 (80%)	
DB>6.8 umol/L				0.452
DB, positive		1 (5%)	12 (15%)	
DB, negative		18 (95%)	69 (85%)	
ALT>40U/L				0.576
ALT, positive		4 (21%)	24 (30%)	
ALT, negative		15 (79%)	57 (70%)	
AST>40U/L				0.856
AST, positive		5 (26%)	23 (28%)	
AST, negative		14 (74%)	58 (72%)	
γ-GT>35 U/L				0.226
γ-GT, positive		13 (68%)	43 (53%)	
γ-GT, negative		6 (32%)	38 (47%)	
LDH>245U/L				0.915
LDH, positive		3 (16%)	12 (15%)	
LDH, negative		16 (84%)	69 (85%)	
ALP>185 U/L				0.578
ALP, positive		1 (5%)	3 (3.7%)	
ALP, negative		18 (95%)	78 (96.3%)	
TBA>15 umol/L				**0.01**
TBA, positive		0	21 (26%)	
TBA, negative		19 (100%)	59 (74%)	
Schistosomiasis		2 (11%)	1 (1.2%)	0.09
Gallstone/ Cholangitis		0	1 (1.2%)	0.626

CLC: Cholangiolocellular Carcinoma; HCC: Hepatocellular Carcinoma; HBV: Hepatitis B Virus; HCV: Hepatitis C Virus; HBsAg: Hepatitis B Surface Antigen; AFP: Alpha Fetoprotein alpha Fetoprotein; CA19-9: Carbohydrate Antigen 19-9; TB: Total Bilirubin; DB: Direct Bilirubin; ALT: Alanine transaminase; AST: Aspartate Transaminase; γ-GT: Gamma-Glutamyl Transpeptidase; LDH: Lactate Dehydrogenase; ALP: Alkaline Phosphatase; TBA: Total Bile Acid

specimens including 19 CLCs and 81 HCCs. According to the histological features, we screened the CLC patients and compared them with HCC patients for clinicopathological data, concluding that the prognosis of CLC patients in both OS and DFS were poorer than those of HCC patients. In clinical characteristics, some CLC patients had HBV/HCV infection (5/19) and abnormal levels of AFP, which is similar to the previous study [17]; in pathological features, the tumor size of CLC was significantly larger than that of HCC and multiple tumors were more common in the CLC group. Furthermore, the proportion of poorly or undifferentiated tumors and neural invasion were significantly higher in the CLC group. However, there was no significant difference in lymph node metastasis between the two groups. Besides, CLC patients can also have liver fibrosis/cirrhosis,

Table 2: Tumor characteristics.

	n	CLC	HCC	*p* value
Tumor size, cm				**0.02**
>5 cm		11 (58%)	24 (30%)	
≤ 5 cm		8 (42%)	57 (70%)	
Tumor number				**0.0075**
Single		13 (68%)	74 (91%)	
multiple		6 (32%)	7 (9%)	
Differentiation				**0.0003**
Well		0	5 (6.2%)	
Moderately		9 (47%)	66 (81.5%)	
Poorly or undifferentiated		10 (53%)	10 (12.3%)	
MVI		5 (26%)	22 (27%)	0.94
Neural invasion		19 (100%)	0	**<0.0001**
Lymph node metastasis		2 (11%)	3 (3.7%)	0.189
TNM Stage				0.1227
I		9 (47%)	45 (55.6%)	
II		8 (42%)	24 (29.6%)	
III		0	10 (12.3%)	
IV		2 (11%)	2 (2.5%)	
Fibrosis/Cirrhosis				**0.0043**
S0,S1 or S2		16 (84%)	38 (47%)	
(S3 or S4)		3 (16%)	43 (53%)	

CLC: Cholangiolocellular Carcinoma; HCC: Hepatocellular Carcinoma; MVI: Microvascular Invasion

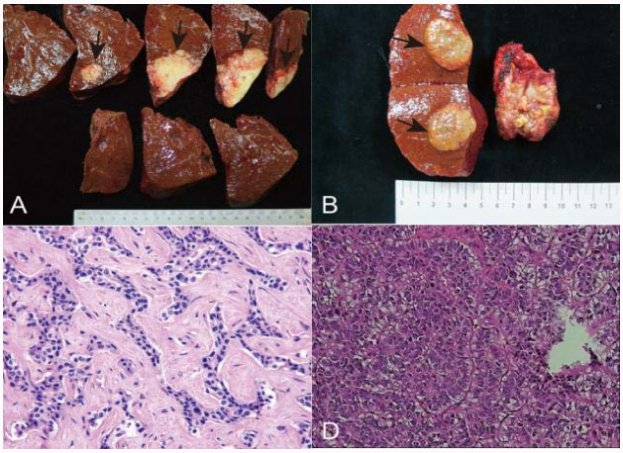

Figure 1: Gross and histological features of CLC and HCC.CLC and HCC showed on macroscopically A and B (arrows). Morphology of CLC and HCC showed on C and D, H&E. Original magnification, C-D: 200.

Table 3: Univariate and multivariate analysis of prognostic factors of patients with CLC and HCC.

	Univariate analysis		Multivariate analysis	
	p	Exp (B)	95% CI	*p*
Group	**0.001**	0.01	0.032-0.547	**0.005**
HBV/HCV	0.276	2.645		
AFP	0.442	2.116		
TBA	0.188	6.405		
Tumor size	0.212	0.374		
Tumor number	0.676	1.443		
Differentiation	**0.037**	7.684	1.278-17.045	**0.02**
MVI	0.554	1.635		
Neural invasion	**0.001**	0.01	0.037-0.558	**0.005**
Lymph node metastasis	0.771	0.51		
Fibrosis/Cirrhosis	0.328	2.439		
TNM Stage	0.195	2.813		

CLC: Cholangiolocellular Carcinoma; HCC: Hepatocellular Carcinoma; HBV: Hepatitis B Virus; HCV: hepatitis c virus; AFP: Alpha Fetoprotein alpha Fetoprotein; TBA: Total Bile Acid; MVI: Microvascular Invasion

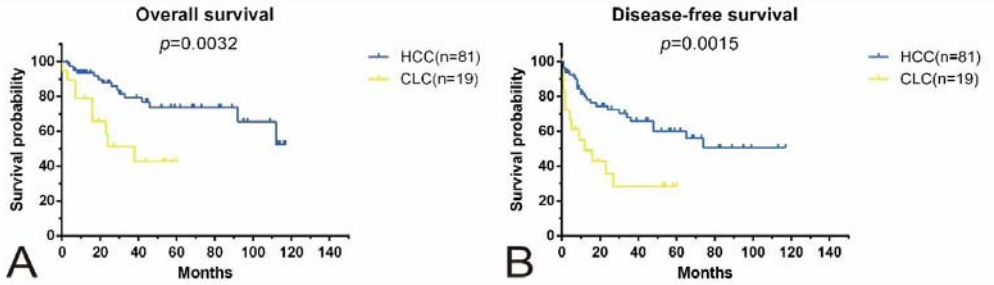

Figure 2: Patients' survival curves who received curative surgery. A: Comparison of overall survival rates between patients with CLC and HCC; B: Comparison of disease-free survival rates between patients with CLC and HCC.

but the proportion was lower than that of HCC. Based on the multivariate analysis data, the types of tumors, the differentiation of the tumor, and neural invasion were independent risk factors for a poorer prognosis of liver cancer.

In 1959, the concept of CLC was first described [18]. It might originate from hepatic progenitor cells [12,19]. With the increasing understanding of CLC, related studies reported that CLC as one kind of liver cancer, its clinical characteristics are similar to HCC, but its morphological features are similar to ICC. It is suggested that CLC cells may originate from Hering's canal or stem cells which have the intermediate characteristics between hepatocytes and bile duct epithelial cells [12,20].

According to the histological feature, hepatic progenitor cells can be further differentiated into hepatocytes and bile duct cells [21]. The characteristics of CLC often show that the tumor cells often produce mucin and have a cubic shape [15]. They express CK7, CK19 and N-CAM, features of hepatic progenitor cells, and their malignancy was supported by p53 and Ki67 [22]. While cICC originates from the large bile duct. The bile duct cells with cylindrical shapes often secrete mucins [15]. The clinicopathological features of HCC and ICC were significantly different, and previous studies also showed that the clinicopathological characteristics and prognosis of CLC and cICC were different [13,23]. CLC and HCC originate from hepatic progenitor cells [16]; therefore, we hypothesized that their clinicopathological features may be similar to some extent. However, there are no relevant research reports.

From the previous study, CLC has various clinicopathological findings [12]; therefore, it is difficult to describe a clear diagnostic criterion for CLC [24]. At present, the diagnosis of CLC mostly can be confirmed by postoperative pathology [25]. It is difficult to make a definite diagnosis before the operation.

Imaging's are important examination methods for preoperative tumor characterization. Reports have shown that the imaging features of CLC, like contrast-enhanced Computed Tomography (CT), Magnetic Resonance Imaging (MRI), and Contrast-Enhanced Ultrasonography (CEUS), largely differ from those of HCC but are similar to those of ICC [26]. CLC has hyper-enhancement or predominantly peripheral enhancement in the early phase and persistent enhancement in the late phase by CT and MRI, CEUS showed diffuse and homogeneous enhancement in the arterial phase and became progressively hypoechoic during the portal vein and late phases [27], it may be one of the characteristic imaging findings of this rare tumor [28]. CLC has the dual imaging features of HCC and cholangiocarcinoma. The absence of fibrous capsule and tumor necrosis, intrahepatic peripheral location, and portal vein penetration in the tumor also appears to be the characteristics [29].

ICC, a primary liver malignancy secondary to HCC, has the characteristics of rapid progression and poor prognosis [8]. Epidemiological data in recent years indicate that the incidence of ICC has been increasing in recent years. Due to a lack of efficient early screening markers, ICC is frequently diagnosed at an advanced stage when curative surgical resection is not an option [11]. For

patients who underwent radical surgical resection had a better prognosis than those who received other treatments [8]. Since Cholangiocarcinoma (CCA) and HCC have different growth patterns and metastasis pathways behavior, CCA is more likely to have lymph node metastasis and nerve invasion, which determines the different surgical procedures for CCA and HCC [7]. For the radical surgical procedure, different types of liver tumors have different surgical procedures. It is generally recognized that the surgical procedure of HCC can be considered as radical as long as the margin is negative. Regional lymph node dissection may not be routinely performed [5].

For the radical surgical procedure of ICC, it is suggested that extensive hepatectomy should be performed. If the surgical margin reached 1 cm or more, then the tumor would have a low recurrence [30]. However, the lymph node dissections should be performed or not is still controversial [10]. Combined hepatic hilar lymph node dissection is recommended worldwide [7,9,11].

A case reported that radical hepatectomy can be an effective measure even for ruptured CLC [31]. Compared with cICC, CLC has a lower incidence of lymph node metastases [13]. Studies have shown that patients with hepatectomy, especially those with liver dysfunction or liver cirrhosis who received major abdominal surgery, are more likely to have complications such as abdominal infection and liver dysfunction after surgery [32-34]. When choosing surgical procedures, we can make a preliminary judgment for CLC based on the patient's history, imaging, and operative exploration. If there is no suspicious lymph node metastasis, major hepatectomy should not be performed. That the margin of the lesion is negative can be considered radical. It is not necessary to dissect regional lymph nodes routinely or just to dissect the suspicious lymph nodes, which can reduce the operation trauma, the operation duration, the incidence of postoperative complications, shorten the recovery time after the surgery, and the cost of hospitalization.

Due to the low incidence of CLC, a lot of current studies are only case reports, and there is no deep understanding of it. Thus, in contrast to the results discussed above, some researchers have shown that since CLC has the characteristics of stem cells, its prognosis is rather poor [35]. Moreover, CLC has a poor prognosis after repeat hepatectomy for intrahepatic recurrence. It clinically resembles ICC and prognosis may be unfavorable [36]. Therefore, the study of the features of CLC appears particularly important.

The main limitations of this study were the small number of CLC cases with a complete follow-up; in addition, the diagnosis of CLC can only be confirmed by postoperative pathology. There are no preoperative diagnosis criteria. Furthermore, the proportion of small bile ducts in CLC has not been unified. Last but not least, there is no definitive range for lymph node dissection, which may result in undetected lymph node metastasis. In future research, the surgical procedure should be standardized, especially the range of lymph node dissection and the detection of immunohistochemistry. The results need to be confirmed by multi centers, large-scale randomized controlled clinical trials.

Authors' Contribution

Study concepts and design: R-PG, MD. Experimental studies /data analysis: MD, LF. Interpretation of data: X-CG, K-ST. Manuscript writing: MD. Manuscript editing: R-PG. All authors have read and approved the final version of the manuscript.

Availability of ata and Materials

The data that support the findings of our research are available from Sun Yat-sen University Cancer Center, but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available.

Ethics Approval and Consent to Participate

The approval of this research was granted by the Medical Ethics Committee of Sun Yat-sen University Cancer Center. All samples in this study were anonymized. No written or verbal informed consent was obtained to use the retrospective data from the patients in the current work since most of them were deceased, and it was not deemed necessary by the Ethics Committee, who waived the need for consent.

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