Research Article

HEPATOLOGY FORUM

Combined hepatocellular-cholangiocarcinoma

doi: 10.14744/hf.2022.2022.0037

Incidental combined hepatocellular-cholangiocarcinoma in liver transplant patients: Does it have a worse prognosis?

Ender Anilir[1], Alihan Oral[2], Tolga Sahin[3], Fatih Turker[4], Yildiray Yuzer[5], Yaman Tokat[6]

[1]Istanbul Aydin University, Medikalpark Florya Hospital, Organ Transplantation Center, Istanbul, Turkiye; [2]Biruni University Faculty of Medicine, Internal Medicine Center, Istanbul, Turkiye; [3]Department of Hepatology and Liver Transplantation Center, Demiroglu Bilim University, Group Florence Nightingale Hospitals, Istanbul, Turkiye; [4]Department of Internal Medicine, Haseki Training and Research Hospital, Istanbul, Turkiye; [5]Liver Transplantation Center, Demiroglu Bilim University, Group Florence Nightingale Hospitals, Istanbul, Turkiye; [6]International Liver Center (ILC), Istanbul, Turkiye

Abstract

Background and Aim: Combined hepatocellular-cholangiocarcinoma (CHC) requires attention clinically and pathologically after liver transplantation (LT) because of its unique biology, difficulties in diagnosis, and being rare. We aimed to present our single-center experience for this incidental combined tumor. It is aimed to present our single-center experience for this incidental combined tumor.

Materials and Methods: Seventeen patients with CHC were included in the study. There were 260 hepatocellular carcinoma (HCC) patients determined as the control group. Patients were evaluated for demographic, etiological, pathological features, and survival.

Results: Macrovascular and microvascular invasion levels were significantly higher in the CHC group ($p<0.05$). P53, CK19, and CK7 levels were significantly higher in the CHC group ($p<0.05$). Hepatocyte-specific antigen level was significantly higher in the HCC group. The mean overall survival was significantly higher in the HCC group ($p<0.05$).

Conclusion: Even though CHC is a rare liver tumor, it has features that need to be clarified regarding both survival and tumor biology. İnvestigating prognostic factors, especially in terms of survival and recurrence, will be very beneficial to identify candidates who will benefit from LT and be included in the indications for LT for CHC. This study evaluated the outcomes of patients showing combined HCC-intrahepatic cholangiocarcinoma in explant pathology.

Keywords: Combined hepatocellular-cholangiocarcinoma; incidental; liver; mixed tumor; transplantation.

Introduction

Combined hepatocellular-cholangiocarcinoma (CHC) with an incidence rate from 0.4% to 14.2% in different regions, characterized by hepatocellular and biliary epithelial differentiation within the same tumor. This unique type of primary hepatic carcinoma is distinct from hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma (ICC).[1,2] CHC requires attention because of its unique biology, histopathology, and clinical behavior, besides the difficulties in diagnosis and being rare (comprising 1–5% of primary liver cancer).[3–6] Both overall survival (OS) and risk for recurrence after liver transplantation (LT) for these patients were significantly worse compared to patients who were found to have HCC after LT.[7] We aimed to present our experience in patients who have undergone LT and detected CHC incidentally on explant specimens and to compare with HCC. Moreover, we aimed to identify the demographics, clinical, pathological, and etiological risk factors of recurrence and prognostic factors of survival after LT.

Materials and Methods

The collected LT database was retrospectively reviewed. Two hundred and seventy-seven patients who underwent LT for a primary liver tumor between September 2004 and November 2019 were included in the study. Among these, there were 17 patients (6.1%) with incidentally detected CHC. Two hundred and sixty HCC patients were determined as the control group. The CHC group was compared with the control HCC group in terms of all parameters. The 2010 WHO classification was used for pathologic classification.[8] Demographic data including age and gender, living donor liver transplantation (LDLT) and deceased donor liver transplantation (DDLT) rates, and blood group rates, were calculated and stated in the study. Gender, age, etiology, MELD, Child score, body mass index, CEA, alpha-fetoprotein (AFP) (ng/mL) and CA 19-9 (U/mL) values, Milan criteria, findings in specimen pathology report such as T stage, tumor grade, presence of microvascular and macrovascular invasion, multicentricity, tumor number, maximum and total tumor size were analyzed statistically. In patients without vascular invasion on tomography, vascular invasion in the specimen pathology report was classified as a macrovascular invasion that is highly discernible (mainly in large-to-medium vessels) or microvascular invasion that can only be identified by microscopic observation (mainly in small vessels such as portal vein branches in portal tracts, central veins in noncancerous liver tissue, and venous vessels in the tumor capsule and/or noncapsular fibrous septa). Furthermore, tumor recurrence, the location of recurrence, and mortality rates of CHC patients were analyzed statistically to determine the difference between the CHC and HCC groups. CK7, CK19, hepatocyte-specific antigen (HSA), CD34, CD56, CD44, CD117, P53, and arginase values were analyzed statistically in terms of whether there was a difference between the HCC and CHC

How to cite this article: Anilir E, Oral A, Sahin T, Turker F, Yuzer Y, Tokat Y. Incidental combined hepatocellular-cholangiocarcinoma in liver transplant patients: Does it have a worse prognosis? Hepatology Forum 2023; 4(3):97–102.

Received: October 06, 2022; **Revised:** April 17, 2023; **Accepted:** May 08, 2023; **Available online:** September 20, 2023

Corresponding author: Ender Anilir; Istanbul Aydin Universitesi, Medical Park Florya Hastanesi, Organ Nakli Merkezi, Istanbul, Turkiye
Phone: +90 506 502 54 60; **e-mail:** dr.enderanilir@gmail.com

groups. OS and disease-free survival (DFS) rates for 1, 3, and 5 years among HCC and CHC patients were analyzed statistically. This study was accepted with the approval number 2020/243 given by the Ethics Committee on December 23, 2020. The study has been reported per the STROCSS criteria.[9]

Preoperative Evaluation and Patient Selection

Detailed biochemistry tests were routinely performed on the patients who applied to our clinic. AFP, CA 19-9, and CEA were examined. Thorax and portal phase abdominal computer tomography (CT) and abdomen magnetic resonance imaging (MRI) were performed on all patients for preoperative evaluation. HCC was diagnosed in patients with radiologically typical enhancement patterns (early arterial enhancement and late venous washout). 18F-FDG-PET/CT was performed to evaluate biological behavior and extrahepatic involvement in patients diagnosed with HCC radiologically. Moreover, patients with atypical contrasting patterns without venous washout after arterial contrast enhancement and biliary tract dilatation were considered suspicious in terms of cholangiocarcinoma or CHC and contraindicated for LT. Serum CA 19-9 levels were also evaluated in correlation with radiological findings. Furthermore, a biopsy was performed for lesions with atypical radiological enhancement patterns or suspicion of cholangiocarcinoma on CT or MRI. Transplantation was performed on the patients whose all test results were HCC compatible in the LT council and deemed appropriate.

Donor selection

Living donors were selected from recipients' first-degree or second-degree relatives or volunteers determined by ethical committee approval decision. The first step in donor evaluation is whole blood tests, viral load, and blood group analysis. Later, all donors are evaluated by transplantation surgery, gastroenterology, pulmonary, cardiologic, and psychiatric teams. Then, MR cholangiography (MRC) is performed with 3D celiac CT angiography to evaluate the hepatic vascular and biliary tree anatomy. If MRC is not satisfactory, intraoperative cholangiography was performed in selected donors. Candidates without any disabilities were selected as donors. Deceased donor LT was performed from our LT waiting list, which was eligible within the national organ distribution system.

Detection of 17 CHC Patients

Total hepatectomy pathology results of 17 patients who underwent LT with the pre-diagnosis of hepatocellular cancer were evaluated. One patient with HBV-related decompensated liver cirrhosis and esophageal variceal bleeding, with an increasing MELD score, was biopsied because of the high CA 19-9 level. However, there was no radiological suspicion of CHC.

Postoperative Follow-up

AFP, CA 19-9, and computed tomography and/or MRI were performed every 3 months in the 1st year after LT and continued every 6 months. Immunosuppressive therapy consisted of calcineurin inhibitor and rapid steroid taper with mycophenolate mofetil (MMF) combination. Immunosuppressive therapy consisted of a calcineurin inhibitor and rapid steroid taper with a combination of MMF. Prednisolone was given at a dosage of 250 mg intravenously in the operating room, followed by a taper from 100 mg to 20 mg for a period of 8 days and from 20 mg to 10 mg after 2 months. MMF was used when lower doses of calcineurin inhibitors were required due to renal dysfunction. Steroids were tapered and stopped in the 6th month; MMF was switched to everolimus, and tacrolimus dose (aimed through level 7–9 ng/mL) was reduced after the 6 weeks.

Statistical Analysis

Nominal and ordinal parameters were described with frequency analysis, whereas scale parameters were described with means and standard deviations. Chi-square test and Chi-square likelihood tests were used for differences between categorical parameters. Kolmogorov–Smirnov test was used for normality of scale parameters. Mann–Whitney U test was used for difference analysis since distributions were non-normal. Spearman's rho correlation and Cox regression tests were used for relational analysis. SPSS 17.0 for Windows program was used at 95% confidence interval. When referring to SPSS versions prior to the IBM acquisition, authors should cite SPSS Statistics for Windows, version 17.0 (SPSS Inc., Chicago, IL, USA).

Results

The median follow-up period was 17.5 months (range: 1–73 months) for CHC. The average age was 53.5 (range: 36–65). There were 13 male (79%) and 4 female (21%) patients. According to the parameters of the American Joint Committee on Cancer Staging, there were 12 (71.4%) and 5 (28.6%) patients with stage 1–2 and 3–4 cancer, respectively. LDLT was 90% (n=15), and DDLT was 10% (n=2) of the transplants. Blood groups were 36% A group, 14% B group, 45% O group, and 5% AB group, respectively. The child A ratio was 50%, the child B ratio was 35%, and the child C ratio was 14%. The mean MELD score was 10.7. In etiology, 52.9% HBV, 23.5% NASH, 5.8% HCV, 5.8% HBV + HDV, and 5.8% primer HCC (without cirrhosis) were observed, respectively (Table 1). There was no statistical difference for AFP (p=0.614), CEA (p=0.356), and CA 19-9 (p=0.910) values between the CHC and HCC groups. Furthermore, there was no statistical difference within and outside Milan groups between the CHC and HCC groups (p=0.518). There were no statistically significant results for the T stage (p=0.679) and grade (p=0.469) compared with the control HCC group. In addition, none of the 17 patients had lymph node metastasis (n=0). Macrovascular invasion and microvascular invasion levels were significantly higher in the CHC group (p=0.001) (Table 2). However, no statistically significant difference was found in terms of OS and DFS between the invasion-positive and invasion-negative CHC groups (p>0.05). P53, CK19, and CK7 levels were significantly higher in the CHC group (p<0.05). HSA level was significantly higher in the HCC group (p<0.05) (Table 3, 4). Multicentricity (p=0.795), tumor number (p=0.769), maximum (p=0.339) and total (p=0.072) tumor size, grade (p=0.469), recurrence (p=0.851), mortality rates (p=0.273), location of recurrence (p=0.468), and PET-CT positivity (p=0.246) did not have any statistical difference among the CHC and HCC groups. CD34 (p=0.243), CD44 (p=0.298), CD56 (p=0.110), CD117 (could not calculate), and arginase (p=0.123) values were statistically insignificant between the CHC and HCC groups (Table 1, 4). There was no statistically significant difference in OS and DFS when we compared the HCC group with CHC in terms of P53, CK19, and CK7 levels. (p>0.05). Mean OS was significantly higher in the HCC group (p<0.05), whereas DFS differences were statistically insignificant (p>0.05) (Table 5 and Fig. 1).

Table 1. Demographic evaluation of patients with CHC components

	CHC	HCC	p
Age	53.57±7.70	56.18±9.91	0.128
Gender (%)			0.474
Female	21.40	13.90	
Male	78.60	86.10	
Etiology (%)			0.321
HBV	52.98	48.80	
HCV	5.88	18.20	
HBV+HDV	5.88	7.30	
Ethanol	0	5.40	
Cryptogenic	5.88	11.30	
NASH	23.5	7.00	
Only HCC	5.88	2.00	
MELD score	10.76±3.76	11.89±4.56	0.394
Child score (%)			0.816
A	50.00	55.50	
B	35.70	32.50	
C	14.30	12.00	
BMI			0.955
Underweight≤18.5	–	–	
Normal weight=18.5–24.9	4 (26.7)	39 (25.7)	
Overweight=25–29.9	7 (46.7)	68 (44.7)	
Obesity=BMI of 30 or greater	4 (26.7)	45 (29.6)	

CHC: Combined hepatocellular and cholangiocarcinoma; HCC: Hepatocellular carcinoma; BMI: Body mass index; HBV: Hepatitis B virus; HCV: Hepatitis C virus; HDV: Hepatitis D virus; MELD: Model for end-stage liver disease.

Table 2. Clinical and pathological evaluation of patients with CHC components

	CHC	HCC	p
AFP (ng/mL)	90.64±182.48	160.03±881.46	0.614
CA 19-9 (U/ml)	23.74±28.44	28.56±14.23	0.910
CEA (ng/mL)	4.53±4.59	3.61±2.45	0.356
Milan criteria (n, %)			0.518
Within	50.00	40.20	
Beyond	50.00	59.80	
T stage (%)			0.679
I-II	71.40	77.90	
III-IV	28.60	22.10	
Grade (%)			0.469
I-II	83.30	74.00	
III-IV	16.70	26.00	
Macrovascular invasion (%)			**0.001**
Present	69.20	20.20	
Absent	30.80	79.80	
Microvascular invasion (%)			**0.001**
Present	61.50	20.40	
Absent	38.50	79.60	
Multicentric tumor (%)			0.795
Present	57.10	52.60	
Absent	42.90	47.40	

CHC: Combined hepatocellular and cholangiocarcinoma; HCC: Hepatocellular carcinoma; AFP: Alpha-fetoprotein; CA: Carbohydrate antigen; CEA: Carcinoembryonic antigen.

Discussion

CHC has not been fully elucidated due to insufficient experience and the number of cases. Studies evaluating explant pathologies revealed different results regarding survival, the biological behavior of the tumor, and prognostic factors affecting these.

It is observed in different studies that CHC has more aggressive behavior, a higher and more rapid recurrence, and a poorer survival rate than HCC. In contrast, a few studies have found no significant difference between the two conditions.[10–15] In several studies, 3-year and 5-year OS values for CHC have ranged from 10.5% to 47% and 9.2% to 40%.[12,15–17] In our analysis, the 1-, 3-, and 5-year OS rates were 80.2%, 57.3%, and 50.1% for CHC and 95.2%, 89.2%, and 80.7% for HCC, respectively. This result was compatible with the relevant literature. In other studies, the mean OS was significantly higher in the HCC group, whereas DFS differences were statistically insignificant, like in our study.[13–17]

Several prognostic factors such as tumor diameter >2 cm or >5 cm, Milan-out criteria, poor differentiation, multicentricity, presence of microvascular or macrovascular invasion, stage 3–4, and high level of CA19.9 have been used to identify CHC.[12–14,16,17] While tumor number and size do not affect the prognosis[12-17], macrovascular invasion and the presence of satellite metastases have been proposed as significant predictors of poor prognosis in different studies.[12,17–21] In our study, macrovascular invasion and microvascular invasion levels were significantly higher in the CHC group. However, no statistically significant difference was found in terms of OS and DFS between the CHC and HCC groups.

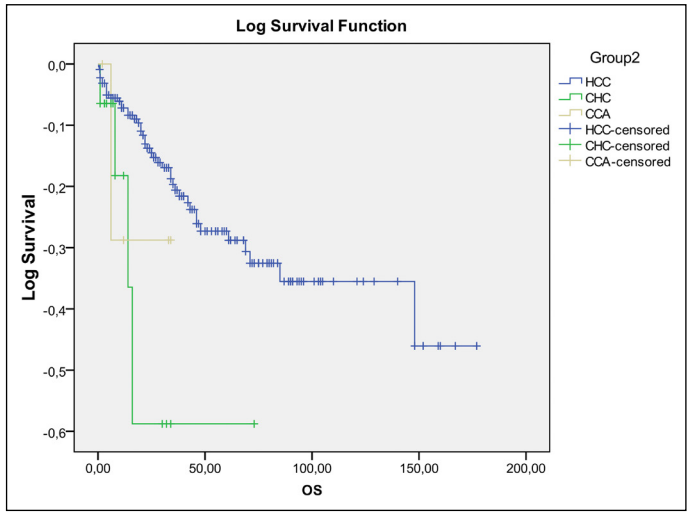

Figure 1. Logarithmic survival function for combined hepatocellular-cholangiocarcinoma.

Despite the fact that tumor markers lack specificity in CHC, the elevation of either AFP or CA19-9 may reflect the proportion of the two components in CHC. CA19-9 is elevated in a fair proportion of CHC patients when cholangiocarcinoma dominates, and AFP is elevated considerably in HCC patients.[16] As a different result from those in the literature, we did not find any statistically significant difference

Table 3. Other pathological, imaging, survival, and recurrence evaluation of patients with CHC components

	CHC	HCC	p
Tumor number (%)			0.769
≤3	76.90	80.30	
>3	23.10	19.70	
Maximum tumor size (%)			0.339
≤2 cm	17.6	27.6	
2–5 cm	52.9	60.4	
>5 cm	29.4	12.0	
Total tumor size (%)			0.072
≤10 cm	69.20	87.20	
>10 cm	30.80	12.80	
^{18}FDG PET-CT (%)			0.246
Positive	80.00	54.60	
Negative	20.00	45.40	
Recurrence (%)			0.851
Positive	21.40	18.60	
Negative	78.60	81.40	
Mortality (%)			0.273
Alive	71.40	82.80	
Death	28.60	17.20	
Location of recurrence			0.468
Liver	–	17.0	
Lung	–	23.4	
Bone	–	10.6	
Multiorgan	2 (50.0)	29.8	
Abdominal outside liver	2 (50.0)	14.9	

CHC: Combined hepatocellular and cholangiocarcinoma; HCC: Hepatocellular carcinoma; ^{18}FDG PET-CT: 18-Fludeoxyglucose positron emission tomography–computed tomography.

Table 4. Pathological markers of patients with CHC components

	CHC	HCC	p
CK 19 (%)			**0.000**
Positive	14.3	92.0	
Negative	85.7	8.0	
CK 7 (%)			**0.000**
Positive	13.3	70.9	
Negative	86.7	29.1	
HSA (%)			0.008
Positive	21.4	5.7	
Negative	78.6	94.3	
CD 34 (%)			0.243
Positive	0.00	21.4	
Negative	100.00	78.6	
CD 56 (%)			0.393
Positive	0.00	42.90	
Negative	100.00	57.10	
CD 44 (%)			0.565
Positive	100.00	75.00	
Negative	0.00	25.00	
CD 117 (%)			0.129
Positive	7.10	3.60	
Negative	92.90	96.40	
P 53 (%)			**0.011**
Positive	60.0	97.6	
Negative	40.0	2.4	
Arginase (%)			0.449
Positive	100.00	83.30	
Negative	0.00	16.70	

CHC: Combined hepatocellular and cholangiocarcinoma; HCC: Hepatocellular carcinoma; CK: Cytokeratin; HSA: Hepatocyte-specific antigen.

Table 5. OS and DFS statistical differences and rates for 1, 3, and 5 years among HCC and CHC

	CHC			HCC			p
	1 year	3 years	5 years	1 year	3 years	5 years	
DFS	0.500	0.500	0.500	0.809	0.463	0.360	0.318
OS	0.833	0.556	0.556	0.931	0.814	0.761	0.045
	CHC			HCC			p
	1 year	3 years	5 years	1 year	3 years	5 years	
DFS%	25.0	0.00	0.00	79.2	57.0	45.4	–
OS%	83.3	55.6	55.6	95.2	89.2	80.7	–

CHC: Combined hepatocellular and cholangiocarcinoma; HCC: Hepatocellular carcinoma; OS: Overall survival; DFS: Disease-free survival; *: Log-rank (Mantel–Cox).

between CHC and HCC in terms of AFP, CEA, or CA19-9 values in our study.[14] These results, once more, show the difficulty of diagnosis in the pre-LT period.

The differences in recurrence rates were not statistically significant among different histopathological types of tumors, and these values were 21.4% for CHC and 18.6% for HCC. This result may reflect the similar outcomes of the CHC and HCC groups in our study.

A viral hepatitis etiology, especially HBV and HCV, has been shown to determine survival among the prognostic factors of CHC.[13,15] In our study, the patients with CHC and those with HCC showed similar clin-

ical and pathological characteristics, including their mean age of onset in the sixth decade, male predominance, and the high incidence of HBV infection underlying chronic liver disease.[12,14] There were also no significant differences between the two groups in our study in terms of age, sex, and etiology. These prognostic factors did not seem to significantly change outcomes and survival rates after LT in both the groups.[13,17,22]

FDG-PET is a useful tool in predicting prognosis in HCC patients. Likewise, FDG-PET/CT has also been found to have high sensitivity for detecting metastases and recurrence. Differentiation is the main determinant of PET/CT effectivity for HCC. Because of its rarity, few studies have evaluated the diagnostic performance of FDG-PET/CT in CHC, although one has reported the pretreatment tumor-to-normal liver SUV ratio as an independent predictor of survival in these patipropensitents. As far as known, areas of hepatocytic components show various degrees of FDG uptake depending on differentiation, and areas of cholangiocytic components show high FDG uptake.[23,24] In our study, no statistically significant difference was found between the CHC and HCC groups in terms of FDG PET/CT positivity.

As known, CK7 and CK19 expression levels increase in the presence of cholangiocarcinoma components, and they appear as positive markers in CHC. CD44 and CD56 are also positive markers for CHC, and CD44 was shown to be prognostic for recurrence and survival.[15] However, CD34 has no prognostic value for CHC, and there is no significant difference in the positivity of these markers in relation to HCC.[16] In this study, P53, CK19, and CK7 levels were significantly higher in the CHC group. On the other hand, HSA levels were significantly higher in the HCC group. Although we found high P53, CK19, and CK7 levels in the CHC group, no difference in OS and DFS values existed between the CHC and HCC groups.

This study had some limitations, including the small number of patients and the retrospective analysis of the CHC cases. Longer survival might also be seen in transplant cases where tumor size and other prognostic criteria are determined prospectively in liver transplant patients for CHC. This study evaluates the outcomes of patients showing combined HCC-ICC in explant pathology instead of evaluating the long-term outcome of patients undergoing liver transplantation (LT) for combined HCC-ICC. The result shall, therefore, provide a relative contribution to the outcome of patients undergoing LT for combined HCC-ICC.

Conclusion

Even though CHC is a rare liver tumor, it has features which need to be clarified regarding survival and tumor biology. Examining prognostic factors, especially in terms of survival and recurrence, will be very beneficial for identifying candidates who will benefit from LT and be included in indications for LT.

Ethics Committee Approval: The Haseki Training and Research Hospital Clinical Research Ethics Committee granted approval for this study (date: 23.12.2020, number: 2020/243).

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – YY, YT; Design – EA; Supervision – EA; Materials – TS, AO; Data Collection and/or Processing – FT, TS, EA; Analysis and/or Interpretation – AO; Literature Search – EA, TS; Writing – EA; Critical Reviews – YY, YT.

Conflict of Interest: The authors have no conflict of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

References

1. Kassahun WT, Hauss J. Management of combined hepatocellular and cholangiocarcinoma. Int J Clin Pract 2008;62(8):1271-1278. [CrossRef]
2. Zhao Q, Yu WL, Lu XY, Dong H, Gu YJ, Sheng X, et al. Combined hepatocellular and cholangiocarcinoma originating from the same clone: a pathomolecular evidence-based study. Chin J Cancer 2016;35(1):82. [CrossRef]
3. Komuta M, Yeh MM. A Review on the update of combined hepatocellular cholangiocarcinoma. Semin Liver Dis. 2020;40(2):124-130. [CrossRef]
4. Bridgewater J, Galle PR, Khan SA, Llovet JM, Park JW, Patel T, et al. Guidelines for the diagnosis and management of intrahepatic cholangiocarcinoma. J Hepatol 2014;60(6):1268-1289. [CrossRef]
5. Endo I, Gonen M, Yopp AC, Dalal KM, Zhou Q, Klimstra D, et al. Intrahepatic cholangiocarcinoma: rising frequency, improved survival, and determinants of outcome after resection. Ann Surg 2008;248(1):84-96. [CrossRef]
6. Sasaki M, Sato Y, Nakanuma Y. Mutational landscape of combined hepatocellular carcinoma and cholangiocarcinoma, and its clinicopathological significance. Histopathology 2017;70(3):423-434. [CrossRef]
7. Lee DD, Croome KP, Musto KR, Melendez J, Tranesh G, Nakhleh R, et al. Liver transplantation for intrahepatic cholangiocarcinoma. Liver Transpl 2018;24(5):634-644. [CrossRef]
8. Theise ND, Park YN, Nakanuma Y. Combined hepatocellular- cholangiocarcinoma. In: Bosman FT, Carneiro F, Hruban RH, Theise ND, editors. WHO classification of tumours of the digestive system. 4th ed. Lyon, France: IARC; 2010. p. 225e7.
9. Agha R, Abdall-Razak A, Crossley E, Dowlut N, Iosifidis C, Mathew G; STROCSS Group. STROCSS 2019 Guideline: Strengthening the reporting of cohort studies in surgery. Int J Surg 2019;72:156-165. [CrossRef]
10. Groeschl RT, Turaga KK, Gamblin TC. Transplantation versus resection for patients with combined hepatocellular carcinoma-cholangiocarcinoma. J Surg Oncol 2013;107(6):608-612. [CrossRef]
11. Lee WS, Lee KW, Heo JS, Kim SJ, Choi SH, Kim YI, et al. Comparison of combined hepatocellular and cholangiocarcinoma with hepatocellular carcinoma and intrahepatic cholangiocarcinoma. Surg Today 2006;36(10):892-897.
12. Connell LC, Harding JJ, Shia J, Abou-Alfa GK. Combined intrahepatic cholangiocarcinoma and hepatocellular carcinoma. Chin Clin Oncol 2016;5(5):66. [CrossRef]
13. Park H, Choi KH, Choi SB, Choi JW, Kim DY, Ahn SH, et al. Clinicopathological characteristics in combined hepatocellular-cholangiocarcinoma: a single center study in Korea. Yonsei Med J 2011;52(5):753-760. [CrossRef]
14. Wakizaka K, Yokoo H, Kamiyama T, Ohira M, Kato K, Fujii Y, et al. Clinical and pathological features of combined hepatocellular-cholangiocarcinoma compared with other liver cancers. J Gastroenterol Hepatol 2019;34(6):1074-1080. [CrossRef]
15. Gera S, Ettel M, Acosta-Gonzalez G, Xu R. Clinical features, histology, and histogenesis of combined hepatocellular-cholangiocarcinoma. World J Hepatol 2017;9(6):300-309.[CrossRef]
16. Sapisochin G, Javle M, Lerut J, Ohtsuka M, Ghobrial M, Hibi T, et al. Liver transplantation for cholangiocarcinoma and mixed hepatocellular cholangiocarcinoma: Working group report from the ILTS Transplant Oncology Consensus Conference. Transplantation. 2020;104(6):1125-1130. [CrossRef]
17. Zhang H, Yu X, Xu J, Li J, Zhou Y. Combined hepatocellular-cholangiocarcinoma: An analysis of clinicopathological characteristics after surgery. Medicine (Baltimore) 2019;98(38):e17102. [CrossRef]
18. Jarnagin WR, Weber S, Tickoo SK, Koea JB, Obiekwe S, Fong Y, et al. Combined hepatocellular and cholangiocarcinoma: demographic, clinical, and prognostic factors. Cancer 2002;94(7):2040-2046. [CrossRef]
19. Koh KC, Lee H, Choi MS, Lee JH, Paik SW, Yoo BC, et al. Clinicopathologic features and prognosis of combined hepatocellular cholangiocarcinoma. Am J Surg 2005;189(1):120-125. [CrossRef]
20. Yano Y, Yamamoto J, Kosuge T, Sakamoto Y, Yamasaki S, Shimada K, et al. Combined hepatocellular and cholangiocarcinoma: a clinicopathologic study of 26 resected cases. Jpn J Clin Oncol 2003;33(6):283-287. [CrossRef]

21. Sapisochin G, Fidelman N, Roberts JP, Yao FY. Mixed hepatocellular cholangiocarcinoma and intrahepatic cholangiocarcinoma in patients undergoing transplantation for hepatocellular carcinoma. Liver Transpl 2011;17(8):934-942. [CrossRef]
22. He C, Zhang Y, Cai Z, Lin X. Competing risk analyses of overall survival and cancer-specific survival in patients with combined hepatocellular cholangiocarcinoma after surgery. BMC Cancer. 2019;19(1):178. [CrossRef]
23. Nagaoka S, Itano S, Ishibashi M, Torimura T, Baba K, Akiyoshi J, et al. Value of fusing PET plus CT images in hepatocellular carcinoma and combined hepatocellular and cholangiocarcinoma patients with extrahepatic metastases: preliminary findings. Liver Int 2006;26(7):781-788. [CrossRef]
24. Ozaki K, Harada K, Terayama N, Kosaka N, Kimura H, Gabata T. FDG-PET/CT imaging findings of hepatic tumors and tumor-like lesions based on molecular background. Jpn J Radiol 2020;38(8):697-718. [CrossRef]