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Comparison of Imaging and Clinically Relevant Features of Combined Hepatocellular Carcinoma and Cholangiocarcinoma with Hepatocellular Carcinoma

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Manuscript Preparation E
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Background: The aim of this study was to compare the clinical, imaging, pathological, and prognostic characteristics of combined hepatocellular carcinoma and cholangiocarcinoma (cHCC-CC) and hepatocellular carcinoma (HCC).

Material/Methods: Medical records of 21 patients with cHCC-CC and 21 patients with HCC were retrospectively reviewed. Patients underwent a computed tomography (CT) examination within 1 month before surgery and did not receive preoperative interventional therapy. Clinical, imaging, pathological, and prognostic characteristics of cHCC-CC and HCC were compared.

Results: On multi-phase contrast-enhanced CT, cHCC-CC could be differentiated from HCC based on the presence of a pseudocapsule ($p<0.0001$; $\chi^2=14.538$) and extensive necrosis ($p=0.009$; $\chi^2=8.400$). The changes in the arterial phase and venous phase (V>A) and arterial phase and delayed phase (D>A) of CT enhanced scanning in HCC and cHCC-CC were statistically significant (both $p<0.0001$, $\chi^2=28.560$ and 25.846). Immunohistochemistry showed more HCC were positive for VEGF ($P=0.012$, $\chi^2=7.785$). A Kaplan-Meier survival analysis showed no statistically significant difference in progression-free survival (PFS) after treatment between patients with cHCC-CC and those with HCC ($p=0.526$).

Conclusions: Multi-phase contrast-enhanced CT may be useful for preoperative diagnosis of cHCC-CC in tumors with a diffuse boundary, no pseudocapsule, extensive necrosis (>50%), and a dilated bile duct, and when the CT value in the delayed phase is higher than in the arterial phase. VEGF expression is more likely to be positive in HCC than cHCC-CC. There was no significant difference between cHCC-CC and HCC in prognosis, but cHCC-CC was more likely to recur after treatment than HCC.

MeSH Keywords: **Carcinoma, Hepatocellular • Prognosis • Radiographic Image Enhancement**

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Background

Primary liver cancer often presents as a malignant tumor, and China accounts for 51% of global liver cancer mortality [1,2]. Histopathologically, primary liver cancer can be divided into 3 types: hepatocellular carcinoma (HCC), cholangiocellular carcinoma (CC), and combined hepatocellular carcinoma and cholangiocarcinoma (cHCC-CC). cHCC-CC consists of 2 components, HCC and CC, and is rare, accounting for 2.4~14.2% of the incidence of primary liver cancer [3]. While CC has typical imaging features such as delayed CT enhancement and bile duct dilation, cHCC-CC is difficult to diagnose because clinical and imaging characteristics overlap with HCC. Typically, a diagnosis of cHCC-CC is confirmed by postoperative pathology and immunohistochemistry. However, evidence suggests that the prognosis of patients with cHCC-CC is worse than for those with HCC [4,5]. Therefore, an accurate differential diagnosis based on preoperative imaging is essential to aid clinical decision-making and improve patient outcomes. In this study, medical records of 21 patients with cHCC-CC and 21 patients with HCC from the First Affiliated Hospital of Guangxi Medical University were retrospectively reviewed. The Guangxi Zhuang Autonomous Region of China is a high-incidence area of HCC, which is the leading cause of death from malignant tumors in the region [6]. Clinical, imaging, pathological, and prognostic characteristics of cHCC-CC and HCC were compared.

Material and Methods

Patients

Medical records of patients with cHCC-CC and HCC diagnosed by pathology after surgery in our hospital between January 2014 and December 2015 were retrospectively reviewed. On immunohistochemistry of pathology, cHCC-CC from all patients were positive for hepatic markers (hepatocyte-1 and glypican-3) and biliary markers (CK7 and CK19), and HCC from all patients was positive for hepatic markers and negative for biliary markers. All patients with cHCC-CC or HCC had a single lesion in the liver. All patients underwent a CT examination within 1 month before surgery and did not receive preoperative interventional therapy.

Imaging protocol

CT examination was performed using GE 64 Light Speed VCT and Siemens Dual Source CT scanners. A non-ionic contrast agent was used for enhanced scanning (300 mgI/ml). A bolus (2.5 ml/kg) of contrast media was injected with a high-pressure syringe through the forearm vein at 3 ml/s. Arterial (delay 22–30 seconds), venous (delay 50–55 seconds), delayed (delay 180 seconds), and continuous spiral scans (delay 6–8 seconds) were obtained with an 8-mm slice thickness, 120 kV tube voltage, 280 mA beam current, and a rotation speed of 0.5 seconds/rotation.

Image evaluation

Multi-phase contrast-enhanced CT images were observed to evaluate lesion size, boundaries, presence of a pseudocapsule, degree of necrosis, satellite lesions, bile duct dilation, venous cancer emboli, multi-phase enhancement mode, and CT values in each phase. The images were reviewed by 2 radiologists with more than 5 years of experience in the diagnosis of cHCC-CC who were blinded to the patients' clinical characteristics. CT values in each phase were measured by taking average values from 3 regions of interest (ROI) over the tumor that had no blood vessels, necrosis, hemorrhage, or steatosis. CT values were measured in these ROIs rather than the whole tumor to avoid inaccuracies caused by the heterogeneity of liver cancer [7]. The liver and tumor were automatically segmented and the ratio of tumor volume to total hepatic volume was determined using a platform established by Huiying Medical Technology.

Pathological assessment

The pathological assessment of specimens was performed using hematoxylin and eosin staining and immunohistochemistry. The pathologic features were graded on the basis of the Edmondson and Steiner grading system [8], in which grade I tumors consist of small cells that are almost indistinguishable from normal liver tissue; grade II tumors have cells with prominent nucleoli, hyperchromatism, and some degree of nuclear irregularity; grade III tumors have pleomorphic cells with angulated nuclei; and grade IV tumors can include large anaplastic cells. Histological features (pathological classification and venous cancer emboli) and vascular endothelial growth factor (VEGF) of immunohistochemistry were evaluated by pathologists who were experts in the diagnosis of liver disease.

Prognosis

All patients with cHCC-CC and HCC underwent resection of the lesion or resection of the segment where the lesion was located, but no lymph node dissection was performed. All patients were followed up by outpatient and telephone visits for 36 months. Tumor recurrence and/or metastasis were determined by enhanced CT or magnetic resonance imaging (MRI). The data cutoff date was December 31, 2018.

Statistical analysis

Statistical analysis was performed with SPSS 22.0. Between-group comparisons were conducted with the chi-squared test

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Table 1. Imaging characteristics of cHCC-CC and HCC.

	Pseudocapsule (cases)	Necrosis >50% (cases)	Satellite lesion (cases)	Bile duct dilation (cases)	Venous cancer emboli (cases)
cHCC-CC	7	7	9	5	4
HCC	19	0	5	1	4
P	<0.0001*	0.009*	0.326	0.184	–
χ^2	14.538	8.400	1.714	3.111	–

* P<0.05 denotes statistical significance.

for categorical variables and the independent-sample *t* test for continuous variables; significance was assessed with the Fisher exact probability method. Multivariate logistic regression analysis was used for multivariate analysis of binary variables. Kaplan-Meier analyses were used for prognostic evaluations. Significance was set at p<0.05.

Result

Patients' baseline characteristics

This study included 21 patients with cHCC-CC (17 males and 4 females) and 21 patients with HCC (19 males and 2 females). The patients with cHCC-CC had a mean age of 44.2±12.8 years (range, 25 to 65 years), 10 patients had liver cirrhosis, and AFP level was elevated in 13 patients. The patients with HCC had a mean age of 46.2±10.6 years (range, 33 to 70 years), 13 patients had liver cirrhosis, and AFP level was elevated in 16 patients. There were no significant differences in baseline characteristics between patients with cHCC-CC and those with HCC (P>0.05).

Imaging findings

Among the 21 patients with cHCC-CC, the tumor boundaries were diffuse in 10 patients and well-defined in 10 patients. A pseudocapsule was present in 7 patients. There was extensive tumor necrosis in 11 patients, and more than 50% of the tumor was necrotic in 7 patients. Satellite lesions were seen in 9 patients, mild bile duct dilation was observed in 5 patients, and venous cancer emboli were detected in 4 patients. Among the 21 patients with HCC, tumor boundaries were diffuse in 5 patients and well-defined in 16 patients. A pseudocapsule was present in 19 patients. There was tumor necrosis in 8 patients, but tumor necrosis did not exceed 50% in any patient. Satellite lesions were seen in 5 patients, mild bile duct dilation was observed in 1 patient, and venous cancer emboli were detected in 4 patients (Table 1). These findings suggest that differential diagnosis of cHCC-CC and HCC may be based on the presence of a pseudocapsule (p<0.0001; χ^2=14.538) and extensive necrosis (>50%) (p=0.009; χ^2=8.400). Multivariate logistic regression analysis showed there were no independent diagnostic factors that aid in the differential diagnosis of cHCC-CC and HCC (P>0.05).

Among the 21 patients with cHCC-CC, 13 patients had massive hepatic tumors (diameter >5 cm), and hepatic tumors were nodular in 8 patients (diameter <5 cm). The tumor volume: total hepatic volume ratio was <5% in 6 patients, ≥5% but <10% in 5 patients, and ≥10% in 10 patients. Among the 21 patients with HCC, 14 patients had massive hepatic tumors, and hepatic tumors were nodular in 7 patients. The tumor volume: total hepatic volume ratio was <5% in 6 patients, ≥5% but <10% in 5 patients, and ≥10% in 10 patients. There was no significant difference in tumor size in patients with cHCC-CC and HCC (P>0.05).

On multi-phase enhanced CT, ccHCC-CC showed 3 distinct enhancement patterns. Type 1 (n=5) demonstrated a fast-in and fast-out enhancement pattern, where enhancement was more obvious in the venous phase than in the arterial phase, and enhancement was decreased in the delayed phase. CT values in each phase were delayed phase (D) <arterial phase (A) <venous phase (V) (Figure 1). Type 2 (n=7) demonstrated continuous edge enhancement, obvious necrosis in the central part of the lesion, and tumor necrosis >50%, which was associated with hemorrhage in 3 patients. CT values in each phase were A<D<V (Figure 2). Type 3 (n=9) demonstrated early enhancement and mild delayed enhancement. CT values in each phase were A<D<V (Figure 3). On multi-phase enhanced CT, all HCC tumors showed a fast-in and fast-out enhancement pattern. CT values of each phase were D<V<A (n=17) and D<A<V (n=4), where enhancement in the venous phase was more obvious than that in the arterial phase, and enhancement in the delayed phase was decreased. Among the 21 patients with cHCC-CC, a comparison of CT values across phases showed V>A in all 21 patients, D>A in 16 patients, and D<A in 5 patients. Among the 21 patients with HCC, a comparison of CT values across phases showed V>A in 4 patients, V<A in 17 patients, and D<A in all 21 patients. The changes in the arterial phase and venous phase (V>A) and arterial phase and delayed phase (D>A) of CT enhanced scanning in HCC and cHCC-CC were statistically significant (both p<0.0001, χ^2=28.560 and 25.846) (Table 2).

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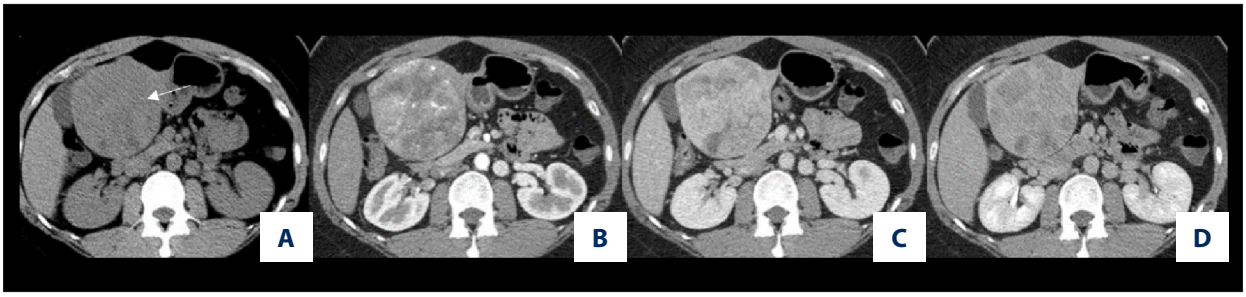

Figure 1. Imaging showing cHCC-CC of the lower segment of the left lateral lobe (arrow) in a 32-year-old female. (**A**) The non-contrast phase shows an inhomogeneous mass, which protrudes from the liver. (**B**) In the arterial phase, the mass is markedly enhanced. (**C**) The venous phase shows further enhancement of the mass. (**D**) The delayed phase shows decreased enhancement.

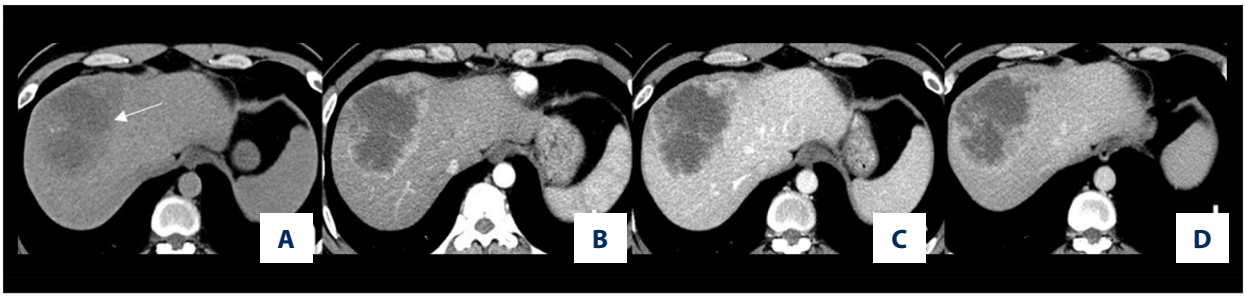

Figure 2. Imaging showing cHCC-CC of the anterior segment of the right upper lobe (arrow) in a 39-year-old male. (**A**) The non-contrast phase shows an uneven dense mass with diffuse edges. (**B**) The arterial phase shows continuous edge enhancement and obvious central necrosis (>50% of the tumor). (**C, D**) The venous phase and delayed phase show continuous edge enhancement and no enhancement of the central necrosis.

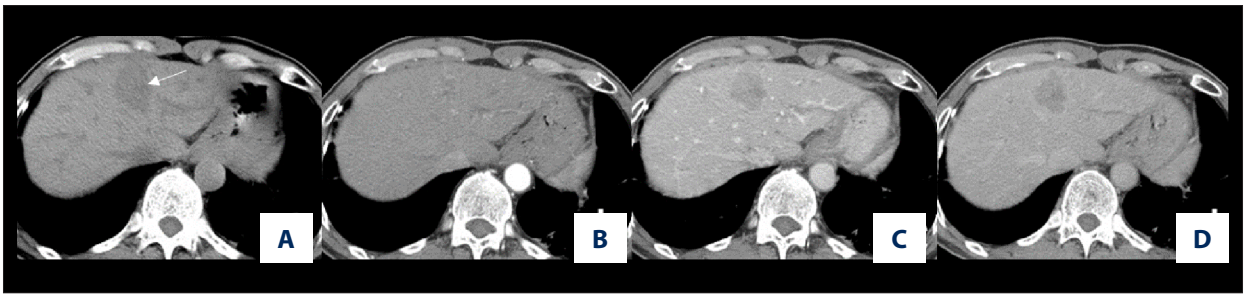

Figure 3. Imaging showing cHCC-CC of the left inner lobe (arrow) in a 65-year-old male. (**A**) The non-contrast phase shows a uniform low-density mass. (**B–D**) The arterial phase, venous phase, and delayed phase show concurrent early enhancement and late mild hyperenhancement.

Table 2. CT values for cHCC-CC and HCC.

	cHCC-CC	HCC	
Enhancement type	1 D<A<V 5 cases 2 A<D<V 7 cases 3 A<D<V 9 cases	1 D<V<A 17 cases 2 D<A<V 4 cases	
V>A	21 cases	4 cases	P<0.0001*, χ^2=28.560
D>A	16 cases	0 cases	P<0.0001*, $\chi^2$2=25.846

A – arterial phase; V – venous phase; D – delayed phase. * P<0.05 denotes statistical significance.

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Pathologic findings

According to the 4-scale Edmondson and Steiner grading system, among the 21 patients with cHCC-CC, biopsy specimens from 12 patients were grade II, and biopsy specimens from 9 patients were grade III. Six patients had venous cancer emboli and 5 patients were positive for VEGF. According to the 4-scale Edmondson and Steiner grading system, among the 21 patients with HCC, biopsy specimens from 9 patients were grade II, and biopsy specimens from 12 patients were grade III. Eleven patients had venous cancer emboli and 14 patients were positive for VEGF. There were no significant differences in pathological grading and incidence of venous cancer emboli between patients with cHCC-CC and HCC, but biopsies from more patients with HCC stained positive for VEGF (P=0.012, χ^2=7.785),

Prognosis

All patients in this study received one or more treatment modalities, including surgery as first-line therapy, post-interventional surgery, or chemotherapy before or after surgery. Among the 21 patients with cHCC-CC, 20 patients (95.2%) were followed up for 36 months. During follow-up, 13 patients had intrahepatic recurrence, including 6 patients with metastasis (lymph nodes [n=5], lung [n=1]), 3 patients had metastasis (lung [n=2], peritoneal cavity and ilium [n=1]) but no intrahepatic recurrence, and 4 patients had no recurrence or metastasis. After 1 and 3 years of follow-up, the no-recurrence rates were 55% and 20%, and overall survival rates were 60% and 35%, respectively. The mean PFS was 18.3 months, and the median PFS was 14.0 months. Among the 21 patients with HCC, 19 patients (90.5%) were followed up for 36 months. During follow-up, 8 patients had intrahepatic recurrence, including 2 patients with metastasis (lymph node [n=1] and metathoracic vertebra and adrenal gland [n=1]), 5 patients had metastasis (lung [n=3], retroperitoneum [n=1], adrenal gland [n=1]), but no intrahepatic recurrence, and 5 patients had no recurrence or metastasis. After 1 and 3 years of follow-up, the no-recurrence rates were 68% and 26%, and overall survival rate were 74% and 33%, respectively. The mean PFS was 20.0 months, and the median PFS was 17.0 months. Kaplan-Meier survival analysis of PFS showed no statistically significant difference in survival after treatment between patients with cHCC-CC and HCC (p=0.526; Figure 4).

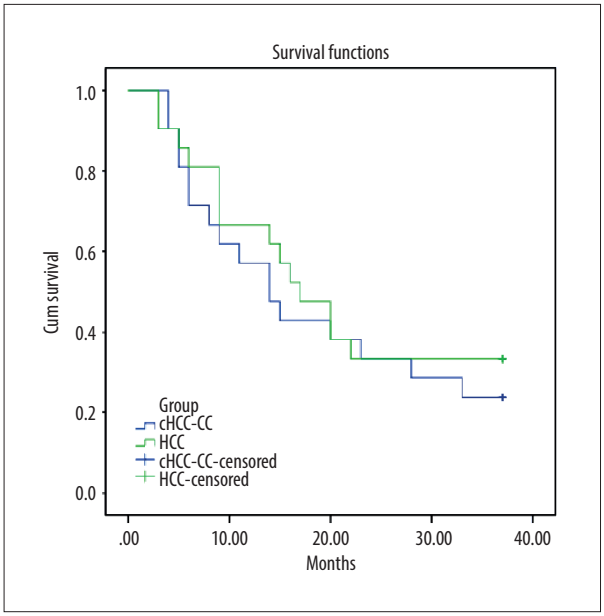

Figure 4. Kaplan-Meier survival analysis of PFS in cHCC-CC and HCC.

Discussion

Clinical characteristics

In 1949, Allen divided cHCC-CC into 3 subtypes: type A (double cancer) consisting of separate but coincidental masses of HCC and CC; type B (combined type), in which HCC and CC are contiguous but distinct; and type C (mixed type), in which HCC and CC are intermixed. It has been proposed that only type C represents a true biphenotypic cHCC-CC [3,9,10]. In the present study, there were 21 cases of Allen type C cHCC-CC. There were no significant differences in sex, age, cirrhosis, or presence of elevated AFP levels between patients with cHCC-CC and HCC, indicating that the clinical characteristics of cHCC-CC and HCC are similar, which is consistent with the findings of Lee et al. and Yu et al. [11,12].

Imaging features

Diagnosis of cHCC-CC on preoperative imaging is rare, and differentiating cHCC-CC from HCC is challenging. In the present study, multi-phase CT enhancement of cHCC-CC showed 3 CT enhancement patterns. Therefore, we propose that cHCC-CC should be suspected when preoperative multi-phase contrast-enhanced CT imaging shows a diffuse boundary, no pseudocapsule, extensive tumor necrosis (>50%), and a dilated bile duct. However, these factors were not identified as independent factors for the diagnosis of cHCC-CC. Furthermore, although the CT enhancement pattern in cHCC-CC appeared as fast-in and fast-out in each phase, this may have been caused by the contrast between enhancement of the tumor and the surrounding liver parenchyma. The CT value on each phase should be compared. When the CT value in the delayed phase is higher than in the arterial phase, a diagnosis of cHCC-CC should be considered.

Aoki divided cHCC-CC into 3 types according to CT enhancement: Type A, demonstrating peripheral enhancement in the early phase and central hyperenhancement and peripheral

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washout on the delayed phase; Type B, in which the entire mass was obviously enhanced in the early phase fading to low density on the delayed phase; and Type C demonstrating low density in the early and delayed phase [13]. In agreement with our findings, Sanada described 3 CT enhancement patterns based on an analysis of 11 cases of cHCC-CC: Type I (n=4), demonstrating hyperenhancement in the early phase followed by washout in the delayed phase; Type II (n=2), demonstrating continuous marginal enhancement, and peripheral enhancement in both the early and delayed phases; and Type III (n=4), demonstrating 2 distinctive enhancement patterns in the same tumor, one showing enhancement with washout in the delayed phase and the second showing delayed enhancement [14]. Chen analyzed 25 cases of cHCC-CC with multi-phase enhancement scanning, and identified 3 enhancement patterns: (1) overall heterogeneous enhancement of the tumor in the arterial phase, and continuous heterogeneous enhancement in the delayed phase (n=12); (2) overall uneven enhancement in the arterial phase, slow diffusion of the contrast agent and a low density or low signal in the delayed phase, with strip-like enhancements in some lesions (n=8); and (3) annular enhancement of the tumor with uneven thickness at the edges in the arterial phase, and annular or irregular enhancement on the delayed phase (n=5) [15]. One hepatobiliary stage tumor showed weak rim enhancement and patchy enhancement at the center, presenting as a "bull's eye".

Pathological features

cHCC-CC contains elements of both HCC and CC. Identification of cHCC-CC is based on evidence of hepatocellular and biliary epithelial features within the same tumor on postoperative pathology. Immunohistochemistry is useful for confirming the presence of hepatocellular markers (e.g., hepatocyte paraffin 1 [HepPar-1], monoclonal antibody, and arginase 1), demonstrating canalicular staining with polyclonal CEA or CD10 and sinusoidal "capillarization" with CD34, and diagnosing the CC component with CK7, CK19, and MOC31, epithelial membrane antigen (EMA), and a mucin stain [16]. In this study, biopsies from more patients with HCC stained positive for VEGF. The growth and metastasis of cancer cells is dependent on the formation of new blood vessels, and VEGF is an effective proangiogenic growth factor. Consistent with our findings, Yan et al. showed a significant difference in VEGF expression between HCC tumors and the surrounding tissue, and proposed that VEGF could be used as an indicator for the diagnosis and prognosis of HCC [17].

Prognostic evaluation

The present study showed no difference in the rate of recurrence or postoperative metastasis in patients with HCC and cHCC-CC after treatment. These results were not consistent with previous reports, perhaps because the incidence of cHCC-CC was low and the sample size of this study was small. However, PFS and overall survival in patients with cHCC-CC were lower than in patients with HCC at 1 and 3 years of follow-up, suggesting that cHCC-CC may recur or metastasize earlier than HCC, which may contribute to poor prognosis.

Previous research shows that prognosis of patients with cHCC-CC is worse than in those with HCC, regardless of whether the tumor is CC dominant cHCC-CC [18]. Qian et al. identified lymph node invasion as an independent risk factor affecting OS in patients with cHCC-CC [19]. Many cHCC-CC cases are misdiagnosed as HCC preoperatively; therefore, lymph nodes are not dissected during surgery, which may explain the high rates of recurrence and postoperative metastasis [20]. In this study, due to the high incidence of HCC, 20 of the 21 cases of cHCC-CC received a preoperative diagnosis of HCC or primary liver cancer, and 1 case was diagnosed as inflammatory myofibroblastoma with no possibility of cHCC-CC, so no lymph node dissection was performed during surgery.

Conclusions

Compared with HCC, cHCC-CC is more likely to recur after treatment and may be associated with a lower survival rate. Improving preoperative diagnosis of cHCC-CC is necessary for effective clinical decision-making. We suggest that multiphase contrast-enhanced CT may be useful for preoperative diagnosis. A diagnosis of cHCC-CC should be considered if a tumor has a diffuse boundary, no pseudocapsule, extensive necrosis (>50%), and a dilated bile duct, and when the CT value in the delayed phase is higher than in the arterial phase. Tumor expression of VEGF was lower in cHCC-CC, suggesting less neovascularization and lower arterial enhancement on CT in cHCC-CC than in HCC.

Limitations

This study has several limitations. First, the incidence of cHCC-CC is very low, and preoperative imaging is based on CT scans, so MRI was not included in this study. Second, although a diffuse boundary, no pseudocapsule, extensive tumor necrosis (>50%), and a dilated bile duct on a preoperative multi-phase contrast-enhanced CT scan may suggest the possibility of cHCC-CC, these were not independent diagnostic factors for cHCC-CC on multivariate analysis.

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