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Case Report

Characteristics, diagnosis, treatment and prognosis of double primary hepatic cancer: experience based on a series of 12 cases

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Abstract: Double Primary Hepatic Cancer (DPHC) which refers to synchronous hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma (ICC) coexisting in the same liver, has rarely been reported. Here we discussed the clinical characteristics, diagnosis, treatment, and prognosis of DPHC based on an analysis of 12 DPHC cases. Meanwhile, data of 60 HCC cases and 60 ICC cases were collected at a ratio of 5:1 and with matched age and gender to DPHC in the same period. A total of 4,626 cases of primary liver cancer were screened, and the proportion of DPHC was approximately 0.26%. Hepatitis B Virus prevalence in the DPHC group (83.3%) was higher than that in the ICC group (38.3%). Lymph node metastasis was more common in the DPHC group (16.7%) compared to the HCC group (1.7%). The median disease-free survival (DFS) and overall survival (OS) for DPHC were 6.0±2.6 months and 15.0±1.7 months, respectively. Pathological diagnosis indicated a significant effect of preoperative adjuvant transarterial chemoembolization (TACE) on HCC, but limited efficacy on ICC. Both alpha fetoprotein and carbohydrate antigen 19-9 levels were elevated in the DPHC group. In conclusion, the preferred treatment for DPHC is radical resection and regional lymphadenectomy. Preoperative TACE is effective for DPHC with large HCC components. The prognosis for DPHC is marked by high recurrence and high mortality.

Keywords: Double primary hepatic cancer, hepatocellular carcinoma, intrahepatic cholangiocarcinoma

Introduction

In 1949, Allen and Lisa categorized the coexistence of hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma (ICC) within the same liver into three types: separated tumors of HCC and ICC without any connection [1]; independent tumors of HCC and ICC, adjacent in their growth; and HCC and ICC mixed within isolated tumors. In 1985, Goodman proposed a new classification standard for HCC and ICC coexistence, dividing them into three types: type I, "collision tumor", where HCC and ICC occur simultaneously in the same liver [2]; type II, "transitional tumor", representing a transition from mature HCC differentiation to mature ICC differentiation; and type III, "fibrolamellar tumor", now generally considered a distinct type of fibrolamellar liver cancer. Allen's type A and type B tumors correspond to Goodman's type I tumors and are considered double primary hepatic cancer (DPHC).

The pathogenesis of DPHC remains unclear. Current discussions on the cellular origin of DPHC are speculative. One hypothesis suggests that the different malignant tumors in DPHC may originate from the same cell. Studies on the cellular origins of HCC and ICC suggest that hepatic progenitor cells (HPC) might be related to the cellular origin of DPHC [3-5]. Hu's report included immunohistochemistry analysis of CD34 and CD117, classical human HPC markers, which showed positive results in both tumors, indicating a possible HPC origin in both HCC and ICC components of DPHC [4, 6]. Another hypothesis posits that the different tumors in DPHC may independently originate

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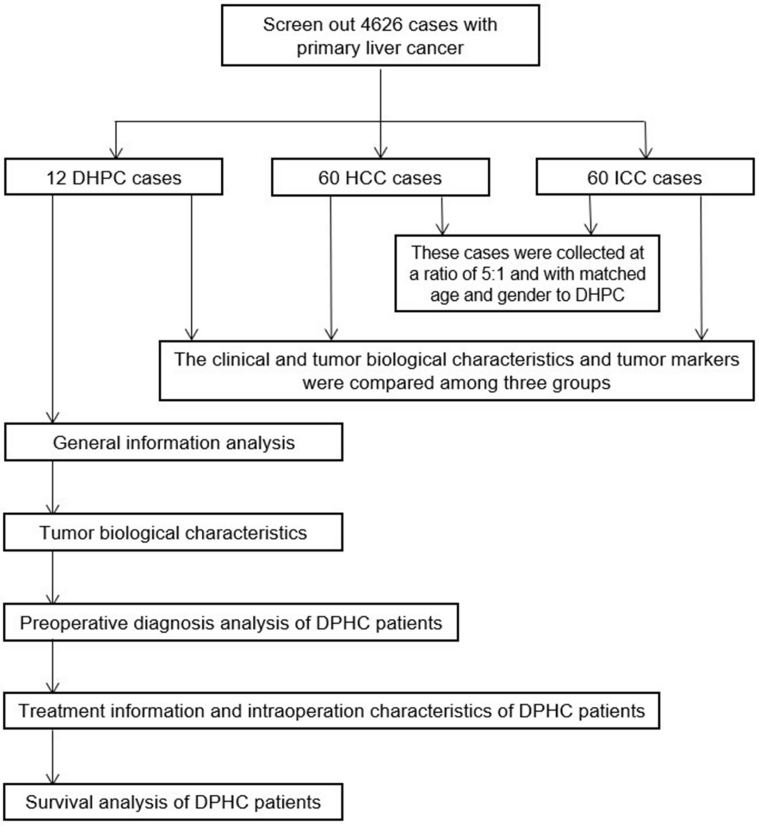

Figure 1. Flow diagram of this study. Note: DPHC, double primary hepatic cancer; HCC, hepatocellular carcinoma; ICC, intrahepatic cholangiocarcinoma.

from hepatocytes and bile duct cells [3]. Mature hepatocytes and bile duct cells, exposed to a common liver environment affected by chronic inflammation and other factors, might undergo malignant transformation, leading to the development of DPHC.

DPHC is a rare form of malignant liver cancer. Cao reported an incidence of approximately 0.25% among primary liver cancers [7]. Due to its rarity, DPHC has seldom been reported. Accurate preoperative diagnosis is generally difficult and relies mainly on histopathological examination of resected specimens. Surgical resection is the primary treatment choice. Information on the prognosis of DPHC is limited. Analyzing the clinical and pathological characteristics is crucial for improving surgical treatment strategies. Therefore, we analyzed 12 cases of DPHC to discuss the clinical and pathological characteristics, diagnosis, treatment, and prognosis of DPHC.

Case selection

This study was approved by the Ethics Committee of Shandong Provincial Hospital. Patients with primary liver cancer from January 2009 to December 2018 at Shandong Provincial Hospital were screened. Data from 12 cases of DPHC (DPHC group) were collected. Additionally, 60 cases of HCC (HCC group) and 60 cases of ICC (ICC group), matched by each at a ratio of 5:1 to the DPHC cases, were collected during the same period. **Figure 1** shows the flow diagram for this study.

Inclusion criteria: (1) Diagnosis of DPHC, HCC, or ICC confirmed by pathology after surgical resection; (2) Availability of preoperative examination; (3) Complete clinical data; (4) Complete follow-up after surgery.

Exclusion criteria were: (1) Combined hepatocellular and cholangiocarcinoma, heterochronous or other pathological types of double primary hepatic cancer; (2) Lack of surgical resection or pathological examination; (3) Lack of preoperative examination; (4) Presence of other malignant tumors or serious diseases affecting survival time.

Data collection and outcome measures

The clinical data of 12 DPHC cases were analyzed including medical history, clinical characteristics, tumor pathological characteristics, hepatitis status, serum tumor markers, imaging examinations, treatment, and prognosis. Clinical and tumor biological data from the included HCC and ICC cases were also collected for comparative analysis with the DPHC cases.

The DPHC patients were followed up until February 2024. Endpoints included death, fol-

Table 1. General information of patients with DPHC

General information	Values
Age (years)	61.1±6.1
Sex	
Male	12 (100%)
Female	0
Complaint	
Health examination	6 (50.0%)
Abdominal pain	4 (33.3%)
Others	2 (16.7%)
Virual hepatitis	
Hepatitis B	10 (83.3%)
Hepatitis C	0
Both	0
None	2 (16.7%)
Liver cirrhosis	9 (75.0%)
Smoking history	4 (33.3%)
Alcohol history	3 (25.0%)
Basic diseases	
Hypertension	6 (50.0%)
Diabetes	2 (16.7%)
Arrhythmia	2 (16.7%)
Chronic renal insufficiency	1 (8.3%)
Leukemia	1 (8.3%)
Pneumonia	1 (8.3%)
Liver function (child-Pugh)	
A	12 (100%)
B	0

Note: DPHC, double primary hepatic cancer.

low-up cutoff, or loss to follow-up. Indicators included OS, defined as the time interval from surgery to endpoints, and DFS, defined as the time interval from surgery to the first tumor recurrence or metastasis.

Statistical analysis

Data were analyzed using SPSS and Excel. Measurement data were compared using t-test, rank sum test, or one-way ANOVA followed by Tukey's test. Count data were compared using chi-square test or Fisher's exact test. Survival was analyzed using Kaplan-Meier survival curves. Risk factors for DFS and OS were analyzed using the Log-rank test and Cox proportional hazards regression model. A *p*-value of <0.05 was considered statistically significant.

Results

General information analysis of DPHC patients

Among 4,626 cases, 12 patients (0.26%) were diagnosed with DPHC with an average age of 61.1±6.1 years old. All patients were male. The basic data of DPHC patients are listed in **Table 1**. Most DPHC patients (50%) were diagnosed with liver tumors via imaging examinations without symptoms. The main symptom reported was abdominal pain (33.3%). Additionally, 83.3% of DPHC patients were hepatitis B surface antigen positive, and 40.0% had high replication of hepatitis B virus (HBV)-DNA. Cirrhosis was present in 75.0% of DPHC cases.

Tumor biological characteristics of DPHC patients

In the 12 DPHC cases, the median longest diameter (quartile range) of HCC tumors was 2.6 (1.8, 5.5) cm, and ICC tumors was 2.8 (1.7, 4.0) cm. The cumulative tumor diameter per case was 7.8 (6.3, 10.0) cm. There were 16 HCC tumors and 14 ICC tumors. Multiple HCC was present in 4 cases (33.3%), and multiple ICC in 1 case (8.3%). The most common tumor location was the right liver lobe, with no cases solely in the left lobe. For HCC tumors, 56.3% were in the right lobe and 43.7% in the left lobe. Most ICC tumors (78.6%) were in the right lobe, with only 3 cases (21.4%) in the left lobe. HCC tumors were primarily grade II (75%) according to Edmondson classification, while most ICC tumors were moderately differentiated (75%). See **Figure 2** and **Table 2**.

Preoperative diagnosis of DPHC patients

No cases were diagnosed as DPHC preoperatively. The primary diagnosis was related to HCC (83.3%), including 5 cases of multiple HCC (41.7%), 3 cases of HCC with intrahepatic metastasis (25.0%), and 2 cases of single HCC (16.7%). Other diagnoses included metastasis and single ICC.

Among the 12 DPHC cases, 66.7% underwent preoperative abdominal ultrasonography, but none had contrast-enhanced ultrasonography. Intraoperative ultrasound was performed in 25.0% of cases. Preoperative abdominal enhanced CT was performed in 91.6% of cases,

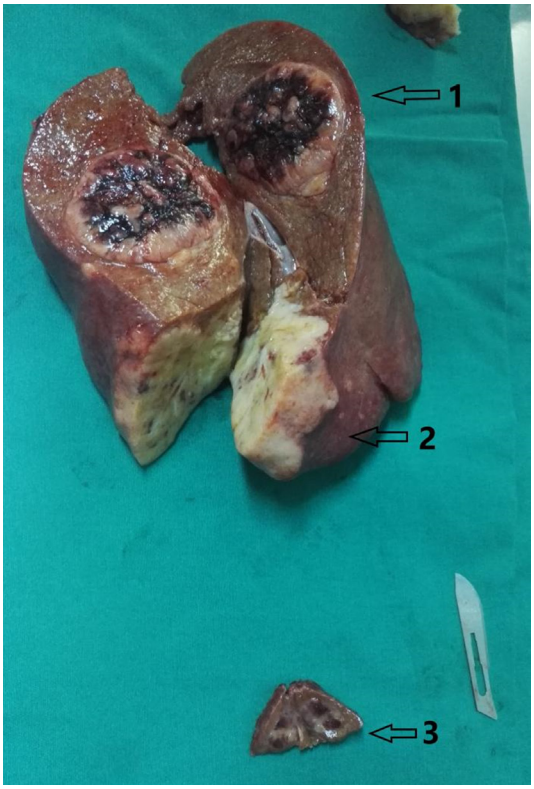

Figure 2. Surgical specimen: tumor 1: HCC; tumor 2: ICC; tumor 3: HCC. Note: HCC, hepatocellular carcinoma; ICC, intrahepatic cholangiocarcinoma.

with common diagnoses including multiple HCC, single HCC, HCC with intrahepatic metastasis, HCC combined with inflammatory pseudotumor, and single ICC. Only 41.7% of patients had preoperative abdominal MRI, with diagnoses including multiple HCC, single HCC, HCC with intrahepatic metastasis, atypical hemangioma, or inflammatory pseudotumor. CT/MRI images showed that only 2 cases of CT and 1 case of MRI showed tumor characteristics of rapid enhancement and delayed washout simultaneously.

One case underwent digital subtraction angiography (DSA) before operation during transhepatic arterial chemotherapy and embolization (TACE). DSA images showed a large pigmented tumor in the right liver lobe with obvious deposition upon iodized oil injection, but no vascular abnormalities or tumor staining in other liver parts. The initial diagnosis was single HCC. Intraoperatively, a small 2 cm tumor was found in the right lobe. Pathology confirmed the large tumor as HCC and the small tumor as ICC. See **Figure 3** and **Table 3**.

Table 2. Information of tumor biological characteristics of DPHC

Tumor biological characteristics	DPHC
Longest diameter of tumor (cm)	
HCC	2.6 (1.8, 5.5)
ICC	2.8 (1.7, 4.0)
Accumulation of the same case	7.8 (6.3, 10.0)
Tumor number	
HCC	
Simple	8 (66.7%)
Multiple	4 (33.3%)
ICC	
Simple	11 (91.6%)
Multiple	1 (8.3%)
Locations	
HCC right + ICC right	5 (41.7%)
HCC right + ICC left	1 (8.3%)
HCC left + ICC right	3 (25.0%)
HCC left + HCC right + ICC left	2 (16.7%)
HCC left + CC right + ICC right	1 (8.3%)
Pathological grade	
HCC (Edmondson grade)	
I	2 (16.7%)
II	9 (75.0%)
III	1 (8.3%)
ICC (differentiation)	
Well	1 (8.3%)
Moderate	9 (75.0%)
Poor	2 (16.7%)
Tumor thrombus	1 (8.3%)
Satellite lesions	2 (16.7%)
Lymphatic metastasis	2 (16.7%)

Note: DPHC, double primary hepatic cancer; HCC, hepatocellular carcinoma; ICC, intrahepatic cholangiocarcinoma.

Comparison of clinical and tumor biological characteristics of DPHC, HCC and ICC groups

The HBV infection rate in the DPHC group (83.3%) was similar to that in the HCC group (83.3%) but significantly higher than in the ICC group (38.3%; P<0.001). The incidence of cirrhosis in the DPHC group (75.0%) was comparable to the HCC group (80.0%) and higher than the ICC group (25.0%; P=0.010). There were no significant differences in liver function (Child-Pugh), tumor number and pathological grade, tumor thrombus, or satellite lesions (all P>0.05). Lymph node metastasis was found in 2 cases in the DPHC group (16.7%), similar to

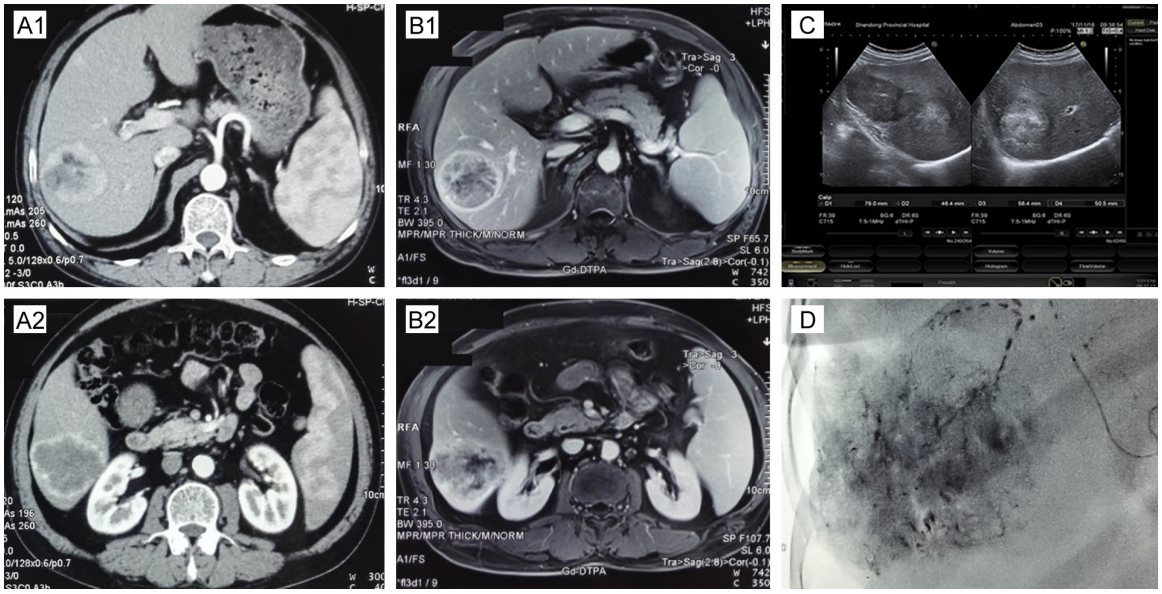

Figure 3. A1. HCC in arterial phase of CT. A2. ICC in arterial phase of CT. B1. HCC inarterial phase of MRI. B2. ICC in arterial phase of MRI. C. US showed hyperechoic and hypoechoic nodules in the liver, suggesting that there may be different degrees of differentiation or different natures in multiple liver cancer. D. DSA: the deposition of lipiodol in HCC tumor. Note: DPHC, double primary hepatic cancer; HCC, hepatocellular carcinoma; ICC, intrahepatic cholangiocarcinoma; US, ultrasound; CT, computed tomography; MRI, magnetic resonance imaging.

Table 3. Preoperative diagnosis and image information of DPHC patients

Diagnosis	DPHC
Preoperative diagnosis	
Multiple HCC	5 (41.7%)
HCC with intrahepatic metastasis	3 (25.0%)
Single HCC	2 (16.7%)
Metastatic liver tumor	1 (8.3%)
Single ICC	1 (8.3%)
Imaging examination	
US	8 (66.7%)
CT	11 (91.6%)
Multiple HCC	4/11
Single HCC	3/11
HCC with intrahepatic metastasis	2/11
HCC with inflammatory pseudotumor	1/11
Single ICC	1/11
MRI	5 (41.7%)
Multiple HCC	2/5
Single HCC	1/5
HCC with intrahepatic metastasis	1/5
Atypical hemangioma/inflammatory pseudotumor	1/5

Note: DPHC, double primary hepatic cancer; HCC, hepatocellular carcinoma; ICC, intrahepatic cholangiocarcinoma; US, ultrasound; CT, computed tomography; MRI, magnetic resonance imaging.

the ICC group (23.3%) but was significantly higher than in the HCC group (1.7%; P=0.018). See **Table 4**.

Comparison of tumor markers and of DPHC, HCC and ICC groups

Among the 12 DPHC cases, 83.3% showed an increase in carbohydrate antigen (CA) 19-9, significantly higher than the HCC group (10%; P<0.001) and the ICC group (50%; P=0.034). There were no significant differences in alpha fetoprotein (AFP), carcinoembryonicantigen, and CA125 levels between the DPHC and HCC groups or the DPHC and ICC groups (P>0.05). See **Table 5**.

Treatment information and intraoperation characteristics of DPHC patients

All 12 patients underwent hepatectomy, with an average operation time of 2.8 (±1.0) hours. The average blood loss during the operation

Table 4. Comparison of clinical and tumor biological characteristics of DPHC, HCC and ICC

	DPHC	HCC	ICC	t/x^2	*P* values
Age (year)	61.1±6.1	56.3±9.2	55.0±9.3	0.047	0.954
Sex (male:female)				2.616	0.270
Male	12 (100%)	51 (85.0%)	49 (81.7%)		
Female	0	9 (15.0%)	11 (18.3%)		
Viral hepatitis				31.11	<0.001
Hepatitis B	10 (83.3%)	50 (83.3%)	23 (38.3%)		
Hepatitis C	0	1 (1.7%)	0		
Both	0	0	0		
None	2 (16.7%)	9 (15.0%)	37 (61.7%)		
Liver cirrhosis	9 (75.0%)	48 (80%)	15 (25.0%)*	41.98	<0.001
Liver function (child-Pugh)				1.775	0.412
A	12 (100%)	53 (88.3%)	52 (86.7%)		
B	0	7 (11.7%)	8 (13.3%)		
Tumor number					
HCC				1.773	1.332
Simple	8 (66.7%)	50 (83.3%)	-		
Multiple	4 (33.3%)	10 (16.7%)	-		
ICC				-	1.667
Simple	11 (91.6%)	-	60 (100%)		
Multiple	1 (8.3%)	-	0		
Pathological grade					
HCC (Edmondson grade)				1.035	0.596
I	2 (16.7%)	2 (3.3%)	-		
II	9 (75.0%)	42 (70.0%)	-		
III	1 (8.3%)	16 (26.7%)	-		
IV	0	0	-		
ICC (differentiation)				0.874	0.646
Well	1 (8.3%)	-	4 (6.7%)		
Moderate	9 (75.0%)	-	51 (85.0%)		
Poor	2 (16.7%)	-	5 (8.3%)		
Tumor thrombus	1 (8.3%)	9 (15.0%)	10 (16.7%)	0.542	0.763
Satellite lesions	2 (16.7%)	2 (3.3%)	7 (11.7%)	3.927	0.140
Lymphatic metastasis	2 (16.7%)	1 (1.7%)*	14 (23.3%)	12.720	0.002

Note: DPHC, double primary hepatic cancer; HCC, hepatocellular carcinoma; ICC, intrahepatic cholangiocarcinoma. Compared with DPHC group, *P<0.05.

was 250 (150-400) ml. Lymph node dissection was performed in 16.7% of DPHC cases, significantly lower than in the ICC group (71.7%; P<0.001). See **Table 5**.

Common early postoperative complications included peritoneal effusion (50%) and pleural effusion (50%). Other complications included fever (25%), hypoproteinemia (16.7%), hyperglycemia (8.3%), and bleeding (8.3%). No perioperative deaths occurred. Preoperative treatments included TACE and HCC resection. Postoperative treatments included prophylactic TACE, TACE after recurrence or metastasis, radiofrequency ablation (RFA), and chemotherapy. See **Table 6**.

Survival analysis of DPHC patients

By the end of the follow-up period, all DPHC cases had experienced recurrence or metastasis. The median DFS was 6.0±2.6 months, with intrahepatic recurrence being the most common (83.3%). The median OS was 15.0±1.7 months. Kaplan-Meier survival curves for DFS and OS are shown in **Figures 4** and **5**.

Table 5. Comparison of tumor marker and intraoperation characteristics of DPHC, HCC and ICC

	DPHC	HCC	ICC	$t/x^2/z$	*P* values
Tumor marker (preoperative)					
AFP>20 ng/ml	3 (25.0%)	37 (61.7%)	5 (8.3%)	38.460	<0.001
CEA>10 ng/ml	1 (8.3%)	0	4 (6.7%)	4.542	0.103
CA19-9>39 U/ml	10 (83.3%)	6 (10.0%)*	30 (50.0%)*	38.410	<0.001
CA125>39 U/ml	1 (8.3%)	5 (8.3%)	9 (15.0%)	1.444	0.4858
AFP>20 ng/ml and CA19-9>39 U/ml	3 (25.0%)	3 (5.0%)	5 (8.3%)	5.236	0.023
Intraoperation					
Bleeding (ml)	250 (150, 400)	200 (100, 400)	250 (200, 300)	4.231	0.987
Blood transfusion	4 (33.3%)	13 (21.7%)	7 (11.7%)	4.054	0.132
Lymphoectomy	2 (16.7%)	2 (3.3%)	43 (71.7%)*	63.160	<0.001
Operation time (h)	2.8±1.0	2.5±0.8	2.8±0.9	1.968	0.144

Note: DPHC, double primary hepatic cancer; HCC, hepatocellular carcinoma; ICC, intrahepatic cholangiocarcinoma; AFP, alpha fetoprotein; CEA, carcinoembryonicantigen; CA, carbohydrate antigen. Compared with DPHC group, *P<0.05.

Table 6. Treatment information of DPHC patients

Treatment	DPHC
Method of operation	
Non anatomical wedge resection	3 (25.0%)
Segmental hepatectomy	1 (8.3%)
Segmental hepatectomy + wedge resection	7 (58.3%)
Hemihepatectomy + wedge resection	1 (8.3%)
Intraoperation	
Bleeding (ml)	250 (150, 400)
Blood transfusion	4 (33.3%)
Operation time (h)	2.8 (±1.0)
Lymphoectomy	2 (16.7%)
Postoperative complications	
Peritoneal effusion	6 (50.0%)
Pleural effusion	6 (50.0%)
Fever	3 (25.0%)
Hypoproteinemia	2 (16.7%)
Hyperglycemia	1 (8.3%)
Blooding	1 (8.3%)
Preoperative treatment	
HCC resection	1 (8.3%)
TACE	1 (8.3%)
Postoperative treatment	
TACE	7 (58.3%)
RFA	1 (8.3%)
Chemotherapy	1 (8.3%)

Note: DPHC, double primary hepatic cancer; HCC, hepatocellular carcinoma; ICC, intrahepatic cholangiocarcinoma; TACE, transhepatic arterial chemotherapy and embolization; RFA, radiofrequency ablation.

Cox proportional hazards regression model was used for multivariate analysis of risk factors for DFS and OS. The data indicated no significantly related risk factors for OS (all P>0.05), while the size of ICC (P<0.05) was identified as a risk factor related to DFS. See **Table 7**.

Discussion

In this study, we reported an incidence of DPHC of 0.26% among primary liver cancer cases, consistent with a previous report by Cao, which found an incidence of 0.25% [7]. The 12 DPHC patients were all males with an average age of 61.1±6.1 years. Similar to published studies, our results showed that the majority of DPHC patients were male [3, 7, 8]. The average age of DPHC patients in China was younger than the global average, suggesting an earlier onset in China.

Previous reports have suggested that HCV-related hepatitis or cirrhosis may play an important role in the pathogenesis of DPHC [3, 9-11]. Our study found that 83.3% of DPHC patients had HBV infection, with no cases of HCV infection. This indicates that both HBV and HCV-related hepatitis or cirrhosis could be important factors in the pathogenesis of DPHC. While AFP and CA19-9 tumor markers alone are not sensitive or specific to DPHC, their simultaneous increase might aid in diagnosis. Our study showed that AFP and CA19-9 were both elevated in 25.0% of DPHC cases, higher than in HCC (5.0%) and ICC (8.3%) cases. Previous

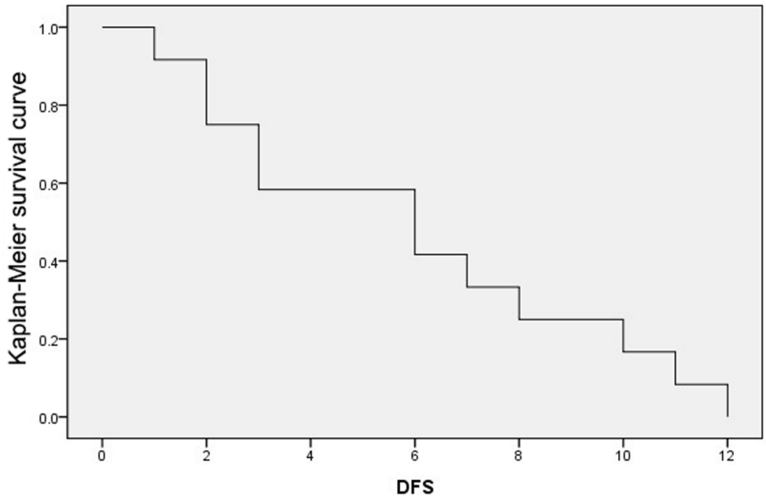

Figure 4. Kaplan-Meier survival curve of disease-free survival.

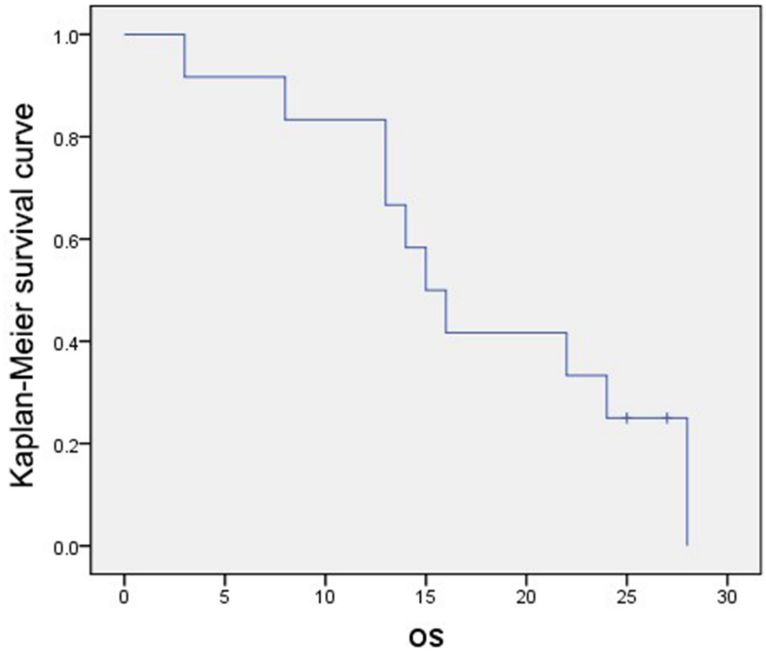

Figure 5. Kaplan-Meier survival curve of overall survival.

studies have reported simultaneous increases of AFP and CA19-9 in 29% [7] and 28.6% [3] of DPHC cases, suggesting that this might be a characteristic feature of DPHC.

Ultrasound examination is commonly used to detect liver tumors for screening and follow-up. The ultrasound manifestations of HCC and ICC tumors are diverse and nonspecific. In this study, the preoperative ultrasound aimed to screen liver lesions rather than provide a differential diagnosis. One DPHC case showed different hyperechoic and hypoechoic nodules on ultrasound, suggesting that multiple liver tumors may have different degrees of differentiation or different natures, even when both CT and MRI diagnosed primary liver cancer without further differentiation. This indicates the sensitivity of ultrasound in detecting different natures of liver tumors when CT and MRI images are atypical. Intraoperative ultrasound was performed in 25.0% of patients, playing an important role in detecting micro tumors and preventing misdiagnosis.

For DPHC, preoperative imaging often results in a diagnosis of "atypical liver cancer". Typical HCC and ICC exhibit distinct characteristics on CT or MRI. HCC generally demonstrates the "fast in and fast out" phenomenon [12], while ICC is often identified based on indirect imaging features such as the expansion of intrahepatic bile ducts and atrophy of related liver parenchyma [13]. Specifically, mass-forming ICC typically shows peripheral enhancement in the arterial phase and progressive centripetal enhancement in the venous and delayed phases, known as delayed enhancement [14]. In DPHC cases, larger tumors may exhibit typical imaging features, facilitating preoperative diagnosis. However, smaller or atypical tumors, particularly in livers affected by chronic hepatitis or cirrhosis, often display no typical imaging signs. In this study, CT/MRI images revealed that only 2 CT cases and 1 MRI case manifested the combined characteristics of "fast in and fast out" and "delayed enhancement". Therefore, careful evaluation of preoperative imaging is crucial for multiple liver cancers. The possibility of DPHC should be con-

Table 7. Multivariate analysis of the risk factor of DFS and OS

	P	HR	95.0% CI for Exp (B)	
			Upper	Lower
OS				
Size of HCC	0.087	1.012	0.94	1.004
Size of ICC	0.068	2.061	0.948	4.483
Postoperative TACE (including recurrence)	0.095	0.999	0.953	1.047
DFS				
Size of ICC	0.043	1.9	1.02	3.541
CA19-9	0.071	1.095	0.992	1.208
Postoperative prophylactic TACE	0.071	0.944	0.887	1.005

Note: DPHC, double primary hepatic cancer; HCC, hepatocellular carcinoma; ICC, intrahepatic cholangiocarcinoma; TACE, transcatheter arterial chemoembolization; CA, carbohydrate antigen; OS, overall survival; DFS, disease-free survival.

sidered when imaging shows characteristics of "fast in and fast out" and "delayed enhancement" in different tumors, although images are typically atypical.

The challenges of diagnosing DPHC include hidden symptoms, nonspecific tumor markers, and its low incidence, which contribute to difficulties in making an accurate diagnosis. Diagnosis typically relies on pathological examination of biopsy specimens. Notably, some cases were accurately diagnosed preoperatively through percutaneous liver biopsy, while others were misdiagnosed as multiple HCC when only one tumor sample was obtained via laparoscopic biopsy [10, 15]. In this study, one case was initially diagnosed as multiple HCC by biopsy pathology; the first liver puncture biopsy indicated atypical hyperplasia, and the second indicated HCC. Subsequent surgical resection and pathological examination confirmed DPHC. This highlights that if sampling is not comprehensive during biopsy, misdiagnosis remains possible.

DSA, examined preoperatively in one patient as described in the results, diagnoses based on abnormal vascular disorder and tumor staining due to aberrant distribution of the tumor's arterial supply. DSA is effective for diagnosing well-vascularized tumors like HCC, but its utility may be limited for diagnosing ICC, especially smaller tumors. ICC tumors, characterized by low vascularity and high fibrosis, often show limited delayed enhancement on DSA images, which is not typical. Studies have reported DSA detection rates for ICC of less than 50% [16]. As an invasive procedure, DSA is often used in conjunction with interventional therapy rather than as a standalone diagnostic tool.

Preoperative diagnosis significantly impacts the treatment strategy for DPHC, which primarily involves surgical resection. However, when multiple liver cancers or intrahepatic metastases involving both HCC and ICC are considered, the efficacy of surgical resection is often deemed limited [13, 17, 18]. Furthermore, the potential for some cases to miss surgical opportunities due to misdiagnosis cannot be ignored. Unlike other malignant tumors, the prognosis for liver cancer depends not only on the tumor's biological characteristics but also on the residual liver function. In DPHC, tumors are rarely distributed within the same liver segment, often necessitating the resection of more normal liver tissue than would be required for a single tumor to achieve a negative margin (R0 resection) [3]. Consequently, it is crucial to consider the tumor's size and location to determine the most suitable approach for hepatectomy.

Lymph node metastasis in DPHC patients parallels that seen in ICC. This study found that 16.7% of DPHC patients had lymph node metastasis, comparable to the ICC group (23.3%) and significantly higher than the HCC group (1.7%). Various studies highlight the importance of lymph node dissection. According to a report by Cao, the rate of lymph node metastasis in DPHC lies between that of HCC and ICC, and it serves as an independent risk factor for overall survival in DPHC [7]. In Zhou's study, the absence of preoperative lymph node dissection, due to misdiagnosis, underscores

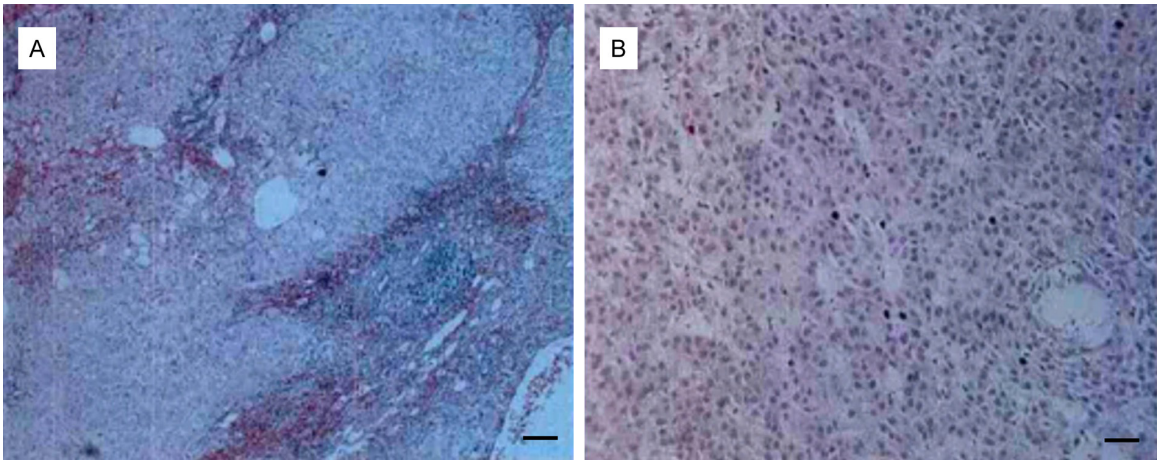

Figure 6. A. TACE one month before operation. The postoperative pathology examination showed HCC (grade II) with extensive necrosis. B. TACE one month before operation. The postoperative pathology examination showed ICC (moderate differentiated) with no obvious necrosis. Note: HCC, hepatocellular carcinoma; ICC, intrahepatic cholangiocarcinoma; TACE, transcatheter arterial chemoembolization.

the value of intraoperative frozen section analysis, which may suggest the necessity for lymph node dissection [19]. Currently, Sotiropoulos has reported only one case of DPHC treated by liver transplantation [15]. For small, strategically located tumors, alternative surgical approaches such as TACE, percutaneous ethanol injection (PEI), microwave ablation, and RFA, may be considered alongside hepatectomy [3, 8]. TACE is recognized as safe and effective for unresectable HCC. However, its use as a preoperative adjunct therapy for resectable HCC is discouraged due to potential complications such as liver inflammation, which can lead to increased adhesions and intraoperative bleeding, complicating surgical resection [20].

In our study, we diagnosed a patient with a 10 cm HCC in the right liver lobe using CT, who had untreated hepatitis B and significant cirrhosis for over a decade. TACE was administered one month prior to surgery, targeting only the identified large HCC through the right hepatic artery. At surgery, hepatectomy revealed minimal increase in perihepatic adhesions or bleeding. Unexpectedly, a 2 cm tumor was discovered in segment V, later identified as DPHC through postoperative pathology. The larger tumor exhibited necrosis and was confirmed as HCC, while the smaller, necrosis-free tumor was identified as intrahepatic cholangiocarcinoma (ICC). These findings underscore the differential impact of TACE on HCC and ICC, with a pronounced effect on the former and limited efficacy on the latter, especially in smaller tumors (**Figure 6**). This suggests that while TACE may be suitable for managing large, complex HCCs, radical resection should be prioritized for DPHC involving large ICCs [21]. The varied responses of HCC and ICC to TACE in DPHC require further investigation, particularly the biological behavior of ICCs, which is not sufficiently characterized.

Systematic prognosis analysis of DPHC has been limited to two studies from Dongfang Hepatobiliary Hospital, which reported high recurrence (77.1%, 76.00%) and mortality rates (71.4%, 66.00%), similar to ICC and worse than HCC [7, 8]. In our cohort, all DPHC cases either recurred or metastasized post-surgery, emphasizing the critical impact of ICC on patient survival.

This study encountered a few limitations. Firstly, the management of patients with recurrence or extrahepatic metastasis was not addressed. The absence of detailed information on the nature of recurrence or metastasis (whether HCC or ICC) hinders a deeper understanding of the mechanisms of DPHC recurrence and metastasis, which is crucial for tailoring further treatment. This should be a primary focus in subsequent research. Secondly, while this and other reported studies offer clinical analyses, they lack research into the pathogenesis of DPHC. Studying DPHC from a cellular and molecular perspective, consider-

ing it provides both HCC and ICC tumors within the same liver environment, could enhance our understanding of this rare condition and inform the biological behaviors of these tumors. Moreover, the statistical robustness of this study is questionable; with only 12 DPHC cases and three independent variables in the logistic and Cox regression models, the models are likely unstable, as indicated by the broad range of 95% confidence intervals. Thus, further data are needed to substantiate these findings.

In conclusion, the preferred treatment for DPHC is radical resection and regional lymphadenectomy. Preoperative TACE is effective for DPHC with large HCC components. The prognosis for DPHC is marked by high recurrence and high mortality.

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Disclosure of conflict of interest

None.

Abbreviations

DPHC, double primary hepatic cancer; HCC, hepatocellular carcinoma; ICC, intrahepatic cholangiocarcinoma; cHCC-CC, combined hepatocellular and cholangiocarcinoma; DFS, disease-free survival; OS, overall survival; HPC, hepatic progenitor cells; HBV, hepatitis B virus; HCV, hepatitis C virus; HDV, hepatitis D virus; PSC, primary sclerosing cholangitis; HBsAg, hepatitis B surface antigen; AFP, alpha fetoprotein; CEA, carcinoembryonicantigen; CA, carbohydrate antigen; US, ultrasound; CT, computed tomography; MRI, magnetic resonance imaging; MRCP, magnetic resonance cholangiopancreatography; DSA, digital subtraction angiography; TACE, transcatheter arterial chemoembolization; PEI, percutaneous ethanol injection; RFA, radiofrequency ablation; AST, aspartate aminotransferase; ALT, alanine aminotransferase; PT, prothrombin time.

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References

[1] Allen RA and Lisa JR. Combined liver cell and bile duct carcinoma. Am J Pathol 1949; 25: 647-655.

[2] Goodman ZD, Ishak KG, Langloss JM, Sesterhenn IA and Rabin L. Combined hepatocellular-cholangiocarcinoma. A histologic and immunohistochemical study. Cancer 1985; 55: 124-135.

[3] Watanabe T, Sakata J, Ishikawa T, Shirai Y, Suda T, Hirono H, Hasegawa K, Soga K, Shibasaki K, Saito Y and Umezu H. Synchronous development of HCC and CCC in the same subsegment of the liver in a patient with type C liver cirrhosis. World J Hepatol 2009; 1: 103-109.

[4] Hu J, Yuan R, Huang C, Shao J, Zou S and Wang K. Double primary hepatic cancer (hepatocellular carcinoma and intrahepatic cholangiocarcinoma) originating from hepatic progenitor cell: a case report and review of the literature. World J Surg Oncol 2016; 14: 218.

[5] Wu C, Bai DS, Jiang GQ and Jin SJ. Synchronous double cancers of primary hepatocellular carcinoma and intrahepatic cholangiocarcinoma: a case report and review of the literature. World J Surg Oncol 2014; 12: 337.

[6] Lo RC, Chan KK, Leung CO and Ng IO. Expression of hepatic progenitor cell markers in acute cellular rejection of liver allografts-an immunohistochemical study. Clin Transplant 2018; 32: e13203.

[7] Cao J, Huang L, Liu C, Li J, Zhang X, Shen J, Li J, Lu L, Xu F, Yan J, Wu M, Lau WY and Yan Y. Double primary hepatic cancer (hepatocellular carcinoma and intrahepatic cholangiocarcinoma) in a single patient: a clinicopathologic study of 35 resected cases. J Gastroenterol Hepatol 2013; 28: 1025-1031.

[8] Li A, Ma S, Pawlik T, Wu B, Yang X, Cui L and Wu M. Surgical treatment of double primary liver cancer: an observational study for a rare type of tumor. Medicine (Baltimore) 2016; 95: e4412.

[9] Inaba K, Suzuki S, Sakaguchi T, Kobayasi Y, Takehara Y, Miura K, Baba S, Nakamura S and Konno H. Double primary liver cancer (intrahepatic cholangiocarcinoma and hepatocellular carcinoma) in a patient with hepatitis C virus-related cirrhosis. J Hepatobiliary Pancreat Surg 2007; 14: 204-209.

[10] Fuji N, Taniguchi H, Amaike H, Oka K, Tsuchihashi Y, Urasaki K and Naito K. Synchronously resected double primary hepatic cancer, hepatocellular carcinoma and cholangiocarcinoma. J Gastroenterol Hepatol 2005; 20: 967-969.
[11] Jung KS, Chun KH, Choi GH, Jeon HM, Shin HS, Park YN and Park JY. Synchronous development of intrahepatic cholangiocarcinoma and hepatocellular carcinoma in different sites of the liver with chronic B-viral hepatitis: two case reports. BMC Res Notes 2013; 6: 520.
[12] Jang HJ, Kim TK and Wilson SR. Imaging of malignant liver masses: characterization and detection. Ultrasound Q 2006; 22: 19-29.
[13] Orcutt ST and Anaya DA. Liver resection and surgical strategies for management of primary liver cancer. Cancer Control 2018; 25: 1073274817744621.
[14] Choi BI, Han JK, Hong ST and Lee KH. Clonorchiasis and cholangiocarcinoma: etiologic relationship and imaging diagnosis. Clin Microbiol Rev 2004; 17: 540-552, table of contents.
[15] Sotiropoulos GC, Molmenti EP, Frilling A, Paul A, Malamutmann E, Broelsch CE and Malagó M. Liver transplantation for double primary hepatic cancer-hepatocellular carcinoma and intrahepatic cholangiocarcinoma. Transplantation 2006; 82: 718-719.
[16] Schernthaner RE, Lin M, Duran R, Chapiro J, Wang Z and Geschwind JF. Delayed-phase cone-beam CT improves detectability of intrahepatic cholangiocarcinoma during conventional transarterial chemoembolization. Cardiovasc Intervent Radiol 2015; 38: 929-936.
[17] Mazzaferro V, Gorgen A, Roayaie S, Droz Dit Busset M and Sapisochin G. Liver resection and transplantation for intrahepatic cholangiocarcinoma. J Hepatol 2020; 72: 364-377.
[18] Ng KK, Vauthey JN, Pawlik TM, Lauwers GY, Regimbeau JM, Belghiti J, Ikai I, Yamaoka Y, Curley SA, Nagorney DM, Ng IO, Fan ST and Poon RT; International Cooperative Study Group on Hepatocellular Carcinoma. Is hepatic resection for large or multinodular hepatocellular carcinoma justified? Results from a multiinstitutional database. Ann Surg Oncol 2005; 12: 364-373.
[19] Zhou R, Zhang M, Cheng N and Zhou Y. Double primary hepatic cancer (hepatocellular carcinoma and intrahepatic cholangiocarcinoma) in a single patient: a case report. Oncol Lett 2016; 11: 273-276.
[20] Paye F, Jagot P, Vilgrain V, Farges O, Borie D and Belghiti J. Preoperative chemoembolization of hepatocellular carcinoma: a comparative study. Arch Surg 1998; 133: 767-772.
[21] Jeong S, Zheng B, Wang J, Chi J, Tong Y, Xia L, Xu N, Zhang J, Kong X, Gu J and Xia Q. Transarterial chemoembolization: a favorable postoperative management to improve prognosis of hepatitis B virus-associated intrahepatic cholangiocarcinoma after surgical resection. Int J Biol Sci 2017; 13: 1234-1241.