

Three-Phase CT Findings of Combined Hepatocellular and Cholangiocarcinomas¹

혼합형 간세포-담관암의 삼중시기 CT소견¹

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Purpose: To evaluate three-phase CT findings of combined hepatocellular and cholangiocarcinomas (cHCC-CCs), with an emphasis on the enhancement pattern.

Materials and Methods: We retrospectively analyzed CT findings in 11 patients with histopathologically proven 11 cHCC-CCs. Three-phase CT findings of cHCC-CCs during the arterial phase (AP), portal venous phase (PVP), and equilibrium phase (EP) were evaluated, based on the morphologic and enhancement pattern.

Results: Two (18%) of all the tumors showed arterial enhancement during the AP and delayed washout during the PVP and EP. Three tumors (27%) showed no arterial enhancement and delayed washout or delayed enhancement during the same phases. The remaining six tumors (55%) showed both arterial enhancement and delayed enhancement during the same phases.

Conclusion: Three-phase CT findings of cHCC-CCs were found to be variable, according to the histologic proportion of HCC or CC components. However, cHCC-CC could be considered when a tumor shows both arterial enhancement and delayed enhancement at three-phase CT.

Index terms

Liver, Neoplasms

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INTRODUCTION

Primary liver cancers can be histologically divided into two categories, hepatocellular carcinoma (HCC) and cholangiocarcinoma (CC). The HCC accounts for more than 80% and CC accounts for 15% of cases of primary liver cancers (1). Combined hepatocellular and cholangiocarcinoma (cHCC-CC) is a rare subtype (1.0-4.7%) of liver cancer displaying components of both HCC and CC, but are increasingly recognized due to more extensive sampling of the surgical specimens with immunohistochemical stain (1, 2).

Since the first description of cHCC-CC was reported by Allen and Lisa (3) in 1949, several pathological classifications of cHCC-CCs have been reported (3-7). Based on the classification of World Health Organization (WHO), cHCC-CC is defined as a

tumor containing unequivocal, intimately mixed elements of both HCC and CC (8). According to 2010 WHO classification, cHCC-CC is broadly classified into two categories with respect to presence of stem cell features. In other words, two categories of cHCC-CC are classical type and subtype with stem cell features. Classical type of cHCC-CC is defined as the ones containing unequivocal elements of both HCC and CC and this type should be distinguished from individual HCC and CC arising in the same liver. Subtype with stem cell features of cHCC-CC is divided into three subtypes according to their histopathology and immunophenotype: a) stem cell features with typical subtype; b) stem cell features with intermediate-cell subtype; and c) stem cell features with cholangiocellular subtype (8).

Most of the cHCC-CCs have transitional or intermediate areas, in which HCC and CC elements are practically indistin-

guishable (8). Therefore, it might be difficult to make a correct diagnosis about cHCC-CC before surgery. Furthermore, even though the biological features of cHCC-CCs have been reported to be similar to those of HCC rather than CC, the prognosis of patients with cHCC-CCs is poorer than in patients with HCC or CC (9-11). Furthermore, aggressive surgical treatment including lymph node dissection might be essential for successful treatment of cHCC-CCs (11). Thus, it is very important to make preoperative diagnosis of cHCC-CCs.

To the best of our knowledge, there have been only a few reports describing the imaging findings of cHCC-CC using ultrasonography and CT because of its rarity (12-17). Most of the reports have described their CT findings of cHCC-CC, and revealed that they resembled HCC or CC depending on their predominant components of HCC or CC. However, there are no reports that describe the characteristic enhancement pattern of cHCC-CC, particularly about the three phases. The purpose of our study was to evaluate three-phase CT findings of cHCC-CC with an emphasis on the enhancement pattern.

MATERIALS AND METHODS

Patients

The institutional review board of our hospital approved this retrospective study and waived the requirement for informed consent. We performed a computerized search of our hospital's surgical records from January 2001 and March 2011 using the search term "combined hepatocellular and cholangiocarcinoma". This search identified 16 patients with cHCC-CCs during histopathologic examination. Of these patients, five patients were excluded from the present investigation because two patients had collision tumors, which were widely separated or close to each other, and three patients did not undergo three-phase CT. The remaining 11 patients (nine men and two women; mean age, 55.8 years; age range, 42-71 years) with 11 cHCC-CCs were selected on the basis of the following inclusion criteria: three-phase [arterial phase (AP), portal venous phase (PVP), and equilibrium phase (EP) imaging] CT scanning performed within one month prior to surgery, and histopathologically proven cHCC-CCs. The mean time interval between the CT examination and surgery was 24 ± 18.7 days (range, 3-64 days). Pathologic diagnoses were obtained with

surgical resection ($n = 10$) or percutaneous liver biopsy ($n = 1$).

Of the 11 patients, ten patients (91%) had liver cirrhosis, and were associated with either hepatitis B ($n = 8$) or alcohol abuse ($n = 2$). Elevated tumor markers including enhanced levels of alpha-fetoprotein (AFP) ($n = 6$), carcinoembryonic antigen (CEA) ($n = 1$), and carbohydrate antigen 19-9 ($n = 2$) were found in nine patients.

Image Acquisition

Eleven patients underwent three-phase CT during the AP, PVP, and EP imaging. Multidetector CT (MDCT) was performed by using one of the following CT scanners: 16-channel CT scanner (Sensation16; Siemens Medical Solutions, Forchheim, Germany) ($n = 3$), and 64-channel CT scanner (Sensation 64; Siemens Medical Solutions, Forchheim, Germany) ($n = 4$). The remaining four patients were imaged with CT scanners outside our institution: 16-channel CT scanner (Somatom Emotion unit; Siemens Medical Solutions, Erlangen, Germany) ($n = 1$), and single slice CT scanner (Asteion CT scanner; Toshiba Medical Systems, Tokyo, Japan) ($n = 3$).

At our institution, the following scanning parameters were used for the 16-, and 64-channel MDCT scanners: detector configurations of 16 parame detector configurations of 16×0.75 , and 64×0.625 mm, respectively; section thicknesses of 3.0-5.0 and 3.0 mm, respectively; reconstruction intervals of 3 mm, respectively; a field of view of 304-360 mm, a tube current-time product of 144-486 mAs, and a peak voltage of 120 kVp. The CT protocols, which were used outside our institution were not identifiable.

A total of 1.2-1.5 mL of nonionic contrast material [Iopromide (370 mg of iodine per milliliter), Ultravist 370; Schering, Berlin, Germany] per kilogram of body weight was usually injected into an antecubital vein of the patient at a rate of 3.0 mL/sec by using a power injector. The scanning delay time was 25-40 seconds for the AP, 80 seconds for the PVP, and 180 seconds for the EP after the contrast injection. A 20-mL flush of normal saline solution was administered immediately after the contrast injection.

Image Analysis

Two abdominal radiologists with 25 and 13 years of clinical experience retrospectively analyzed the CT images by consen-

sus. Various parameters were analyzed for the morphologic and enhancement patterns. For the morphologic pattern, the tumor size, location, shape, and ancillary findings (fibrous capsule, portal vein thrombosis, and bile duct dilatation) were evaluated. The shape of the tumor was classified as round, lobulated, and irregular. For the enhancement pattern, the tumor attenuation was evaluated according to the following classification: 1) Type I was defined as an enhancing tumor at the AP (i.e., arterial enhancement), which showed progressive decrease in attenuation during the PVP and EP (i.e., delayed washout), 2) Type II was or without rim enhancement at the AP, which showed delayed washout or progressive increase in attenuation (i.e., delayed enhancement) during the PVP and EP, and 3) Type III was defined as a tumor with arterial enhancement and delayed enhancement.

Pathologic Analysis

A pathologist with 30 years of clinical experience in hepatobiliary pathology retrospectively reviewed the pathology slides without any previous knowledge of the CT findings. All the cHCC-CCs were diagnosed as combined type of Allen classification (3) and transitional tumor of Goodman classification (6) instead of recent WHO classification (8), because most of them were histopathologically diagnosed before 2010. Nevertheless, the histologic proportion of HCC and CC components was evaluated for each tumor in order to compare it with CT findings. In all the tumors, further immunohistochemical stainings were performed in order to confirm the presence of either of the HCC component (HepPar 1, AFP, and CH 8-18) or CC component (CEA, CK7, and CK19).

RESULTS

For the morphologic pattern, the mean diameter of all the tumors was 4.8 cm (range, 1.3 of 11.0 cm) and all of them were located in the right lobe. The tumor shape was round, lobulated, and irregular in six, four, and one tumor, respectively. Ancillary findings such as fibrous capsule, portal vein thrombosis, and bile duct dilatation were found in two, one, and one patient, respectively.

For the enhancement pattern, two tumors (18%) showed Type I enhancement pattern, which histopathologically confirmed

that most of the parts of the tumors were composed of HCC components (Fig. 1). Three tumors (27%) showed Type II enhancement pattern, which histopathologically confirmed that most parts of the tumors were composed of CC components (Fig. 2). One of these tumors showed rim enhancement, and others showed delayed enhancement. Six tumors (55%) showed Type III enhancement pattern, which histopathologically confirmed that the tumors were variably composed of both HCC and CC components without any predominant component (Fig. 3). Altogether, eight tumors (73%) showed arterial enhancement, while the other eight tumors (27%) showed delayed enhancement.

DISCUSSION

Most of the studies have reported that patients with cHCC-CCs show similar clinical and pathological features as patients with HCCs including the male predominance, high incidence of hepatitis B virus infection, underlying chronic liver disease, and elevated serum AFP levels (18-20). Although the clinical features of cHCC-CCs are similar to those of HCC, the prognosis of cHCC-CCs is poorer than HCC or CC (4, 9-11). The cHCC-CCs show frequent portal vein invasion and lymph node metastasis at a higher incidence than HCC or CC (4, 12).

Only a few studies have described the resemblance between CT findings of cHCC-CC and HCC or CC depending on the predominance of HCC or CC components (12-17). Previously, it has been reported that a confident diagnosis of cHCC-CC is not possible on the basis of CT findings alone because of the lack of specific imaging characteristics, and it was difficult to differentiate cHCC-CC from HCC or CC based on CT alone (15-17). Furthermore, various causes of misdiagnosis of cHCC-CCs have been reported, such as the atypical enhancing pattern, small size of HCC or CC components within the tumor, and presence of intermediate tumor cells (12).

In our study, two of the 11 tumors showed type I enhancement pattern, suggestive of the presence of HCC-like component. As expected, they were mostly composed of HCC component, and CC component were observed focally or sporadically at the time of histopathological examination. Three cHCC-CCs showed type II enhancement pattern, suggestive of the presence of CC-like component. They were mostly composed of

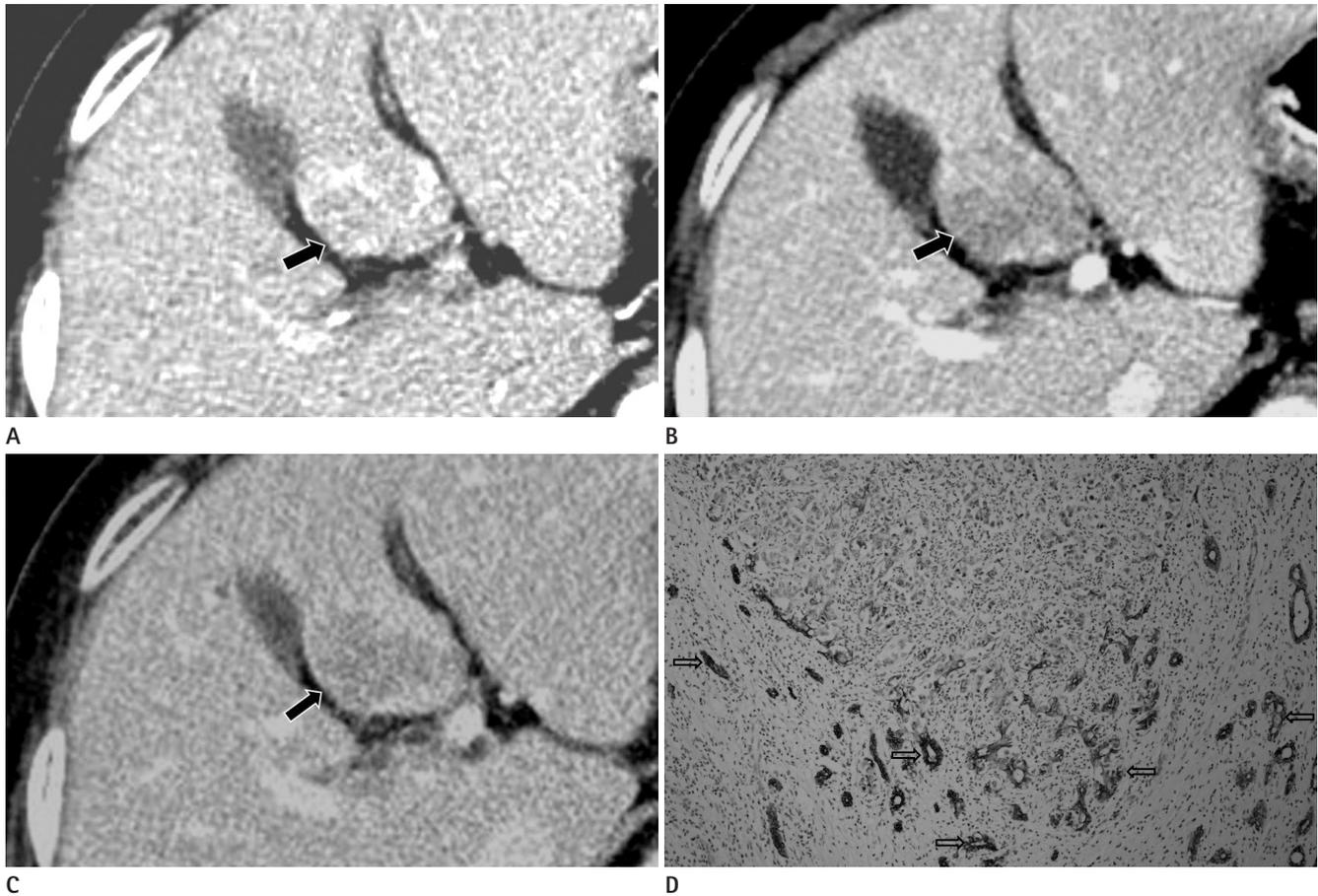


Fig. 1. A 71-year-old woman with combined hepatocellular and cholangiocarcinoma showing arterial enhancement and delayed washout (Type I). Arterial phase CT image **(A)** shows a 3.4 cm, enhancing mass (arrow) in the segment 4 of the liver. Portal venous phase **(B)** and equilibrium phase **(C)** images show the same mass (arrow) with delayed washout. **(D)** Immunohistochemical staining for CK19 for HCC and CC components shows a large area of HCC components with negative cytoplasmic staining, and sporadic CC components with positive cytoplasmic staining (open arrow), representing HCC-dominant cHCC-CC (magnification, $\times 100$).
 Note. –cHCC-CC = combined hepatocellular and cholangiocarcinoma

CC component, and HCC component was present focally or sporadically at the time of histopathological examination. The remaining six cHCC-CCs showed type III enhancement pattern, suggestive of the presence of both HCC-like and CC-like components. They had both HCC and CC components at the time of histopathological examination, but there were no predominant HCC or CC component. Thus, we considered that arterial enhancement of cHCC-CCs during the AP was mostly due to hypervascularity within HCC component, and delayed enhancement of cHCC-CCs during the EP was mostly due to abundant fibrosis within the CC component.

Aoki et al. (15) reported the classification of enhancement patterns of cHCC-CCs into three types at dynamic CT. According to their report, type A were demonstrated as low attenuating masses with high attenuating periphery in the early phase

and subsequently transformed into masses with peripheral low attenuation and central high attenuation in the late phase; type B were high attenuating masses in the early phase and became low attenuating masses in the late phase; type C were low attenuating masses in both early and late phases. They also reported that differentiation of type A cHCC-CC from CC was difficult with dynamic CT alone. When our results were compared with report by Aoki et al. (15), type A and C of Aoki's classification corresponded well to type II of our classification, while type B corresponded to type I of our classification. However, cHCC-CC of type III in our classification was not described in Aoki's classification.

Sanada et al. (14) reported that the enhancement patterns of cHCC-CCs were classified as three types and their results were also similar to our results. According to this report, type A

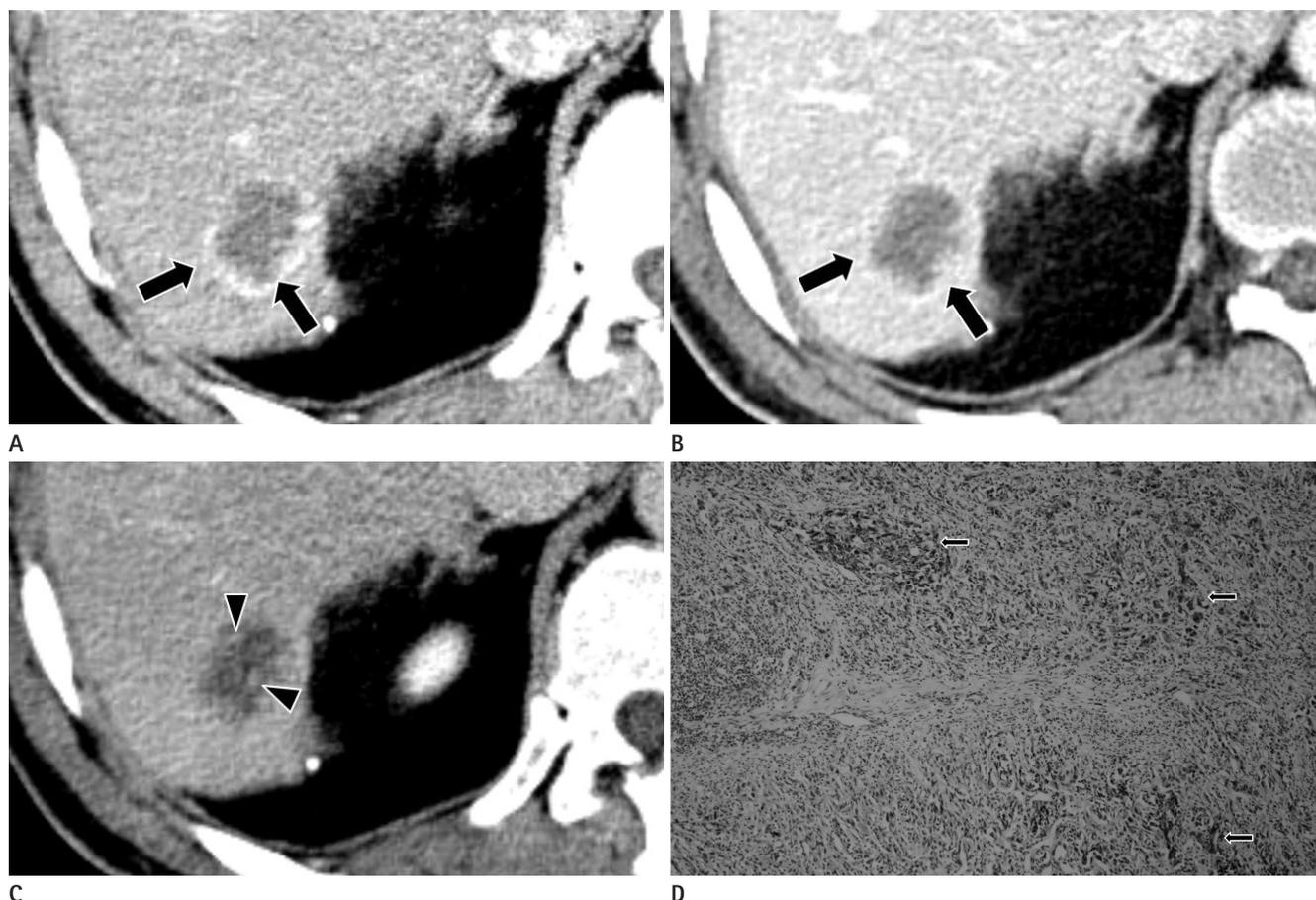


Fig. 2. A 51-year-old man with combined hepatocellular and cholangiocarcinoma showing no arterial enhancement and delayed enhancement (type II). Arterial phase CT image **(A)** shows a 2.5 cm, non-enhancing mass (arrows) in the segment 6 of the liver. Portal venous phase image **(B)** shows the same mass (arrows) with peripheral rim enhancement. Equilibrium phase image **(C)** shows the same mass with delayed enhancement (arrowheads). **(D)** Immunohistochemical staining for HCC and CC components shows a large area of CC components with diffuse fibrosis and negative cytoplasmic staining for HepPar 1, and sporadic HCC components with positive cytoplasmic staining (black arrows) for HepPar 1, representing CC-dominant cHCC-CC (magnification, $\times 100$).

Note.—cHCC-CC = combined hepatocellular and cholangiocarcinoma

showed an area of high attenuation in the early phase and of low attenuation due to washout of contrast agent in the late phase. Type B showed an area with peripheral enhancement in the early and late phases. Type C was presented as an area of high attenuation in the early phase and an area of slight delayed enhancement in the late phase. In our study, Type III enhancement pattern was similar to type C enhancement pattern of late phase, as described by Sanada et al. (14). Kim et al. (21) reported that 71% of intrahepatic mass-forming CCs showed typical enhancement pattern of hypoattenuation during the AP and hypo-, iso-, or hyperattenuation during the PVP and/or EP, and the remaining 29% showed atypical enhancement with respect to that they showed arterial enhancement with or without delayed washout in 4 and 24% of CCs, respectively. In this respect,

cHCC-CCs of type III may resemble intrahepatic CCs. In addition, other hepatic tumors including inflammatory pseudotumor and HCC variants with fibrous tissue such as fibrolamellar HCC, sarcomatoid HCC, and sclerosing HCC may show arterial enhancement and delayed enhancement (21-24). Therefore, these tumors should be considered in the differential diagnosis of cHCC-CCs.

Dilation of the intrahepatic bile ducts is an important feature in the diagnosis of CC (25). However, Aoki et al. (15) reported that none of the cases of cHCC-CCs showed dilatation of the intrahepatic bile ducts. In our study, dilatation of the intrahepatic bile duct was observed in only one case, representing that this finding is not considered a characteristic feature of cHCC-CCs (17).

Our study has some limitations. First, we could not directly correlate CT findings of cHCC-CC with specific histopathologic findings such as the predominance of HCC or CC compo-

nent because we could not obtain multisectional tumor specimens. However, we could realize that three types of our cHCC-CCs correlated quite well with their corresponding predominance

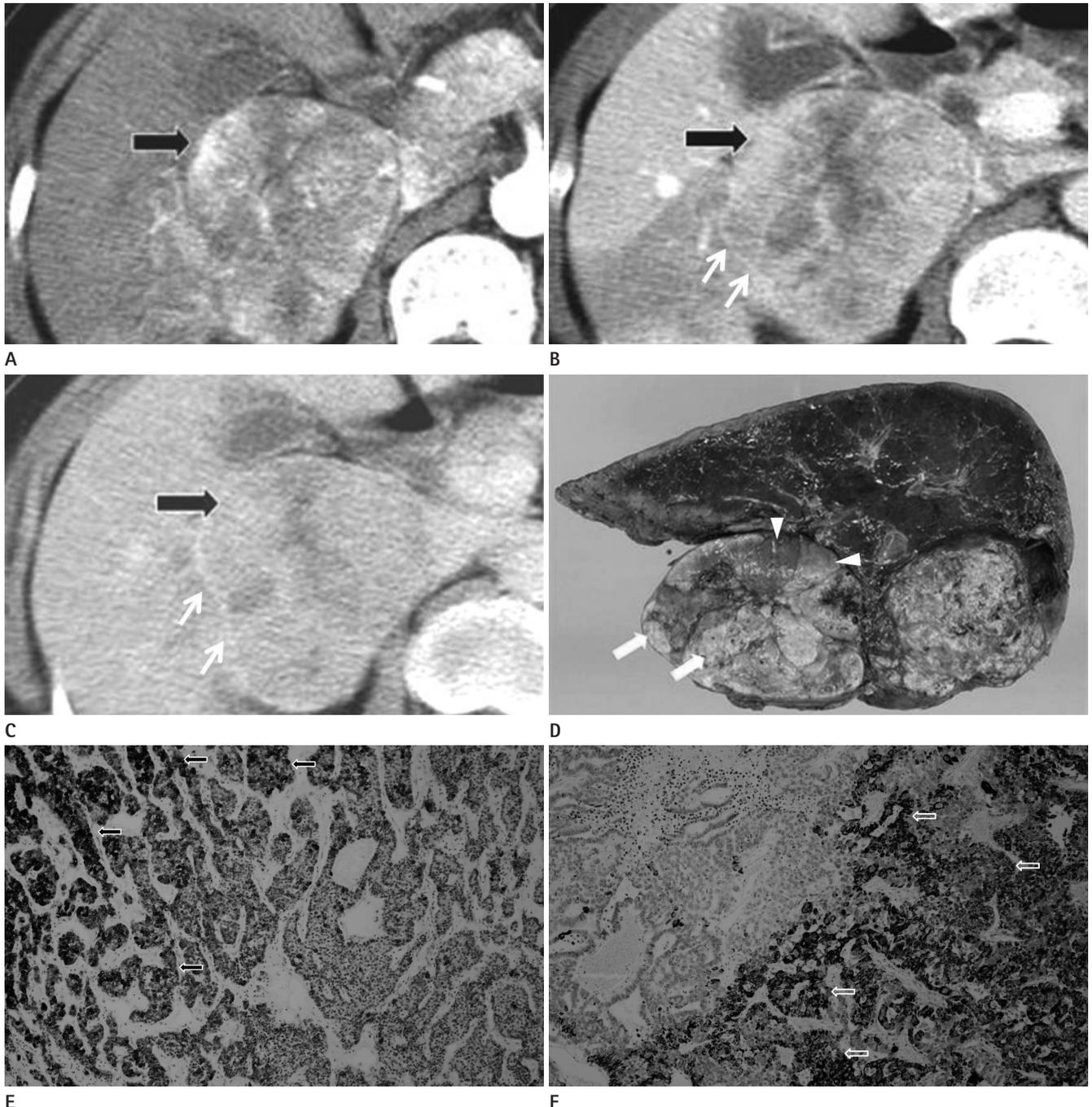


Fig. 3. A 48-year-old woman with combined hepatocellular and cholangiocarcinoma showing both arterial enhancement and delayed enhancement (Type III). Arterial phase CT image **(A)** shows a 11 cm, enhancing mass (black arrow) involving the segments 1, 6, 7, and 8 of the liver. Portal venous phase image **(B)** shows the same mass (black arrow) with capsular enhancement (white arrows). Equilibrium phase image **(C)** shows the same mass (black arrow) with delayed enhancement. **(D)** Photograph of the gross specimen shows a tumor mixed with bile stained yellowish mass of component of HCC (arrowheads) and whitish mass of component of CC (white arrows). Immunohistochemical staining for components of HCC and CC shows HCC components with positive cytoplasmic staining (black arrows) for HepPar 1 **(E)**, and CC components with positive cytoplasmic staining (open arrows) for CK19 **(F)** (magnification, $\times 200$). Note.—CC = cholangiocarcinoma, HCC = hepatocellular carcinoma

of HCC or CC component. Second, the number of cases was too small to obtain statistically significant results. Therefore, we could only suggest the correlation between the enhancement patterns of our cHCC-CCs and their histopathologic characteristics. Third, we could not use the same CT protocols in that they included eight cases using MDCT and three cases using single slice CT, because we collected these rare cases from the past 10 years.

In conclusion, three-phase CT findings of cHCC-CCs were variable, particularly in their enhancement pattern according to the histologic proportion of HCC and CC components. However, cHCC-CC could be considered, when a tumor shows both arterial enhancement and delayed enhancement at three-phase CT.

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혼합형 간세포-담관암의 삼중시기 CT소견¹

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목적: 혼합형 간세포-담관암의 삼중시기 CT소견에서 조영증강 양상을 중심으로 평가하고자 하였다.

대상과 방법: 11명의 환자에서 조직병리학적으로 확진된 11예의 혼합형 간세포-담관암의 삼중시기 CT소견을 후향적으로 분석하였다. CT소견에서 형태 및 조영증강 양상에 대해 평가하였다.

결과: 11예의 혼합형 간세포-담관암 중 2예(18%)는 동맥성 조영증강과 지연성 씻김을 보였다. 3예(27%)는 동맥성 조영증강은 보이지 않았고 지연성 씻김 또는 지연성 조영증강을 보였다. 6예(55%)는 동맥성 조영증강 및 지연성 조영증강을 동시에 보였다.

결론: 혼합형 간세포-담관암의 CT소견은 종양의 간세포암 및 담관암의 구성 성분에 따라 다양하였다. 그러나 종양이 동맥성 조영증강 및 지연성 조영증강을 동시에 보일 경우 혼합형 간세포-담관암의 가능성을 고려할 수 있다.

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