Combined Hepatocellular and Cholangiocarcinoma: CT Findings with Emphasis on Multiphasic Helical CT

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Objective: *To describe CT findings of patients with combined hepatocellular carcinoma and cholangiocarcinoma (HCC-CC) in correlation with clinical data and histopathological results.*
Material and Method: *Ten from 31 cases whose CT study was available were reviewed retrospectively in the aspect of imaging findings, clinical data, and pathological results.*
Results: *Most of the tumors were hypodense solitary mass with gradually enhanced after contrast administration. Bile duct dilatation was observed in two cases. The overall CT findings were more similar to CC rather than HCC despite the pathological result showing predominant HCC component. Serum alpha-fetoprotein level was normal or mildly elevated while an elevated concentration of carbohydrate antigen 19-9 was observed. Hepatitis profiles showed positive to hepatitis B virus infection in four cases and hepatitis C virus infection in one case.*
Conclusion: *The diagnosis of combined HCC-CC should be considered if the tumor has similar findings to CC without bile duct dilatation on cirrhotic liver and the patient has normal or low rising of the AFP level with or without elevated CA 19-9 level. In non-cirrhotic liver, the finding is non-specific.*

Keywords: *Tomography, Spiral Computed Carcinoma, Hepatocellular cholangiocarcinoma*

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Combined hepatocellular and cholangiocarcinoma (HCC-CC) first described comprehensively by Allen and Lisa in 1949 is a primary liver carcinoma comprised of histopathological morphology of hepatocellular carcinoma and cholangiocarcinoma. This rare type of liver cancer is about 1.0-4.7% of the primary liver carcinoma[1]. The cellular origin of this tumor remains unknown and patients with combined HCC-CC share similar clinical and pathological features with patients presenting with HCC or CC depending on the series studied[2-5]. The genetic components of the combined HCC-CC are reported closer to CC than HCC[6].

Prognosis of combined HCC-CC is poorer than the HCC[1,6]. The distinction of combined HCC-CC is important in deciding on a treatment method, including complete removal of lymph nodes and it should be unequivocally diagnosed[7]. Most cases were rarely diagnosed by imaging studies and sometimes misled clinical data resulting in improper management. Familiarity with the imaging findings and clinical clues of this particular tumor can help to make a correct diagnosis or at least be aware of its existence. The present study aimed to describe computed tomography (CT) findings of patients with combined HCC-CC in correlation with clinical data and histopathological results.

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Material and Method

The patients diagnosed as combined HCC-CC histopathologically from January 1996 to November 2004 were searched from the electronic pathological database and identified 31 cases. Nineteen patients were excluded due to unavailable CT study in Ramathibodi Hospital. Pathologic specimens were analyzed to confirm diagnosis. Two patients were excluded due

to diagnosis change on the pathological reviewing process. The study was approved by the ethics committee. All pertinent clinical information was recorded, which included age and gender of the patients; the presence of risk factors for hepatocellular carcinoma, including evidence of hepatitis B and C virus infection; and the level of serum alpha-fetoprotein (AFP), carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA 19-9) before treatment.

Imaging studies and image analysis

All CT scans of the abdomen were performed with 4-slices-multidetector spiral computed tomography (LightSpeed plus, General Electric Medical System, Milwaukee, USA) and the protocol; shown in Table 1.

CT studies were retrospectively reviewed by two radiologists without knowledge of specific clinical and pathologic findings, but with knowledge of the diagnosis of combined HCC-CC. The image analyses of all cases were done on e-film workstation version 1.8.3 (Merge e-film medical system, USA) on the Windows 2000 operating system. (Microsoft Corporation, USA). Disagreements were few and minor, and were resolved by consensus. CT findings of the tumor were recorded as tumor location, number, size, shape, margin, transitional zone, presence of capsule, extension, internal characteristics, density and patterns of enhancement in various phases, and presence of rapid washout. The other findings were recorded, including liver density in various phases, presence of liver cirrhosis, and lymph nodes. The attenuation of liver parenchyma was obtained by measuring three regions of interest (ROI) in the liver. The median value was used as a representative value.

Patterns of enhancement

The enhanced patterns were assessed objectively and subjectively by using the method described by Loyer et al[8]. In objective analysis, the CT attenuation coefficients of the tumor were measured in all obtained phases. The ROIs were chosen by two radiologists. In the heterogeneous enhancement, the ROI was placed in the area of more homogeneous. If more than one region of interest was selected in a large heterogeneous enhancing tumor, then the ROI used for analysis was chosen by consensus. By using these data, time-attenuation curves and curves of difference in attenuation curves between tumor and liver parenchyma were established.

In subjective analysis, the attenuation was graded with respect to the surrounding liver parenchyma. The images were evaluated with both narrow (window width, 100 HU; window level, 60-90 HU) and soft-tissue (window width, 400 HU; window level, 70-80 HU) window settings. The grading was classified into three categories according to their conspicuity: 1, barely visible against the surrounding liver parenchyma; 2, intermediately obvious; or 3, extremely obvious. Consequently, the following categories were defined: hyperattenuating 3, hyperattenuating 2, hyperattenuating 1, isoattenuating, hypoattenuating 1, hypoattenuating 2, and hypoattenuating 3. By using these data, a curve of the relative attenuation of the tumor over time was established for each lesion.

Pathological results

The pathology results were reviewed by one pathologist. The diagnosis of combined HCC-CC is based on the criteria of World Health Organization i.e., tumors containing unequivocal elements of both hepatocellular carcinoma and cholangiocarcinoma[9]. Hepatocellular differentiation was diagnosed when there were intercellular bile canaliculi, bile production, and a trabecular growth pattern. Biliary differentiation was defined when there was glandular morphology, mucin production, and dense fibrous tissue. The re-

Table 1. CT Protocol

Pre-contrast study: Axial 10-mm collimation (5-mm in one case) with 1.5:1.0 pitch in craniocaudal direction from lung bases to lower pole of kidneys
Post-contrast study: single breath hold in each phase with 1.5:1.0 pitch in craniocaudal direction with the same coverage
Early arterial phase (one case): 3.75 mm collimation at 20 second
Late arterial phase: 2.5 - 3.75 mm collimation at 40 second
Portovenous phase: 3.75 mm collimation at 70 second
Delayed scan: 3.75 mm collimation at 5 minutes (10 minute in one patient)

Note : one patient that accidentally found lesion during chest scan, using 10 mm and 2.5 mm in pre and post contrast study with delayed scan at 5 minute

Contrast media : nonionic contrast media, rate 2.5 cc/s with total volume 90-100 cc

Table 2. Patient characteristics and clinical data (n = 10)

Patient characteristics and clinical data	Number % (n)
Age (yrs) (median, range)	53.54 (30-71)
Sex (percent, cases)	
Male	70% (7)
Female	30% (3)
Viral infection (percent, cases)	
Negative	30% (3)
Hepatitis B	40% (4)
Hepatitis C	10% (1)
Unknown	20% (2)
Tumor markers	
AFP (ng/ml) Median (range)	69.92 (2.15-322.6, n = 10)
Normal (< 5.4) (percent, case)	50% (5)
< 20	20% (2)
20-200	10% (1)
200-500	20% (2)
> 500	0
CEA (ng/ml) Median (range)	
Median (range)	56.84 (1.25-26.64, n = 7)
< 5 (percent, case)	57 (4/9)
≥ 5	42.8 (3/9)
CA19-9 (U/ml) Median (range)	361.88 (0.1-26.7, n = 5)
< 37 (percent, case)	60% (3)

CEA = Carcinoembryonic antigen
CA19-9 = Carbohydrate antigen 19-9

sults were also recorded as the dominancy of the tumor type (CC or HCC) and the presence of vascular or biliary invasion.

The results were presented with percent and number in the form of frequency, tables, and figures.

Results

Clinical data

There were 10 cases included in the present review. Seven were male and three were female. Their ages ranged from 30 to 71 years old (mean = 53 years 6 months, SD = 11 year 5 months). Serum tumor markers included alpha-fetoprotein assay in all patients; seven patients had serum assays of CEA and five patients had serum assay of CA19-9. The age, gender, and details of laboratory data are shown in Table 2.

After dividing the cases into two groups by the presence of liver cirrhosis on the imaging study, the cirrhotic appearance group had low rising AFP (mean = 13.86 ng/ml) and CEA (mean = 7.73 ng/ml) levels, but the CA 19-9 level was rising (mean = 157.94 U/ml). Non-cirrhotic group had higher AFP level (mean = 125.98 ng/ml) and lower CA 19-9 level (mean = 15.33 U/ml).

CT findings

Five patients had cirrhotic liver appearance. There were solitary masses in seven patients and more than one in three patients. The diameter of the masses varied from 1.2 to 13.0 cm with a mean of 5.0 cm. The tumor was located in the right lobe in six cases and in the left lobe in four cases. Most were located in the subcapsular region (6 cases), but only one had capsular invasion. Portal vein involvement was found in one case. Two cases had mild dilatation of intrahepatic bile duct adjacent to the tumor. Tumor capsule was identified in three cases. None had significant enlarged lymph node (less than 1 cm).

Neither calcification nor fat component was present in the tumor. The intratumoral hemorrhage was seen in one case, which had a huge 13-cm tumor. The internal necrosis was identified in 1 case (tumor size 1.9 cm). Most of the tumors (8 cases) were relatively hypodensity to the liver parenchyma and two cases were

Table 3. CT findings

Findings	% (number)	Cirrhosis* case (n = 5)	Non-cirrhosis* case (n = 5)
Tumor Number			
Solitary	70% (7)	3	4
Multiple	30% (3)	1	2
Tumor size			
Mean diameter (cm) (range)	5.03 (1.2-13)	4.58 (1.9-7)	5.48 (1.2-7)
Location			
Central location	40% (4)	1	3
Subcapsular location	60% (6)	4	2
Capsular extension	10% (1)	0	1
Portal vein invasion	10% (1)	0	1
Bile duct invasion	20% (2)	1	1
Presence of capsule	30% (3)	2	1
Contrast enhancement			
Homogeneous	20% (2)	0	2
Heterogeneous	20% (2)	1	1
Peripheral	50% (5)	3	2
Nodular	10% (1)	1	0
Margin			
Smooth	50% (5)	3	2
Lobulated	50% (5)	2	3
Transitional zone			
Well-defined	70% (7)	3	4
Ill-defined	30% (3)	2	1
Shape			
Round/ovoid	60% (6)	3	3
Irregular	40% (4)	2	2

* Based on imaging findings

isodensity. The CT findings are summarized in Table 3. In addition, based on the CT findings that suggested liver cirrhosis, the patients were categorized into two groups, cirrhotic and non-cirrhotic appearance.

Enhancement pattern

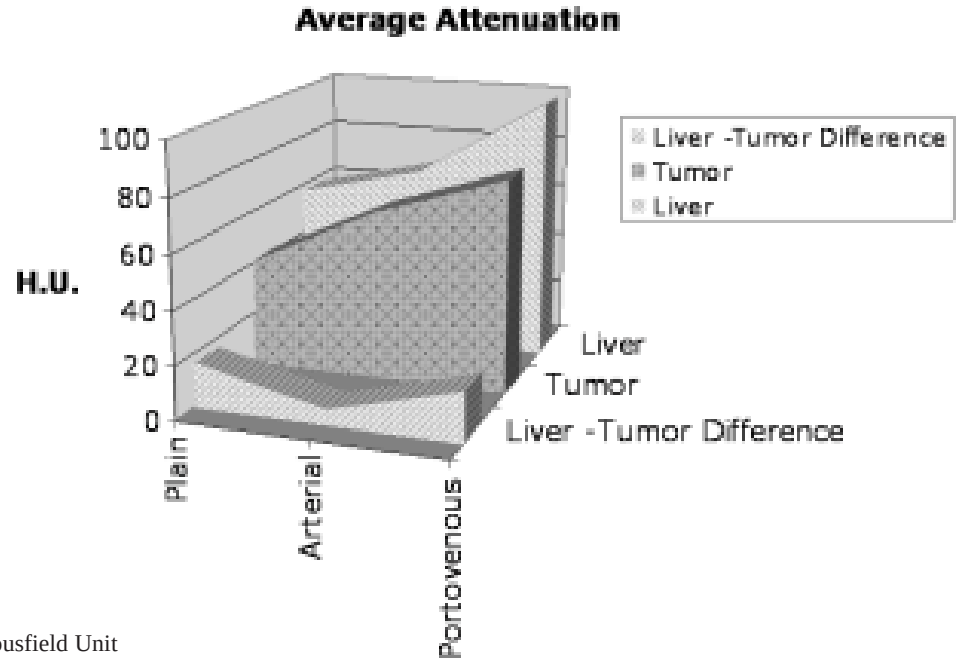
Ten cases were analyzed. One case underwent three phases scan after contrast administration without delayed scan. Five cases underwent 2 phases post contrast liver scan with delayed scan. Three cases underwent 2 phases post contrast liver scan without delayed scan. One case underwent CT scan of the chest (venous phase and delayed 5 minute). The mean attenuations of liver, tumor, and tumor-to-liver values are plotted in Fig. 1. Tumor showed homogeneous enhancement in two cases, heterogeneous enhancement in two cases, peripheral enhancement in five cases, and central nodular enhancement in one case. Four cases showed delayed enhancement in its central portion. None of them showed rapid washout.

Grading of subjective enhancement showed that most of the tumors had isodensity or slight relatively hyperdensity in the arterial phase and returned to relatively hypodensity in the portovenous and delayed phases (Fig. 2).

Pathological results (with CT correlation)

Completely excised tumors were obtained in 4 cases; all of them showed predominant HCC component and one case had predominant fibrous tissue in the background on histopathological review, however, there was no delayed enhancement on CT in these masses. Fatty change of HCC component was found in one case, which was not detected in CT.

Core biopsies were available in the remaining six cases, two cases had predominant CC component and the remaining four cases had predominant HCC component. In one predominant CC case, CT showed intrahepatic bile duct dilatation and portal vein invasion. Background of fibrous tissue was found in three



H.U. = Housfield Unit

Fig. 1 Average CT attenuation in plain, arterial and portovenous phases of liver, tumor, and differences between liver and tumor

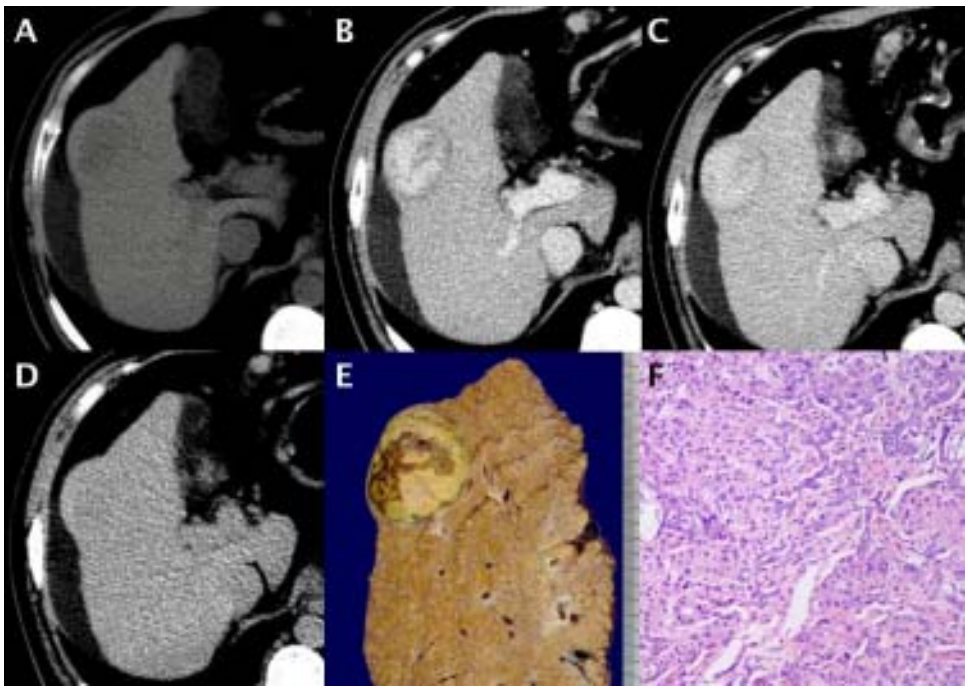


Fig. 2 A 45 year-old male with combined HCC-CC at right hepatic lobe. CT appearance: relatively hypodense in precontrast study (A), relatively hyperdense in arterial phase (B), remain hyperdense in portovenous phase (C) and appear iso-slightly hypodense in delay image at 10 minutes (D). The gross appearance (E) and histopathology of the mass (F)

cases. Fatty change of HCC component was found in one case. Four cases that showed late enhancement of the central area of the tumor comprised of predominant CC and fibrous tissue in two cases and predominant HCC without fibrous tissue in other two cases.

Discussion

In the present study, the CT findings of combined HCC-CC were presented with emphasis on multiphasic helical CT study. The general appearance of the liver showed cirrhotic appearance in half of cases. Most of the tumors were solitary, round, non capsulate, well-defined hypodensity in the precontrast study without bile duct or vascular invasion. No calcification or hemorrhage was present. Difference in CT attenuation value between tumor and liver parenchyma was increased in the arterial and portovenous phases and slightly decreased in the delay phase. The peripheral rim enhancement that was mentioned in the prior report was also found in the present study[10]. Some of them showed enhancement in the central area of the tumor, which was similar to the enhancing pattern of cholangiocarcinoma; however, the pathological result showed predominantly HCC component in most cases. Interestingly, tumor markers showed normal or minimal rising of serum AFP levels and slight elevation of CA 19-9 levels. The rising of CA 19-9 level in combined HCC-CC was reported by Uenishi et al[11] studied in four patients. Fukukura et al[7] also reported minimal rising of the AFP level, less than 200 ng/ml. Jarnagin et al[4] reviewed clinicopathologic results of 27 combined HCC-CC cases and found that rising serum AFP levels in this group were lower than the HCC group and the mean level of the AFP was lower than 200 ng/ml. However, Okuda reported that rising AFP level > 200 ng/ml could be found up to 36%[12]. The hepatitis profiles showed positive to hepatitis B viral infection in four cases and hepatitis C viral infection in one case, which contrast to a prior study that found hepatitis C viral infection more than the hepatitis B viral infection.

After dividing the cases into two groups by the presence of liver cirrhosis, which is more practical in the daily practice of the radiologist in differential diagnosis of liver mass, the present study showed that combined HCC-CC in the cirrhotic group had the pattern of enhancement similar to cholangiocarcinoma, however, there was no bile duct dilatation. This group also had low rising AFP and CEA level, but the CA 19-9 level was increased. In the non-cirrhotic group, CT appearances showed no difference from the cirrhotic group, however, a higher AFP level and lower CA 19-9 were observed.

Fukukura et al[7] examined 15 combined HCC-CC patients and divided the tumor appearances into two groups: resembling HCC or CC. In the CC type, the imaging findings resembled CC, but there was positive viral marker and rising serum AFP. The present study had a similar result in tumor predominated CC component. Unfortunately, there was no definite HCC-like pattern in our case series. In the subjective enhancement analysis, however, there were three cases that had hyperattenuation during the arterial phase, which could be misinterpreted as HCC. Meanwhile, these masses showed rising attenuation in both arterial and portovenous phases and a slight drop in the delayed phase, but none showed rapid wash out.

Osama et al[10] examined 30 cases and suggested that the diagnosis of combined HCC-CC should be considered when a hepatic tumor has CT features of both HCC and CC. In the present study, there was no appearance of the HCC and CC in the same mass. From the present study, the diagnosis of combined HCC-CC should be considered if the tumor has similar findings to CC without bile duct dilatation on the background of cirrhotic liver in a patient who has normal or low rising of the AFP level with or without elevated CA 19-9 level. In the non-cirrhotic liver, making diagnosis may be more difficult, but should be included in the differential diagnosis if there is a solitary CC-like pattern liver mass without bile duct dilatation. It should be noted that even the majority of cases were mainly HCC in the histopathological studies; however, the CT appearance resembled CC. This might be explained by the study on genetic component of the combined HCC-CC, which resembled to CC[6]. Study on angiogenesis may help to understand imaging characteristics of this tumor[13,14].

The present study contained some limitations. First, the sample size was small, which was due to the rare occurrence of the tumor. There might be some missed cases in the present series because giving diagnosis of combined HCC-CC usually needs a good specimen, special immunohistochemical staining, and awareness of this existing entity by pathologists. Second, the specimens were not all surgically resected. Most were from core biopsy, which did not represent the whole mass, so the major component of the tumor could not be confidently evaluated and the radiologic-pathologic correlation could not be done. Even in the resected specimens, pathological study could not be perfectly mapped with the imaging. How-

ever, the authors hope that the present study would bring attention to the diagnosis of combined HCC-CC into clinical concern, particular when the clinical data and imaging findings are not characteristics for either HCC or CC. This information must be passed to pathologists who need to handle the specimen.

Conclusion

The diagnosis of combined HCC-CC should be considered if the tumor has similar CT findings to CC without bile duct dilatation on the background of cirrhotic liver and patient has normal or low rising of serum AFP level with or without elevated CA 19-9 level. In non-cirrhotic liver, the differential diagnosis should be included if there is a solitary CC-like pattern mass without bile duct dilatation.

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การศึกษาภาพเอกซเรย์คอมพิวเตอร์ของมะเร็งตับที่เกิดร่วมกับมะเร็งท่อน้ำดี

สิทธิ์ พงษ์กิจการุณ, ธนพ ศรีสุวรรณ, พัฒนา ศรมยุรา, จันทร์จิรา ชัชวาลา

วัตถุประสงค์: *ความชุกของการเกิดร่วมกันของมะเร็งตับและมะเร็งท่อน้ำดีมีค่อนข้างต่ำ ซึ่งส่วนใหญ่มีรายงานอยู่ในการศึกษาทางพยาธิวิทยา แต่ลักษณะทางภาพรังสีวินิจฉัยยังไม่มีการรายงานมากนักโดยเฉพาะในประเทศไทย การศึกษานี้แสดงลักษณะภาพเอกซเรย์คอมพิวเตอร์ของมะเร็งทั้งสองชนิดนี้โดยเปรียบเทียบกับผลการตรวจชิ้นเนื้อ*

วัสดุและวิธีการ: *จากฐานข้อมูลทางพยาธิวิทยาของโรงพยาบาลในช่วงปี พ.ศ. 2539 ถึง พ.ศ. 2547 พบมะเร็งตับที่เกิดร่วมกับมะเร็งท่อน้ำดี 31ราย มี 10 รายที่มีภาพเอกซเรย์คอมพิวเตอร์และข้อมูลทางคลินิกครบถ้วน*

ผลการศึกษา: *ก้อนเนื้องอกส่วนใหญ่จะ hypodense กว่าเนื้อตับทั่วไปและเมื่อฉีดสารทึบรังสีจะเห็นการเข้าของสารทึบรังสีช้าๆ และคงอยู่นาน มี 2 รายที่พบท่อน้ำดีในเนื้อตับอุดตัน โดยรวมลักษณะทางเอกซเรย์คอมพิวเตอร์จะคล้ายกับที่พบในมะเร็งท่อน้ำดีในเนื้อตับ ถึงแม้ว่าจากการตรวจทางพยาธิจะพบสัดส่วนของมะเร็งตับในก้อนมากกว่ามะเร็งท่อน้ำดี โดยค่าซีรัม AFP อาจจะปกติหรือสูงขึ้นเล็กน้อยและพบค่าซีรัม CA19-9 สูงขึ้นได้ ผู้ป่วยมีโรคตับแข็งอยู่ 5 ราย พบการติดเชื้อตับอักเสบ บี 4 รายและตับอักเสบ ซี 1 ราย*

สรุป: *อาจจะสงสัยมะเร็งชนิดนี้เมื่อพบก้อนในผู้ป่วยตับแข็งที่ให้ลักษณะทางเอกซเรย์คอมพิวเตอร์คล้ายมะเร็งท่อน้ำดี และตรวจไม่พบการเพิ่มขึ้นของซีรัม AFP แต่ในผู้ป่วยที่ไม่มีตับแข็ง ภาพทางเอกซเรย์คอมพิวเตอร์อาจแยกได้ยากจากมะเร็งท่อน้ำดี*