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Prognostic Factors of Survival and Comparison of Surgically Resected Combined Hepatocellular-cholangiocellular Carcinoma, Hepatocellular Carcinoma, and İntrahepatic Cholangiocarcinoma

Yigit Duzkoylu[1,*], Mehmet Akif Ustuner[1], Nesrin Turhan[2] and Erdal Birol Bostanci[1]

[1] Gastroenterological Surgery Clinic, Turkiye Yuksek Ihtisas Education and Research Hospital, Ankara, Turkey
[2] Pathology Department, Turkiye Yuksek Ihtisas Education and Research Hospital, Ankara, Turkey

*** *Corresponding author:*** Yigit Duzkoylu, Gastroenterological Surgery Clinic, Turkiye Yuksek Ihtisas Education and Research Hospital, Ankara, Turkey. Tel: +905332612533; Email: dryigit@gmail.com

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Abstract

Background: Hepatocellular carcinoma (HCC) and cholangiocarcinoma (CC) are the most common primary malignancies of the liver. The combined form of these two tumors (i.e., cHC-CC) is a considerably rare type of liver cancer displaying both malignant components.
Objectives: The present study aimed to explore the factors affecting survival in patients with HCC, ICC, and cHC-ICC through referring to statistical analysis, including demographics, histopathological, and operative and laboratory findings.
Methods: In this research, 53 patients were evaluated retrospectively, who had undergone an operation for primary liver tumors in a single tertiary center. Data were analyzed in terms of demographics, operation, tumor features, histopathological analysis, and their relationship with survival.
Results: The study groups consisted of 20 (37.7%) and 33 (62.3%) females and males, respectively, with a mean age of 62.3 years. It was revealed that the survival rate was significantly higher in HCC, compared to other groups (P<0.05). Moreover, alpha-fetoprotein (AFP) was significantly higher in the HCC group than in the intrahepatic cholangiocarcinoma (ICC) group, and carbohydrate antigen 19-9 levels and the presence of jaundice and perineural invasion were significantly higher in the ICC group, compared to HCC patients. In the HCC group, macroscopic vascular invasion, perineural invasion, and T staging were statistically significant. It was also found that in the ICC group, the macroscopic vascular invasion was statistically significant, and in the cHC-ICC group, the increased levels of AFP showed a statistically significant effect on survival (P<0.05).
Conclusion: To the best of our knowledge, the current research was one of the very few studies performed focusing on each group of liver tumors in a single study. Based on the findings of this research, there were statistically significant results in all three groups and their comparison with each other.

Keywords: Cholangiocarcinoma, Combined hepatocellular and cholangiocellular carcinoma, Hepatocellular carcinoma, Primary liver tumors, Survival factors

1. Background

Hepatocellular carcinoma (HCC) represents more than 90% of all cases among primary liver tumors being the most frequent form of adult liver cancer and the fifth most common cancer worldwide (1). Deaths caused by HCC have increased in recent years, with a rate higher than that of any other malignancy (2). Surgery is the gold standard curative therapy for HCC, including segmental hepatic resections and liver transplantation. Although the mechanisms influencing HCC survival time and their relative importance in disease progression are not still exact, various studies have been published involving racial studies showing that Asian patients have the highest survival time, while African-American patients have the lowest (3). In the USA, advanced age and age-associated comorbidities, such as diabetes or coronary artery disease, have been shown to have adverse effects on survival (4, 5).

Cholangiocarcinoma (CC) is a relatively rare group of neoplasms originating from the intrahepatic or extrahepatic bile duct epithelium. Cholangiocarcinoma is encountered in 3% of all gastrointestinal cancers and 10%–15% of liver malignancies worldwide (6). Among all CC tumors, up to 5%–20% of them are intrahepatic and arise from peripheral bile ducts within the liver parenchyma proximal to the secondary biliary subdivisions (7). Similar to the changes in HCC epidemiology, incidence and mortality rates of intrahepatic cholangiocarcinoma (ICC) have increased worldwide, especially in the elder population for the past few decades (7, 8). Surgery is the curative therapy method for survival, and there are published studies showing female gender, absence of microvascular invasion, lymphocyte/ monocyte ratio, systemic inflammation score, and carbohydrate antigen (CA) 19-9 level were found to be significantly effective in the prognosis and survival of ICC patients undergone surgery (9).

Combined hepatocellular and intrahepatic cholangiocarcinoma (cHC-ICC) is a very rare primary liver malignancy involving two components, one with hepatocellular and one with cholangiocellular differentiation, that accounts for only 1.0%-6.3% of liver tumors (10, 11). The heterogenous presence of

HCC and ICC components with various ratios makes the histologic diagnosis and postoperative prognostic expectations unclear (10). Allen and Lisa reported 5 cases of cHC-ICC in 1949 and classified them into 3 types as the first investigators (11). Later, the Liver Cancer Study Group revised and updated the classification (12). A review of published literature has shown that the survival rate following surgery is lower in patients with cHC-ICC than that of those with HCC or CC (13). Although the relationship between survival and the percentage of cHC-ICC occupied by HCC or ICC has not been investigated and confirmed yet, generally, the sarcomatous component has been known to have a poorer prognosis (14).

2. Objectives

The present study aimed to explore the factors affecting survival in patients with HCC, ICC, and cHC-ICC through referring to statistical analysis, including demographics, histopathological, and operative and laboratory findings. To the best of our knowledge, this is one of the very few studies in the literature focusing on each group of liver tumors showing similarities and differences among three groups of patients regarding survival in a single study.

3. Materials and Methods

3.1. Study design

The statistical population of the present study involved patients operated for malignant liver tumors in a tertiary center within January 2011-September 2018. The clinicopathologic features of the patients were evaluated retrospectively and a total of 53 patients with histopathologically confirmed hepatocellular cancer, intrahepatic cholangiocancer, or combined form of both tumor types were entered into the study. Ont the other hand, the patients with cholangio cancer other than intrahepatic type, liver metastases of various tumors, tumors of the gallbladder, or the ones whose postoperative survival follow-up had not been completed successfully were excluded from the study.

3.2. Demographics, variables, and survival analysis

Patient demographics, tumor characteristics and the type of performed surgery, underlying liver disease, laboratory findings, and their effect on survival rates were evaluated and compared both in each group and between groups. The demographic information included gender and age. The tumor characteristics were histopathological tumor type, T stage, Edmondson-Steiner grade, presence of invasion and/or necrosis, differentiation, and single/multiple localization. The type of surgery evaluation referred to anatomical (including liver transplantation) or non-anatomical resections. Underlying liver disease included the presence of cirrhosis, steatosis, or biliary obstruction/cholangitis. Laboratory findings involved the level of tumor markers and the presence of jaundice and hepatitis markers at diagnosis.

3.3. Statistical analysis

Statistical analysis was performed in the SPSS software package (version 22; SPSS, Inc., Chicago, IL, USA) using Mann-Whitney U and Kruskal Wallis tests to evaluate patient's gender and age variables, respectively. All the variables and their comparisons between groups were examined using Fisher's exact test. The effect of each variable on survival was evaluated using Kaplan Meier survival analysis. The p-values of < 0.05 were accepted as statistically significant.

4. Results

In this research, a total of 53 patients were investigated, among which 20 (37.7%) and 33 (62.3%) cases were respectively females and males with a mean age of 62.3 years. There were not any statistically significant differences in the dispersion of gender or age variables between HCC, ICC, and cHC-ICC groups.

The between-group distribution and comparison of gender, survival, type of operation, laboratory findings, and tumor features are presented in Table 1. In the laboratory findings, the tumor markers and viral hepatitis B and C markers were accepted high if they had been measured over the upper level of the normal range of the laboratory. Invasion refers to tumor invasion of major vascular structures which have been resected with tumor and needed vascular reconstruction. Jaundice refers to both clinical and biochemical jaundice which had been confirmed by increased levels of direct bilirubin with alkaline phosphatase and gamma-glutamyl transferase. Due to statistical analysis, survival was significantly higher in the HCC group, compared to the ICC and cHC-ICC groups ($P<0.05$). While alpha-fetoprotein (AFP) was significantly higher in the HCC than in the ICC group, CA-19-9 levels, presence of jaundice, and perineural invasion were significantly higher in the ICC group than in the HCC patients ($P<0.05$). There were not any statistically significant differences between the groups regarding the other variables. AFP: Alpha fetoprotein; CEA: carcinoembryonic antigen; Perineural and vascular inv: Histopathological confirmation of tumor invasion; CA 19-9: Carbohydrate antigen 19-9; HCV: hepatitis C virus; HbsAg: Hepatitis B surface antigen

The survival analysis of HCC patients due to the Kaplan Meier method is tabulated in Table 2. The number of patients was 21, including 15 males and 6 females. The references of laboratory findings, jaundice, and invasion are similar to Table 1. Single/multiple defines the number of tumor foci in the liver. Statistical analysis revealed that the presence

Table 1. Distribution and comparison of gender, type of operation, laboratory findings, and tumor features survival between groups (Fisher's exact test)

		Groups						X^2	P
		HCC		ICC		cHC-ICC			
		n	%	n	%	n	%		
Gender	Male	15	71.4	15	55.6	3	60.0	1.373	0.498
	Female	6	28.6	12	44.4	2	40.0		
Survival	Exitus	2	9.5	14	51.9	4	80.0	13.205	0.001
	Survived	19	90.5	13	48.1	1	20.0		
Resection type	Anatomic	5	23.8	23	85.2	2	40.0	19.293	0.000
	Nonanatomic	16	76.2	4	14.8	3	60.0		
Invasion	Positive	2	9.5	6	22.2	1	20.0	1.578	0.487
	Negative	19	90.5	21	77.8	4	80.0		
HbsAg	High	4	19.0	4	14.8	3	60.0	4.524	0.088
	Normal	17	81.0	23	85.2	2	40.0		
HCV	High	3	14.3	-	-	1	20.0	5.240	0.083
	Normal	18	85.7	27	100.0	4	80.0		
AFP	High	5	23.8	-	-	2	40.0	9.937	0.004
	Normal	16	76.2	27	100.0	3	60.0		
CEA	High	-	-	1	3.7	-	-	1.672	1.000
	Normal	21	100.0	26	96.3	5	100.0		
CA 19-9	High	3	14.3	15	55.6	2	40.0	8.790	0.009
	Normal	18	85.7	12	44.4	3	60.0		
Jaundice	Positive	1	4.8	11	40.7	-	-	9.593	0.003
	Negative	20	95.2	16	59.3	5	100.0		
Perineural inv	Positive	3	14.3	16	59.3	1	20.0	10.752	0.004
	Negative	18	85.7	11	40.7	4	80.0		
Vascular inv	Positive	5	25.0	16	59.3	3	60.0	5.862	0.058
	Negative	15	75.0	11	40.7	2	40.0		
T	T4	2	9.5	6	22.2	1	20.0	15.202	0.089
	T3	4	19.0	5	18.5	-	-		
	T2	1	4.8	5	18.5	2	40.0		
	T1b	10	47.6	4	14.8	1	20.0		
	T1a	2	9.5	7	25.9	1	20.0		
	T1	2	9.5	-	-	-	-		

Table 2. Survival analysis of hepatocellular carcinoma patients due to Kaplan Meier method (Log Rank [Mantel-Cox])

		Median				X^2	p
		Estimate	Std. Error	95% CI			
Gender	Female	43.0	9.19	25.00	61.00	1.022	0.312
	Male	25.0	8.69	7.96	42.04		
Resection type	Nonanatomic	43.0	9.00	25.36	60.64	2.237	0.135
	Anatomic	25.0	9.86	5.68	44.32		
Invasion	Negative	43.0	8.71	25.94	60.06	6.644	0.010
	Positive	16.0	-	-	-		
HbsAg	Normal	39.0	7.55	24.21	53.79	0.437	0.509
	High	25.0	13.50	0.00	51.46		
HCV	Normal	36.0	14.85	6.90	65.10	0.172	0.678
	High	52.0	16.33	19.99	84.01		
AFP	Normal	43.0	9.00	25.36	60.64	2.436	0.119
	High	24.0	3.29	17.56	30.44		
CEA	Normal	39.0	8.39	22.55	55.45	-	-
	High	-	-	-	-		
CA 19-9	Normal	36.0	7.42	21.45	50.55	0.435	0.510
	High	48.0	26.13	0.00	99.21		
Jaundice	Negative	39.0	12.30	14.90	63.10	0.250	0.617
	Positive	36.0	-	-	-		
Single/multipl	Single	48.0	9.02	30.33	65.67	0.290	0.590
	Multiple	24.0	5.51	13.20	34.80		
Differantiation	Well	39.000	4.472	30.235	47.765	1.372	0.504
	Medium	43.000	28.324	0.000	98.514		
	Poor	25.000	3.266	18.599	31.401		
Perineural inv	Negative	43.0	9.55	24.29	61.71	5.927	0.015
	Positive	21.0	4.08	13.00	29.00		
Vascular inv	Negative	48.0	9.02	30.33	65.67	0.121	0.728
	Positive	24.0	3.29	17.56	30.44		
Steatosis	Negative	39.0	4.47	30.23	47.77	0.196	0.658
	Positive	24.0	16.74	0.00	56.82		
Cirrhosis	Negative	24.0	2.05	19.97	28.03	0.396	0.529
	Positive	48.0	8.39	31.56	64.44		

Table 2. Continued

Necrosis	Negative	43.0	15.46	12.70	73.30	0.232	0.630
	Positive	32.0	6.74	18.80	45.20		
Portal HT	Negative	43.0	7.79	27.72	58.28	1.064	0.302
	Positive	24.0	4.47	15.23	32.77		
Grade (Ed-St)	Grade II	32.0	9.53	13.33	50.67	1.991	0.158
	Grade III	48.0	7.45	33.39	62.61		
T	T1	24.000	-	-	-	20.379	0.001
	T1a	68.000	-	-	-		
	T1b	48.000	8.696	30.955	65.045		
	T2	12.000	-	-	-		
	T3	25.000	9.500	6.380	43.620		
	T4	16.000	-	-	-		

AFP: Alpha fetoprotein; CEA: Carcinoembryonic antigen; Perineural and vascular inv: Histopathological confirmation of tumor invasion; Ed-St: Edmondson-Steiner grading; CA 19-9: Carbohydrate antigen 19-9; HCV: hepatitis C virus; HbsAg: Hepatitis B surface antigen

of invasion (requiring vascular reconstruction), perineural invasion, and T staging were found to be statistically significant considering survival (P<0.05).

Table 3 tabulated the survival analysis of ICC patients due to the Kaplan Meier method. The number of patients was 27, including 15 males and 12 females. The reference of laboratory findings, jaundice, and invasion are similar to previous tables. Biliary obstruction and cholangitis refer to clinicopathologic confirmation. Statistical analysis revealed that the presence of invasion (requiring vascular reconstruction), was found to be statistically significant in means of survival, similar to HCC patients (P<0,05). Other variables were not found to have significant effects on survival.

The survival analysis of cHC-ICC patients due to the Kaplan Meier method is shown in Table 4. The number of patients was 5, including 3 males and 2 females. The reference of laboratory findings, jaundice, and invasion are similar to those in the

Table 3. Survival analysis of intrahepatic cholangiocarcinoma patients due to Kaplan Meier analysis (Log Rank [Mantel-Cox])

		Median				X^2	p
		Estimate	Std. Error	95% CI			
Gender	Female	14.0	5.20	3.82	24.18	1.119	0.290
	Male	29.0	7.73	13.85	44.15		
Resection type	Nonanatomic	8.0	2.00	4.08	11.92	0.819	0.365
	Anatomic	29.0	6.59	16.09	41.91		
Invasion	Negative	30.0	7.63	15.05	44.95	4.396	0.036
	Positive	13.0	1.22	10.60	15.40		
HbsAg	Normal	29.0	6.59	16.09	41.91	0.268	0.605
	High	10.0	2.00	6.08	13.92		
HCV	Normal	23.0	9.52	4.34	41.66	-	-
	High	-	-	-	-		
AFP	Normal	23.0	9.52	4.34	41.66	-	-
	High	-	-	-	-		
CEA	Normal	19.0	7.65	4.01	33.99	0.025	0.874
	High	35.0	-	-	-		
CA 19-9	Normal	17.0	12.99	0.00	42.46	1.356	0.244
	High	23.0	7.73	7.85	38.15		
Jaundice	Negative	17.0	5.00	7.20	26.80	0.202	0.653
	Positive	30.0	8.26	13.82	46.18		
Differantiation	Well	37.0	9.17	19.04	54.96	6.070	0.048
	Medium	14.0	4.24	5.68	22.32	-	-
	Poor	33.0	-	-	-	-	-
Perineural inv	Negative	18.0	4.95	8.29	27.71	0.019	0.890
	Positive	29.0	7.00	15.28	42.72		
Vascular inv	Negative	30.0	9.04	12.28	47.72	0.093	0.760
	Positive	18.0	2.00	14.08	21.92		
T	T1a	30.0	4.58	21.02	38.98	8.387	0.078
	T1b	10.0	16.00	0.00	41.36		
	T2	18.0	1.10	15.85	20.15		
	T3	35.0	17.53	0.65	69.35		
	T4	12.0	3.06	6.00	18.00		
Biliary obs	Negative	14.0	18.71	0.00	50.67	0.002	0.960
	Positive	23.0	6.59	10.08	35.92		
Cholangitis	Negative	29.0	19.00	0.00	66.24	0.087	0.768
	Positive	19.0	3.30	12.53	25.47		

AFP: Alpha fetoprotein; CEA: Carcinoembryonic antigen; Perineural and vascular inv: Histopathological confirmation of tumor invasion; Biliary obs: Biliary obstruction; CA 19-9: Carbohydrate antigen 19-9; HbsAg: Hepatitis B surface antigen; HCV: hepatitis C virus

previous tables. Portal hypertension and cholestasis refer to clinicopathologic confirmation, and HCC/ICC refers to the dominant component of the tumor following histopathological confirmation. Statistical analysis revealed that the presence of increased levels of AFP had a statistically significant effect on survival (P<0,05), while the other variables lacked such effect.

Table 4. Survival analysis of combined hepatocellular and intrahepatic cholangiocarcinoma patients due to Kaplan Meier analysis (Log Rank [Mantel-Cox])

		Median				X^2	p
		Estimate	Std. Error	95% CI			
Gender	Female	5.0	-	-	-	0.260	0.610
	Male	30.0	16.33	0.00	62.01		
Resection type	Nonanatomic	30.0	16.33	0.00	62.01	0.297	0.586
	Anatomic	5.0	-	-	-		
Invasion	Negative	30.0	21.50	0.00	72.14	0.871	0.351
	Positive	10.0	-	-	-		
HbsAg	Normal	5.0	-	-	-	0.260	0.610
	High	30.0	16.33	0.00	62.01		
HCV	Normal	10.0	12.50	0.00	34.50	2.009	0.156
	High	52.0	-	-	-		
AFP	Normal	48.0	14.70	19.19	76.81	4.263	0.039
	High	5.0	-	-	-		
CEA	Normal	30.0	21.91	0.00	72.94	-	-
	High	-	-	-	-		
CA 19-9	Normal	48.0	31.03	0.00	108.81	1.591	0.207
	High	5.0	-	-	-		
Jaundice	Negative	30.0	21.91	0.00	72.94	-	-
	Positive	-	-	-	-		
HCC/ICC	HCC	48.0	35.11	0.00	116.81	0.825	0.364
	ICC	10.0	-	-	-		
Perineural invasion	Negative	30.0	21.50	0.00	72.14	0.871	0.351
	Positive	10.0	-	-	-		
Vascular invasion	Negative	48.0	-	-	-	3.446	0.063
	Positive	10.0	4.08	2.00	18.00		
Steatosis	Negative	48.0	-	-	-	0.098	0.754
	Positive	10.0	12.50	0.00	34.50		
Cirrhosis	Negative	30.0	20.41	0.00	70.01	0.074	0.786
	Positive	10.0	-	-	-		
Necrosis	Negative	48.0	-	-	-	3.446	0.063
	Positive	10.0	4.08	2.00	18.00		
Portal HT	Negative	10.0	21.50	0.00	52.14	0.082	0.774
	Positive	30.0	-	-	-		
T	T1a	52.0	-	-	-	3.870	0.276
	T1b	48.0	-	-	-		
	T2	5.0	-	-	-		
	T4	10.0	-	-	-		
Cholestasis	Negative	5.0	-	-	-	0.260	0.610
	Positive	30.0	16.33	0.00	62.01		

AFP: Alpha fetoprotein; CEA: Carcinoembryonic antigen; Portal HT: Portal hypertension; CA 19-9: Carbohydrate antigen 19-9; HbsAg: Hepatitis B surface antigen; HCV: hepatitis C virus; HCC: Hepatocellular carcinoma; ICC: İntrahepatic cholangiocarcinoma

5. Discussion

Hepatocellular carcinoma is not only the most common type of adult liver cancer but also the third leading cause of death among cancer-related mortality worldwide (10, 15). Although the spectrum is wide, the etiology of the tumor is well-known, with primary or toxic/alcohol-related cirrhosis as the most common type. Despite the recent advances both in diagnosis and treatment methods of liver malignancies, survival rates are still low due to metastases at the diagnosis or high rates of relapse. Although it is even possible to implement surgical resection, including segmental resection or transplantation, 5-year survival rates are found to be 27%-70% and 44%-78%, respectively (16).

Even though the results are not always promising, surgery remains the gold standard treatment method. In addition to these adverse mortality rates, the results of studies show that the incidence of HCC is increasing worldwide (2). Based on the findings of studies published in the USA, as the population becomes older, the rate of HCC patients will concomitantly rise in the future and these newly diagnosed HCC patients will have even

poorer survival, compared to younger individuals (17) highlighting the importance of determining the factors affecting survival more clearly. Although the etiological factors have been widely searched and reported, the factors affecting survival rates are not well-known yet.

According to the results of one of the recent studies, such factors as Child-Pugh class B or C, AFP levels over 400 ng/ml, the existence of vascular thrombosis, and tumor stage of C/D were among the factors worsening survival (18). Bauschke et al. showed that higher tumor, node, and metastasis stage was associated with shorter survival (19). The present study evaluated the survival of HCC patients regarding gender, operation type, tumor features, T stage, and the state of the liver (Table 2). Considering the statistical analysis, perineural invasion and T stage were found to be statistically significant concerning shorter survival.

Cholangiocarcinoma is the second most common primary malignancy of the liver, following HCC with a rate of 10%–15% worldwide (6). Although they are usually of extrahepatic origin, they can also be originated from peripheral bile ducts within the liver parenchyma proximal to the secondary biliary subdivisions, which are defined as ICC, making 5%-20% of all CC cases (7). When ICCs are diagnosed initially as solid masses in the liver, they may appear similar to HCCs; however, they differ in etiological factors, diagnostic parameters, and survival rates. An increase in the incidental and mortality rates, especially among the elder population, is similar to the changes in HCC (7, 8).

Surgery is the curative therapy method for ICCs; nevertheless, survival rates are even lower than HCC cases, with 30%-40% 5-year survival rates and median survival of only 12-15 months in unresectable cases (20, 21) which are not rare, lowering resectability rates to only 10%-20% in published series (22). Although more studies evaluating the treatment modalities and survival are needed, the results of more recent studies show that 5-year survival may approach 20%-40% with a median survival of 20-40 months in resectable patients (21). Sotiropoulos et al. found that female gender, CA 19-9 levels of < 100 U/ml, and the absence of microvascular invasion resulted in improved outcomes for ICC patients undergone surgery (23).

In one of the most recent studies, Uhlig et al. evaluated ICC cases in terms of socioeconomic status, demography, cancer factors, and the US geography and showed the importance of surgery and interventional oncology as the first-line treatment depending on these variables (24). The current research evaluated the survival of ICC patients regarding gender, operation type, tumor features, T stage, and the state of the liver, including biliary obstruction and cholangitis (Table 3). According to statistical analysis, the invasion of major vessels requiring reconstruction was found to be statistically significant in terms of survival, similar to HCC patients ($P<0.05$). T stage of tumor was found to have a prognostic effect on survival although its effect was not significant.

Combined hepatocellular and cholangiocarcinoma of the liver is a rare primary malignancy. Due to the low incidence of the tumor, there are a limited number of case reports and series in the published literature, which results in a very limited survival analysis of the tumor. The incidence is also low worldwide, accounting for 1.0%-6.3% of liver tumors (10, 11), with a male predominance in some of the reports (25). It is known that the tumor involves two separate components, one with hepatocellular and one with cholangiocellular differentiation; nonetheless, the heterogeneous structure of the tumor complicates the histologic diagnosis. While some investigators report that cHCC-ICC originates from standard HCC (26), others consider that stem cells or oval cells in the liver can differentiate both HCC and CCC in the liver (27).

Although cHCC-ICC was first described by Wells in 1903 (28), the first comprehensive description and classification were reported in 1949 by Allen and Lisa who reported 5 cases of cHC-ICC and classified them into three types (11). Later, the Liver Cancer Study Group of Japan classified the tumor based on this initial classification as (i) double cancer, (ii) combined type, and (iii) mixed type. Based on this classification, mixed-type cHCC-CCC (mixed HCC and CCC) was defined histologically as a mixture of HCC and CCC in the same tumor, combined in a manner suggesting the development of both at the same site.

Today, the study of Maeda et al. is still one of the largest studies involving 36 cases (29). The histopathological challenges and rarity of the tumor are two important obstacles in defining the factors for survival analysis. In many studies, the survival of cHC-ICC after surgery was worse than HCC. In their survival analysis, Yano et al.reported that cHC-ICC patients had a significantly lower rate of postoperative survival than patients with either HCC or CC (25). Uenishi et al. indicated that the CC component of combined tumors determined the prognosis since metastases were usually composed of CC elements, suggesting that the postoperative recurrence and survival pattern of cHC-ICC were more similar to CC rather than to HCC (30). Additionally, the sarcomatous component is known to have a poorer prognosis in cHC-ICC patients (14).

This study evaluated the survival of ICC patients in terms of gender, operation type, tumor features, T stage, and the state of the liver, including portal hypertension and cholestasis (Table 4). The

statistical analysis of the current research revealed that the presence of increased levels of AFP had a statistically significant effect on survival (P<0.05), which was inconsistent with the results of a study performed by Uenishi et al.. Although the results were not significant, the presence of vascular invasion and necrosis were also found to have adverse effects on survival.

The rarity of the tumor also limits the number of published studies concerning the survival factors among patients with HCC, ICC, and cHC-ICC. Although the researchers did not evaluate the survival factors separately in each group and showed the similarities or differences, in one of the very few studies comparing the survival rates of cHC-ICC patients with those of HCC and ICC patients, Tang et al. reported that survival rates were highest in the HCC group, followed by the cHCC-CC group, while they were the lowest in the CCC group, which was consistent with our results. Patients in the cHCC-CC and HCC groups had similar median survival rates, although the results were not statistically significant (13). The present study compared all three groups in terms of gender, survival, type of operation, laboratory findings, and tumor features both separately and with each other. Moreover, it determined that survival was significantly higher in the HCC group than in the ICC and cHC-CC groups (P<0.05). It was also revealed that AFP was significantly higher in the HCC patients than in the ICC group, and CA-19-9 levels, the presence of jaundice, and perineural invasion were significantly higher in the ICC group, compared to HCC patients (P<0.05).

The main limitation of our study was related to the small size of each group. Another limitation affecting the first one was the inability of following up with all the patients who had undergone operation for hepatic tumors regularly.

6. Conclusion

This study aimed to evaluate the survival factors in patients with HCC, ICC, and cHC-ICC, among which the last one was rarely observed in primary liver tumors. The published studies concerning cHC-ICC tumors are very limited and usually composed of single case reports or series. Although the best curative treatment method for each group of liver tumors is surgical resection, future studies with an extended number of patients revealing prognostic factors are needed for not only defining new prognostic scores but also the optimal patient selection for surgery. The number of patients with combined tumors was also limited in our study; however, to the best of our knowledge, this research was one of the very few studies in the literature focusing on each group of liver tumors showing similarities and differences in terms of survival in a single study.

Footnotes

Informed Consent: Informed consent was obtained from all the participants.

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