

Clinical features and prognostic factors of cryptogenic hepatocellular carcinoma

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Background: To explore the clinical features and prognostic factors of cryptogenic hepatocellular carcinoma (cHCC).

Methods: The clinical data of 59 cHCC patients who had undergone radical surgery in our center from February 1999 to December 2010 were retrospectively analyzed. Survival analysis was performed by using the Kaplan–Meier method. Univariate and multivariate regression analyses were carried out for the assessment of potential prognostic factors.

Results: Among these 59 patients, there were 49 men and 10 women aged 27 to 84 years (mean: 61.4 years). Sixteen patients (27.12%) had nonalcoholic fatty liver disease (NAFLD), whereas hepatitis virus serologic markers were not completely negative in 43 patients (72.88%; non-all-negative group). All patients received radical resection in our hospital. HCC was confirmed after postoperative pathologic examinations in all these 59 patients. Pathology revealed that 34 patients also had cirrhosis, and the manifestations of cirrhosis significantly differed between all-negative group and non-all-negative group. Forty-three patients (72.88%) died within follow-up. The postoperative 3- and 5-year survival rates were 44.07% and 35.59%, respectively. The longest disease-free survival after the operation was 195 months, and the median survival time was 32 months. Multivariate analysis showed that HBcAb (+) and NAFLD were independent prognostic factors for the postoperative survival of patients with cryptogenic HCC (HR =2.558, 95% CI: 1.146–5.711, P=0.022; HR =2.067, 95% CI: 1.056–4.049, P=0.034).

Conclusions: cHCC is a relatively rare disease and occurs mainly in elderly obese males. The development of cHCC is associated with NAFLD and hepatitis B virus Infection. HBcAb (+) status and NAFLD are independent prognostic factors for the postoperative survival of cHCC patients.

Keywords: Cryptogenic hepatocellular carcinoma (cHCC); nonalcoholic fatty liver disease (NAFLD); HBcAb (+) status; treatment; prognosis

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Introduction

The incidence and mortality of liver cancer rank fifth and third among all cancers (1). The common causes of liver cancer include viral hepatitis and alcoholic liver cirrhosis (1,2). The early vaccination of hepatitis B vaccine and the increased safety of blood products have significantly reduced the incidence of viral liver cancer; furthermore, alcoholic liver cirrhosis-associated liver cancer has also been controlled in recent years (3). Unfortunately, the proportions of cryptogenic hepatocellular carcinoma (cHCC), caused by non-viral hepatitis and nonalcoholic cirrhosis and with unknown etiologies, have gradually increased (4). In this article, we retrospectively analyzed the clinical data of 59 cHCC patients who had been managed in the Department of Hepatobiliary Surgery of our hospital from 1999 to 2010, with an attempt to investigate the clinical features and prognostic factors of cHCC.

Methods

Inclusion criteria

The diagnostic criteria of cHCC were as follows (5-8): (I) pathologically confirmed as primary liver cancer; (II) alcohol consumption: ≤ 20 g/d for men and ≤ 10 g/d for women; (III) both HBsAg and anti-HCV antibody were negative; and (IV) liver cancer caused by hemoglobin diseases, autoimmune hepatitis, and/or other chronic liver diseases were excluded.

Follow-up

From January 1999 to December 2010, there were 908 patients with primary hepatocellular carcinoma who underwent radical operation in our department, among whom 59 patients met the diagnostic criteria of cHCC. Patients were regularly followed up, and data including tumor recurrence and patient survival were recorded. The deadline of the follow-up was September 1, 2017.

The time interval between surgery and recurrence was defined as the disease-free survival (DFS), and the period from surgery to death/final follow-up visit as the overall survival (OS). Factors (including sex, age, BMI, ALT, AST, TBIL, DBIL, GGT, TG, CHOL, ALB, TP, blood glucose, AFP, nonalcoholic fatty liver disease (NAFLD), serological markers for hepatitis viruses, tumor size, tumor number, and pathological grade) that might affect the outcome of a cHCC surgery were analyzed.

Statistical analysis

All data were analyzed using the SPSS 22.0 software. The comparisons of the categorical variables and the continuous variables were based on χ^2 test and Kruskal-Wallis test, respectively.

Survival analysis was performed by using the Kaplan-Meier method. Univariate regression analysis was carried out for the assessment of potential prognostic factors. Variables with a P value of < 0.1 entered the multivariate Cox regression model. A P value of < 0.05 was considered significantly different.

Results

Clinical features

A total of 59 patients (6.49% of the 908 patients with primary liver cancer during the same period) were included in the analysis. These subjects had a mean age of 61.4 years and a BMI of (24.55 ± 3.23) kg/m². The male/female ratio was 4.9. Sixteen patients had NAFLD; the hepatitis virus serologic markers were all negative in 16 patients (all-negative group) but were not all negative in the remaining 43 patients (non-all-negative group, with HBcAb expression in each subject). Detection of tumor markers showed AFP ≥ 7 ng/mL in 23 cases (38.98%), whereas CEA was normal in all patients.

Liver function tests showed: ALT > 50 U/L in 13 cases (22.3%); AST > 40 U/L in 10 cases (16.95%); TBil > 17.1 μ mol/L in 10 cases (16.95%); and TG > 1.69 mmol/L in 10 cases (16.95%). The clinical data of these 59 patients are summarized in *Table 1*.

Imaging examinations

All 59 patients underwent CT and ultrasonography, and 40 patients received magnetic resonance imaging (MRI). The imaging data showed that 16 patients (27.12%) were suffering from fatty liver.

Clinical treatment and prognosis

All the 59 patients underwent radical surgical treatment, among whom 17 also received postoperative interventional therapy, radiotherapy, chemotherapy, radiofrequency (RF) ablation, and other treatments. The median follow-up duration for these 59 cHCC patients was 32 months, and

Table 1 Clinicopathologic data of the all-negative group and the non-all-negative group

Clinical features	All-negative group (n=16)	Non-all-negative group (n=43)	All patients (n=59)	P
Gender, n (%)				0.822
Male	13 (26.53)	36 (73.47)	49	
Female	3 (30.00)	7 (70.00)	10	
Age (years)	58.43±15.78	62.63±12.23	61.49±13.27	0.322
BMI (kg/m ²)	24.66±3.33	24.27±3.04	24.55±3.23	0.562
Fasting blood sugar (mmol/L)	5.67±1.29	5.73±1.87	5.71±1.73	0.495
AFP (ng/mL)	399.96±855.19	2,107.59±7,788.62	1,644.51±6,669.08	0.651
ALT (U/L)	39.12±36.98	46.44±136.93	44.46±118.08	0.232
AST (U/L)	34.62±20.77	47.09±129.44	43.71±110.79	0.343
ALP (U/L)	83.56±39.77	80.74±34.53	81.51±35.69	0.871
GGT (U/L)	39.56±20.19	58.19±50.75	53.14±45.17	0.484
TBiL (μmol/L)	11.17±3.66	13.23±4.97	12.67±4.71	0.152
DBiL (μmol/L)	3.36±1.41	4.13±2.27	3.92±2.09	0.268
CHOL (mmol/L)	4.30±1.19	4.28±0.90	4.28±0.97	0.621
HDL-CHO (mmol/L)	1.03±0.36	2.48±6.39	2.09±5.48	0.167
LDL-CHO (mmol/L)	2.43±0.81	2.65±0.79	2.59±0.80	0.458
TG (mmol/L)	7.85±20.47	3.64±16.30	4.78±17.45	0.014
TP (g/L)	69.64±8.57	70.50±7.15	70.27±7.49	0.973
ALB (g/L)	41.05±5.07	40.91±3.80	40.95±4.13	0.733
NAFLD, n (%)				0.823
Yes	4 (25.00)	12 (75.00)	16	
No	12 (27.91)	31 (72.09)	43	
Longest tumor diameter (cm)	7.12±5.48	6.18±3.48	6.44±4.09	0.980
Tumor number, n (%)				0.318
Single	13 (25.00)	39 (75.00)	52	
Multiple	3 (42.86)	4 (57.14)	7	
Pathologic grade, n (%)				0.101
Highly differentiated	5 (55.56)	4 (44.44)	9	
Moderately differentiated	7 (20.00)	28 (80.00)	35	
Poorly differentiated	4 (26.67)	11 (73.33)	15	
Pathologic findings, n (%)				0.324
Hepatitis	9 (56.25)	18 (41.86)	27	
Non-hepatitis	7 (21.87)	25 (78.13)	32	
Pathologic findings, n (%)				0.000
Cirrhosis	3 (8.33)	33 (91.67)	36	
Non-cirrhosis	13 (56.52)	10 (43.48)	23	

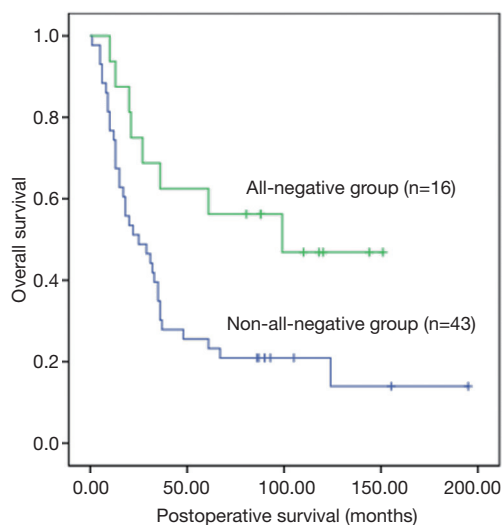


Figure 1 Postoperative total survival curves of all-negative group and non-all-negative group ($P=0.015$).

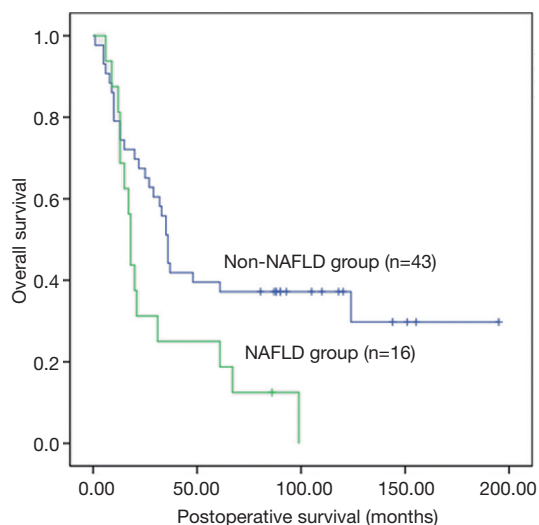


Figure 2 Postoperative total survival curves of NAFLD group and non-NAFLD group ($P=0.02$).

the post-operative 1-, 3-, and 5-year survival rates were 81.36%, 44.07%, and 35.59%, respectively; the longest DFS was 195 months, and the median survival time reached 32 months.

Post-operative pathology

HCC was confirmed after postoperative pathologic examinations in all these 59 patients.

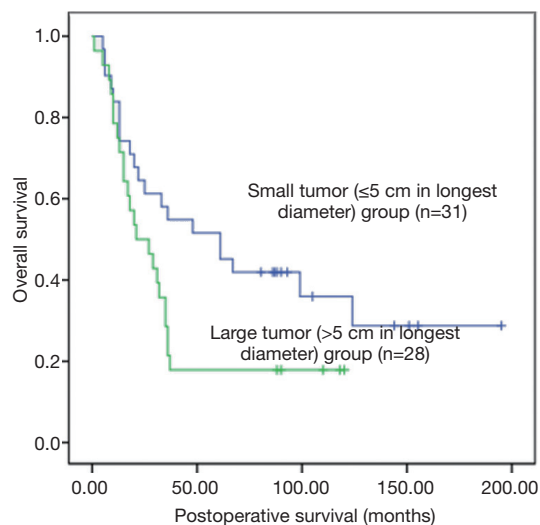


Figure 3 Postoperative total survival curves of large tumor (>5 cm in longest diameter) group and small tumor (≤ 5 cm in longest diameter) group ($P=0.045$).

According to the 2010 WHO Classification of Digestive Tumors, the tumors were highly differentiated in 9 cases, moderately differentiated in 35 cases, and poorly differentiated in 15 cases.

There were 14 cases of liver cirrhosis complicated with hepatitis and 10 cases without any hepatitis or liver cirrhosis. The tumors were single in 52 cases and multiple in 7 cases. No metastasis was noted in all 59 cases. The tumor size ranged 1.7–18 cm. The distribution of hepatitis virus serologic markers significantly differed between all-negative group and non-all-negative group ($P=0.000$) (Table 1).

Influences of clinical indicators on the postoperative OS

Univariate analysis showed that the postoperative survival was significantly superior in the all-negative group ($n=16$) than in non-all-negative group ($\chi^2=5.918$, $P=0.015$) (Figure 1), whereas that in the non-NAFLD group ($n=43$) was significantly longer than in NAFLD group ($\chi^2=5.401$, $P=0.02$) (Figure 2). The survival time of small tumor (≤ 5 cm in longest diameter) group was longer than that of large tumor (>5 cm in longest diameter) group ($P=0.045$) (Figure 3). Variables with a P value of <0.1 entered the multivariate Cox regression model. Multivariate analysis showed that positive HBcAb expression (HR =2.558, 95% CI: 1.146–5.711, $P=0.022$), NAFLD (HR =2.067, 95% CI: 1.056–4.049, $P=0.034$), and large tumor (>5 cm in longest

diameter) (HR =2.190, 95% CI: 1.155–4.154, P=0.016) were the independent factors that affected the OS (Table 2).

Discussion

The concept of cryptogenic liver cirrhosis was proposed by Stephen *et al.* in 2004 (9). On this basis, some authors further described the definition of cHCC (5–8). “Cryptogenic” does not mean unknown etiology. Rather, cHCC specifically refers to liver cancers that are not caused by hepatitis B, alcoholic cirrhosis, and other specific pathogenic factors but caused by relatively obscure etiologies (7,8).

It has been reported that NAFLD and other metabolic syndromes are closely related to the occurrence of cHCC (10). With the change of lifestyle and the increase of obese populations, the proportion of cHCC associated with NAFLD and metabolic liver diseases are increasing (4,11). In Europe and North America, the number of cHCC patients has shown an increasing trend (8,12). In China, however, few literature has described such primary hepatocellular carcinoma.

cHCC is a relatively rare disease and occurs mainly in elderly obese males (Table 3). As shown in our current study, cHCC cases accounted for 6.49% of the primary liver cancer patients that were treated during the same period. These cHCC patients had a mean age of 61 years and a BMI of (24.55 ± 3.23) kg/m². The male/female ratio was 4.9. These findings were consistent with the above conclusions. HW Kwak *et al.* have demonstrated that HBcAb-positive cHCC accounted for about 84.6% of all cHCC cases in hepatitis B virus endemic area (8). A prospective cohort study indicated that HBsAg would be cleared with age in patients with hepatitis B virus infection, along with HbcAb expression; in some patients, liver cancer occurred within 7.3 years after the removal of HBsAg (13).

These phenomena may be explained by the fact that the HBsAg clearance is related only to the increasing age. HBsAg removal often takes a long period of time; therefore these patients have longer exposure to the destructive effect caused by HBV DNA integration, and such destructive effect is reflected in the following mechanism: by integrating into hepatocyte genome, the HBV DNA causes long-term inflammation and human hepatocyte genome mutation, and their persisting effects lead to the occurrence of liver cancer (14). Thus, these HBcAb-positive cHCC occurred actually following hepatitis B virus infection accompanied by HBsAg clearance and HBV DNA

integration. It has been reported that more than half of the cHCC cases in non-viral hepatitis endemic countries are NAFLD-related cHCC (10,15,16). NAFLD is a group of diseases that are radiologically or histologically manifested as the fatty change of hepatocyte and are not caused by excessive alcohol use, drugs, or hereditary diseases (17). The pathogenic mechanism of NAFLD-associated cHCC is as follows: excessive deposition of liver fat caused by obesity and drugs may induce the increase of TNF α and IL-6 and thus cause inflammation in liver, eventually leading to the occurrence of liver cancer (18). In our current series, HBcAb-positive cHCC accounted for 72.88% and NAFLD patients accounted for 27.12%. China has a high prevalence of hepatitis virus infection, along with a large proportion of hepatitis patients. The proportion of samples in this study is consistent with our national conditions.

Few literatures have described the prognosis of patients with cHCC after surgery. In our current series, the post-operative 3-, and 5-year survival rates were 44.07% and 35.59%, respectively; the longest DFS was 195 months, and the median survival time reached 32 months. Whether cHCC has a better prognosis than non-cHCC remains controversial. In HW Kwak *et al.*'s study (8), the prognosis of cHCC was superior to that of virus-associated liver cancer; however, Sang SL's study has demonstrated that the prognosis of cHCC was not significantly different from those of viral HCC and alcoholic liver cancer (6).

Up to now no study has investigated the prognostic factors of cHCC. In our current study, univariate analysis showed that the median survival time of HBcAb-positive group, NAFLD group, liver cirrhosis accompanied with hepatitis group, and large tumor size (>5 cm) group was significantly shorter than their counterparts. Multivariate analysis showed that HBcAb (+), NAFLD, and large tumor size (>5 cm) were independent prognostic factors for the postoperative survival of cHCC patients. Clinically HBcAb (+) status and NAFLD can be used as important prognostic predictors for cHCC patients after surgery. Compared with the HBsAg (+) status and alcoholic fatty liver, HBSAG (-) HBcAb (+) status and NAFLD are often neglected and their treatments are delayed due to the lack of specific clinical features.

In summary, cHCC is a relatively rare disease and occurs mainly in elderly obese males. The development of cHCC is associated with NAFLD and hepatitis B virus infection. HBcAb (+) cHCC is the predominant type in hepatitis B virus endemic area. HBcAb (+) and NAFLD are independent prognostic factors for the postoperative

Table 2 Univariate and multivariate analyses of the factors influencing the postoperative survival of cHCC patients

Clinical features	n	Median survival [95% CI]	Univariate analysis			Multivariate analysis		
			HR	95% CI	P	HR	95% CI	P
Gender								
Males	49	33 [15–51]						NS
Females	10	31 [26–36]	1.288	–	0.566			
Age (years)								
≤60	23	33 [23–42]						NS
>60	36	31 [10–52]	0.985	0.533–1.820	0.963			
BMI (kg/m ²)								
≤23.9	24	22 [13–30]						NS
>23.9	35	36 [30–41]	0.654	0.358–1.195	0.167			
Blood sugar (mmol/L)								
≤6.38	50	27 [14–39]						NS
>6.38	9	67 [0–154]	0.691	0.290–1.647	0.405			
AFP (ng/mL)								
≤7	36	29						NS
>7	23	36	0.661	0.306–1.427	0.292			
ALT (U/L)								
≤50	46	29 [15–43]						NS
>50	13	36 [22–50]	0.661	0.306–1.427	0.292			
AST (U/L)								
≤40	49	31 [16–46]						NS
>40	10	32 [18–46]	0.839	0.373–1.887	0.671			
ALP								
≤125	53	35 [27–43]						NS
>125	6	12 [0–24]	1.825	0.710–4.689	0.212			
GGT (U/L)								
≤60	41	35 [26–44]						NS
>60	18	25 [15–35]	1.485	0.791–2.787	0.219			
TBIL (μmol/L)								
≤17.1	49	29 [14–44]						NS
>17.1	10	36 [33–39]	0.908	0.420–1.960	0.805			
DBIL (μmol/L)								
≤5.1	49	25 [13–37]						NS
>5.1	10	37 [0–76]	0.749	0.345–1.624	0.464			
CHOL (mmol/L)								
≤5.69	55	32 [22–42]						NS
>5.69	4	18 [0–42]	1.463	0.522–4.106	0.469			

Table 2 (continued)

Table 2 (continued)

Clinical features	n	Median survival [95% CI]	Univariate analysis			Multivariate analysis		
			HR	95% CI	P	HR	95% CI	P
HDL-CHO (mmol/L)								
<0.90	18	37 [0–89]			0.257		NS	
0.90–1.45	38	29 [12–46]	1.176	0.605–2.287	0.632			
>1.45	3	22 [0–47]	2.950	0.813–10.708	0.1			
LDL-CHO (mmol/L)								
≤3.34	52	32 [23–41]					NS	
>3.34	7	20 [15–25]	1.396	0.584–3.334	0.453			
TG (mmol/L)								
≤1.69	49	31 [20–42]					NS	
>1.69	10	36 [0–108]	0.694	0.292–1.649	0.408			
TP (g/L)								
<65	6	36 [16–56]					NS	
≥65	53	31 [19–43]	1.231	0.439–3.453	0.693			
ALB (g/L)								
≥40	56	31 [21–41]					NS	
<40	3	37 [0–82]	0.841	0.203–3.487	0.811			
Serum markers for hepatitis virus								
All-negative group	16	99						
Non-all-negative group	43	25 [8–42]	2.503	1.154–5.426	0.015	2.558	1.146–5.711	0.022
NAFLD								
Yes	43	36 [32–40]						
No	16	18 [16–20]	2.084	1.098–3.955	0.025	2.067	1.056–4.049	0.034
Longest tumor diameter (cm)								
≤5.0	31	61 [24–98]						
>5.0	28	21 [7–35]	1.845	0.996–3.417	0.045	2.190	1.155–4.154	0.016
Tumor number								
Single	52	31 [16–46]					NS	
Multiple	7	35 [14–56]	1.187	0.500–2.821	0.697			
Pathologic grade								
Highly differentiated	9	61 [0–134]			0.953		NS	
Moderately differentiated	35	29 [15–43]	1.119	0.483–2.596	0.793			
Poorly differentiated	15	32 [13–51]	1.071	0.673–1.704	0.762			
Pathologic findings								
Non-hepatitis virus-caused cirrhosis	45	36 [31–41]						
Hepatitis virus-caused cirrhosis	14	17 [11–23]	2.156	1.117–4.161	0.022	1.696	0.844–3.408	0.138

Table 3 Clinical features of cHCC in literature

Author	Country	Year	Number of cases	cHCC/HCC	Sex ratio (M/F)	Age	BMI	HBcAb(+)	NAFLD(+)
Fukushima (5)	Japan	2010	24	–	20/4	67.1±10.1	22.6±3.3	11/24	–
Song (6)	Korea	2012	36	–	26/10	72.4±11.0	24.1±4.2	–	–
Lee (7)	Korea	2013	35	35/512	20/15	68.3±10.5	24.6±3.0	–	–
Kwak (8)	Korea	2016	162	162/1,784	125/37	61.9±10.4	23.5±3.2	137/162	43/162

survival of cHCC patients. However, our current study was limited by its single-center retrospective design and small sample size, and its conclusions need to be confirmed by more randomized controlled studies with larger sample sizes.

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None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The study was approved by the ethics committee board of National Cancer Center/Cancer Hospital (No. 17-194/1450) and written informed consent was obtained from all patients.

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