



Usefulness of ^{18}F -FDG PET/CT and Multiphase CT in the Differential Diagnosis of Hepatocellular Carcinoma and Combined Hepatocellular Carcinoma-Cholangiocarcinoma

간세포암종과 혼합성 간세포암종-담관암종에서
 다위상 전산단층촬영술 소견과 ^{18}F -FDG PET/CT에서
 섭취율 차이에 대한 분석

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Purpose The purpose of this study was to evaluate the usefulness of multiphase CT and ^{18}F -fluorodeoxyglucose (FDG) PET/CT for the differentiation of combined hepatocellular carcinoma-cholangiocarcinoma (cHCC-CCA) from hepatocellular carcinoma (HCC).

Materials and Methods From January 2007 to April 2016, 93 patients with pathologically confirmed HCC ($n = 84$) or cHCC-CCA ($n = 9$) underwent CT and PET/CT imaging. Contrast enhancement patterns were divided into three types based on the attenuation of the surrounding liver parenchyma: type I (early arterial enhancement with delayed washout), type II (early arterial enhancement without delayed washout), and type III (early hypovascular, infiltrative appearance, or peripheral rim enhancement).

Results cHCC-CCAs (89%) had a higher PET/CT positive rate than did HCCs (61%), but the PET/CT positive rate did not differ significantly ($p = 0.095$). Among the 19 cases of the type II enhancement pattern, 3 (21%) of 14 HCCs and 4 (80%) of 5 cHCC-CCAs were PET/CT positive. cHCC-CCAs had a significantly higher PET/CT positive rate ($p = 0.020$) in the type II enhancement pattern.

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Conclusion The PET/CT positive rate of cHCC-CCA was significantly higher than that of HCC in lesions with a type II enhancement pattern. The ^{18}F -FDG PET/CT can be useful for the differentiation of cHCC-CCA from HCC in lesions with a type II enhancement pattern on multiphasic CT.

Index terms Carcinoma, Hepatocellular; Positron Emission Tomography Computed Tomography; Tomography, X-Ray Computed

INTRODUCTION

Primary liver cancers are divided into three histologic categories: hepatocellular carcinoma (HCC), cholangiocarcinoma (CCA), and combined hepatocellular carcinoma-cholangiocarcinoma (cHCC-CCA). cHCC-CCA, also known as mixed hepatobiliary carcinoma, is defined as a primary liver cancer consisting of unequivocal elements of both HCC and CCA that are closely admixed, with a reported incidence ranging from 1.0% to 6.5% of all primary liver cancers (1, 2). In 2010, the WHO classified cHCC-CCA into two types: the classical type and a subtype with stem-cell features. Classical type cHCC-CCA is characterized by the presence of typical HCC-like and CCA-like areas within the same tumor. cHCC-CCA with stem cell features is predominantly composed of tumor cells with hepatic stem/progenitor cell differentiation (1). However, later studies showed that the 2010 WHO classification of cHCC-CCA does not fully account for the histologic heterogeneity of cHCC-CCA. Thus, the community of international pathologists, radiologists, and clinicians has recently proposed a new consensus classification and terminology for primary liver cancer with both hepatocyte and cholangiocytic differentiation (3). Although the clinical and prognostic implications of this classification system remain controversial, accurate diagnosis of cHCC-CCA is important because it has a different prognosis compared with other primary liver cancers (4-6).

According to the current guidelines of the American Association for the Study of Liver Diseases, the European Association for the Study of the Liver, and Japanese Society of Hepatology for the management of HCCs, HCCs in cirrhotic livers can be diagnosed through typical imaging features on multiphasic liver CT or on MRI without histologic confirmation. The guidelines define a typical HCC vascular pattern, which is the presence of homogenous hyperenhancement (wash-in) in the arterial phase followed by wash-out in the venous or late phase (7, 8). However, some cases of cHCC-CCA show marked enhancement on the arterial-phase of multiphasic liver CT that resembles typical findings of HCC (9, 10). Based on a previous study using multiphasic CT findings, in cHCC-CCA, the gross appearance of HCC-component-predominant lesions and CCA-component-predominant lesions resembled those of HCC and CCA, respectively (11, 12).

Positron emission tomography/computed tomography (PET/CT) using ^{18}F -fluorodeoxyglucose (FDG) is a useful diagnostic tool for tumor characterization (13). However, several reports suggest that the sensitivity of ^{18}F -FDG PET for detection of HCC is insufficient (50–65%) (14, 15). On the other hand, the sensitivity of FDG PET/CT for detection of CCA is higher than that for HCC (84%–94%) (16, 17). However, whether ^{18}F -FDG PET/CT can be used for differential diagnosis of HCC and cHCC-CCA is uncertain. The purpose of this study was to evaluate mul-

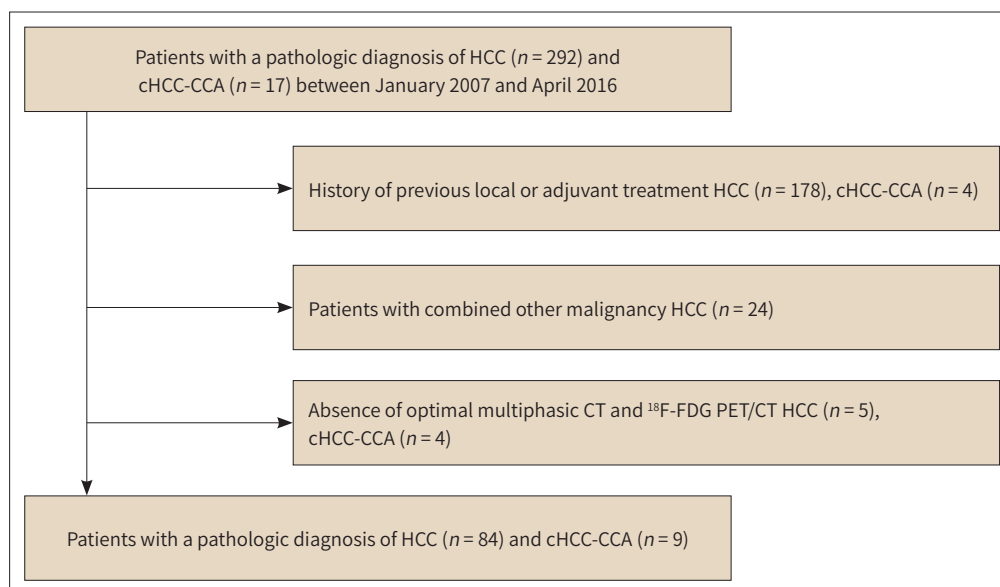
tiphasic CT and ^{18}F -FDG PET/CT findings for their usefulness in differentiating cHCC-CCA from HCC.

MATERIALS AND METHODS

PATIENTS

We retrospectively searched the database and records of the Department of Pathology dating from January 2007 to April 2016 using the search terms HCC and cHCC-CCA. The diagnosis of HCC and cHCC-CCA was based on the 2010 WHO classification. We identified 292 patients with a diagnosis of HCC and 17 patients with a diagnosis of cHCC-CCA, as confirmed by a pathologist (B.H, with 29 years of experience in pathology). The study population was selected from these patients using the following inclusion criteria: preoperative optimal multiphase liver CT studies, including unenhanced, hepatic arterial phase, portal venous phase, and equilibrium phase, and availability of ^{18}F -FDG PET/CT. Exclusion criteria for the study were as follows: (a) a history of previous adjuvant treatment such as transarterial chemoembolization, radiofrequency ablation (RFA), and surgery and (b) other combined malignancy. The final study population comprised 84 patients diagnosed with HCC and 9 patients diagnosed with cHCC-CCA (Fig. 1). Diagnosis in 33 patients was histologically confirmed by examination of a surgical specimen and in 60 patients, it was histologically confirmed by examination of gun-biopsy specimen. A retrospective review of imaging studies, clinical data, and demographic information for the patients was also conducted. A total of 93 patients (mean age, 57 years; age range, 36–78 years), consisting of 80 men and 13 women, met our inclusion criteria and formed our study population (Table 1). This study was approved by our Institutional Review Board (IRB No. 2018-07-016-003).

Fig. 1. Flow chart of enrolled patients.



cHCC-CCA = combined hepatocellular carcinoma-cholangiocarcinoma, FDG = fluorodeoxyglucose, HCC = hepatocellular carcinoma

CT PROTOCOL

Multiphasic CT images were acquired using a 64-MDCT scanner (Somatom Sensation 64, Siemens Healthcare, Erlangen, Germany) or a dual energy CT scanner (Somatom Definition Flash; Siemens Healthcare). The CT scanning parameters were as follows: reconstruction at a slice thickness of 3 mm, with 3 mm slice intervals and a 120 kVp quality reference 210 mAs for the dose modulation system (CareDose 4D; Siemens Medical Solutions). A total of 100–150 mL of nonionic contrast medium (350 mgI/mL) was injected at the rate of 4 mL/s through an 18-gauge IV cannula using a power injector. The scan delay was determined according to an automatic bolus triggering software program (Syngo Acquisition Workplace; Siemens Healthcare). The late arterial phase scanning and portal venous phase scanning were started at 15 and 55 seconds, respectively, after the trigger threshold was reached (100 Hounsfield units on the abdominal aorta). The delayed phase scanning was performed 180 seconds after the initiation of the contrast material injection.

PET/CT PROTOCOL

All patients in the study fasted for at least six hours before intravenous FDG administration. The dose range of intravenously injected FDG was 370–444 MBq, depending on patient weight. PET/CT images were acquired using a Biograph Duo PET/CT scanner (Siemens Healthcare) or a Biograph 16 PET/CT scanner (Siemens Healthcare). Prior to the PET scan, a CT scan (5 mm slice thickness) at an interval of 5 mm was acquired without contrast enhancement for attenuation correction.

IMAGING ANALYSIS

Multiphasic liver CT findings were retrospectively analyzed by two radiologists (J.G.P and K.S.O, with 8 and 19 years of experience in abdominal imaging, respectively) by reaching a consensus. Tumor enhancement patterns were divided into three types based on the attenua-

Table 1. Patient Characteristics According to Pathology

	HCC	cHCC-CCA	p-Value
No. of patients	84	9	N/A
Age (years)*	56.9 ± 9.6 (36–78)	59.2 ± 7.8 (46–69)	0.44
Sex (M:F)	72:12	8:1	0.07
Chronic liver disease			
HBV	61 (72.6)	6 (66.7)	0.71
HCV	12 (14.3)	0 (0)	0.22
Liver cirrhosis	53 (63.1)	4 (44.4)	0.28
AFP (ng/mL) [†]	13 (1.2–121000)	11.8 (2.35–8111)	0.67
CA 19-9 (U/mL) [†]	25 (0.63–400)	94 (12–27178)	0.02

Except where indicated, data are numbers of patients, with percentages in parentheses.

*Data are means ± standard deviations. Numbers in parentheses are ranges.

[†]Data are medians. Numbers in parentheses are ranges.

AFP = alpha-fetoprotein, CA = carbohydrate antigen, cHCC-CCA = combined hepatocellular carcinoma-cholangiocarcinoma, HBV = hepatitis B virus, HCC = hepatocellular carcinoma, HCV = hepatitis C virus, N/A = not available

tion of the tumor compared with the surrounding liver parenchyma: type I (early arterial enhancement with delayed washout), type II (early arterial enhancement without delayed washout), and type III (early hypovascular, infiltrative appearance or peripheral rim enhancement). Lesions with a non-homogenous enhancement pattern on contrast-enhanced images were categorized according to the attenuation of the predominant lesions parts (> 50%), as described in previous work (18).

Associated findings were assessed, including tumor size (maximum diameter), tumor number (single or multiple), capsular retraction, capsule appearance, and invasion of vessel.

¹⁸F-FDG PET/CT images were qualitatively evaluated to assess whether FDG uptake in the tumor was significantly higher than the surrounding noncancerous hepatic parenchyma. FDG accumulation was analyzed quantitatively by calculating the standardized uptake value (SUV) in the regions of interest placed over the tumor and the normal liver.

$SUV = PET \text{ count} \times \text{calibration factor (mCi/g)}$.

STATISTICAL ANALYSIS

To determine differences in clinical, radiological, and ¹⁸F-FDG PET/CT features according to tumor type (HCC vs. cHCC-CCA), Student's *t*-tests, chi-square tests, and Fisher's exact tests were used. To determine the differences in the enhancement patterns and ¹⁸F-FDG PET/CT features according to tumor type (HCC vs. cHCC-CCA), chi-square tests and Student's *t*-test were used. All analyses were conducted using standard statistical software (SPSS 20.0 for Windows; IBM Corp., Armonk, NY, USA) and results were considered significant when the *p* value was less than 0.05.

RESULTS

Patient characteristics are shown in Table 1. Seventy-three of the 84 HCC patients had chronic hepatitis: 61 had hepatitis B and 12 had hepatitis C. Six of the 9 cHCC-CCA patients had chronic hepatitis: all had hepatitis B. No significant differences were observed in the incidence of chronic liver disease or liver cirrhosis according to pathological type (*p* > 0.05). In HCC patients, the median level was 13 ng/mL for alpha-fetoprotein (AFP) and 25 U/mL for carbohydrate antigen (CA) 19-9. For cHCC-CCA patients, the median level was 11.8 ng/mL for AFP and 94 U/mL for CA 19-9. CA 19-9 levels were significantly higher in patients with cHCC-CCA compared to patients with HCC (*p* = 0.019).

Imaging features of HCCs and cHCC-CCAs are shown in Table 2. Of the 84 HCCs, 58 (69%) showed a type I enhancement pattern (Fig. 2), 14 (17%) showed a type II enhancement pattern, and 12 (14%) showed a type III enhancement pattern. Of the 9 cHCC-CCA patients, no patients showed type I enhancement pattern, 5 (56%) showed type II enhancement pattern (Fig. 3), and 4 (44%) showed type III enhancement pattern (Fig. 4). Type I enhancement pattern was more common in the HCC group, while the type II/III enhancement patterns were more common in the cHCC-CCA group. Enhancement patterns of HCC and cHCC-CCA showed significant differences (*p* < 0.001). A significant difference was observed in the presence of the capsular appearance between HCC and cHCC-CCA (*p* = 0.006). Forty (48%) of the 84 HCC patients showed a capsular appearance. No capsular appearance was observed in the cHCC-CCA patients. How-

Table 2. Imaging Findings of HCC and cHCC-CCA Cases

	HCC	cHCC-CCA	p-Value
Enhancement pattern			<0.001
Type I	58 (69)	0 (0)	
Type II	14 (16.7)	5 (55.6)	
Type III	12 (14.2)	4 (44.4)	
Tumor size (cm)*	6.2 ± 3.2	6.3 ± 4.6	1.576
Tumor number			0.498
Single	56 (66.7)	7 (77.8)	
Multiple	28 (33.3)	2 (22.2)	
Capsular appearance	40 (47.6)	0 (0)	0.006
Capsule retraction	10 (11.9)	2 (22.2)	0.301
Vessel invasion	7 (8.3)	1 (11.1)	0.778
PET			0.095
Positive status	51 (60.7)	8 (88.9)	
Negative status	33 (39.3)	1 (11.1)	

Except where indicated, data are numbers of patients, with percentages in parentheses.

*Data are means ± standard deviations.

cHCC-CCA = combined hepatocellular carcinoma-cholangiocarcinoma, HCC = hepatocellular carcinoma

Fig. 2. Hepatocellular carcinoma with type I enhancement pattern in a 60-year-old man.

A. Arterial-phase CT image shows typical early enhancement of the mass (arrow).

B, C. Portal venous and delayed phase images show washout of the mass (arrows) relative to the liver.

D. Fused PET/CT shows no definite abnormal fluorodeoxyglucose uptake into the mass.

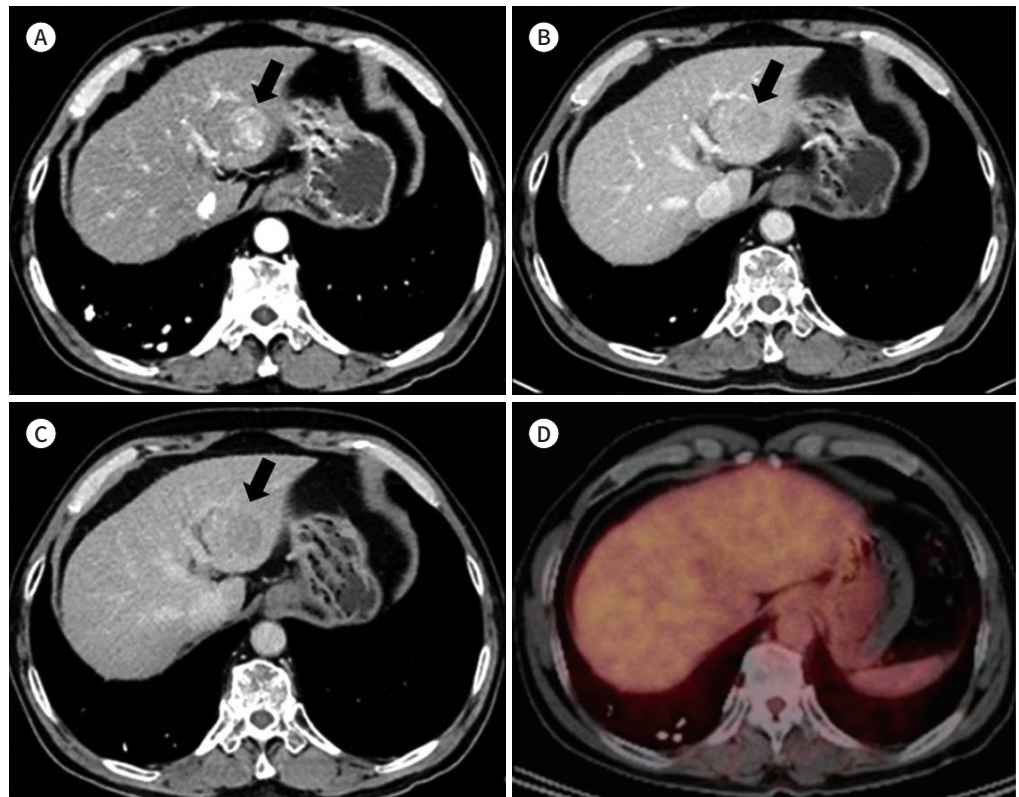
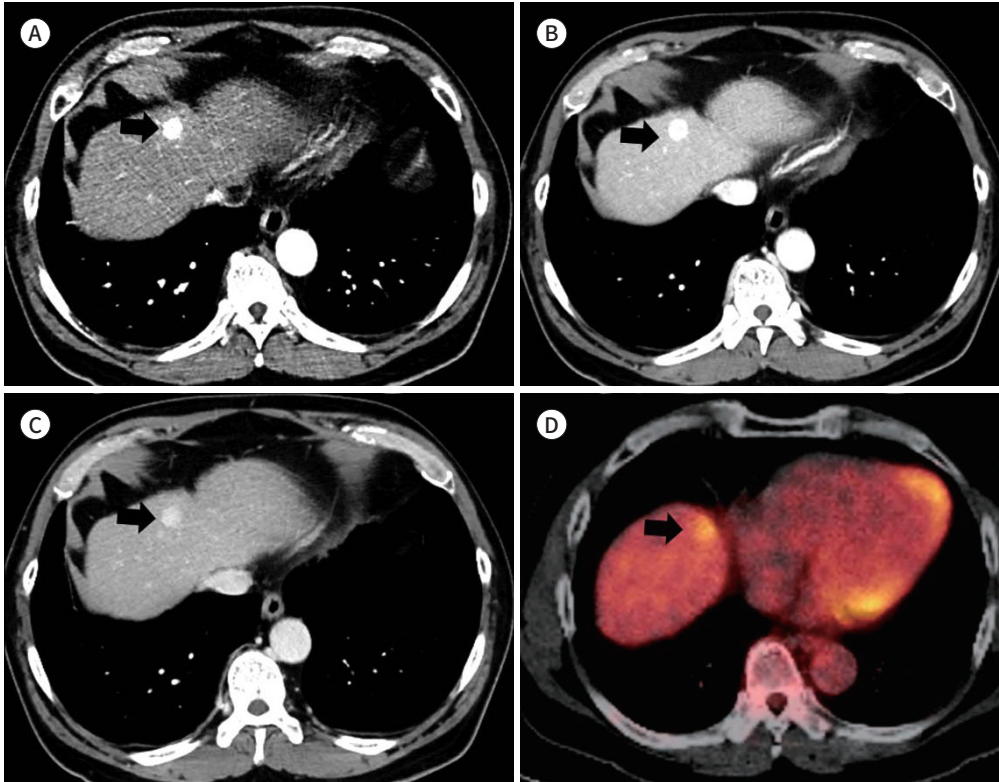


Fig. 3. Combined hepatocellular cholangiocarcinoma with type II enhancement pattern in a 58-year-old man. **A.** Arterial-phase CT image shows typical early enhancement of the mass (arrow). **B, C.** Portal- and delayed-phase images show prolonged enhancement of the mass (arrows) without washout. **D.** Fusion PET/CT image shows definite fluorodeoxyglucose uptake into the mass (arrow) relative to the liver.



ever, no significant differences were found in tumor size, tumor number, capsule retraction, and vessel invasion between HCC and cHCC-CCA ($p > 0.05$).

Further, 60.7% (51/84) of HCCs and 88.9% (8/9) of cHCC-CCAs were PET-positive. The cHCC-CCA had a higher PET-positive rate than did the HCCs, but the difference was not significant ($p = 0.095$). Of the 59 HCCs with type I enhancement pattern, 37 (64%) were PET-positive. None of the cHCC-CCAs was found to have type I enhancement pattern. Among 19 cases with type II enhancement pattern, 21% (3/14) of HCCs were PET-positive and 80% (4/5) of cHCC-CCAs were PET-positive. cHCC-CCAs showed a significantly higher PET-positive rate ($p = 0.020$) in cases with type II enhancement pattern. Among the 16 cases with type III enhancement pattern, 92% (11/12) of HCCs and 100% (4/4) of cHCC-CCAs were PET-positive ($p = 0.551$) (Fig. 5).

In addition, cHCC-CCA showed a significantly higher ^{18}F -FDG uptake (mean SUV max 6.14 ± 2.84) than did HCC (mean SUV max 3.90 ± 2.69) ($p = 0.048$). The mean SUV max of ^{18}F -FDG uptake in HCCs with type I enhancement pattern was 3.87 ± 2.83 . For those with type II enhancement pattern, mean SUV max of ^{18}F -FDG uptake in cHCC-CCA (mean SUV max 4.54 ± 2.07) was significantly higher than that of HCCs (mean SUV max 2.60 ± 0.21) ($p = 0.002$).

For those with type III enhancement pattern, there was no significant difference in the mean SUV max values of ^{18}F -FDG uptake between cHCC-CCA (mean SUV max 8.15 ± 2.48) and HCC (mean SUV max 5.58 ± 2.76) ($p = 0.135$).

DISCUSSION

HCC is the most common primary liver cancer and one of the most prevalent causes of death due to malignant tumors. Early diagnosis of HCC has been facilitated by advances in the image

Fig. 4. Combined hepatocellular carcinoma-cholangiocarcinoma with type III enhancement pattern in a 68-year-old man.

- A. A hypovascular mass (arrow) is seen on an arterial phase image.
- B, C. Portal- and delayed-phase images show persistent poor enhancement of the mass (arrows).
- D. Fusion PET/CT image shows definite fluorodeoxyglucose uptake into the mass relative to the liver.

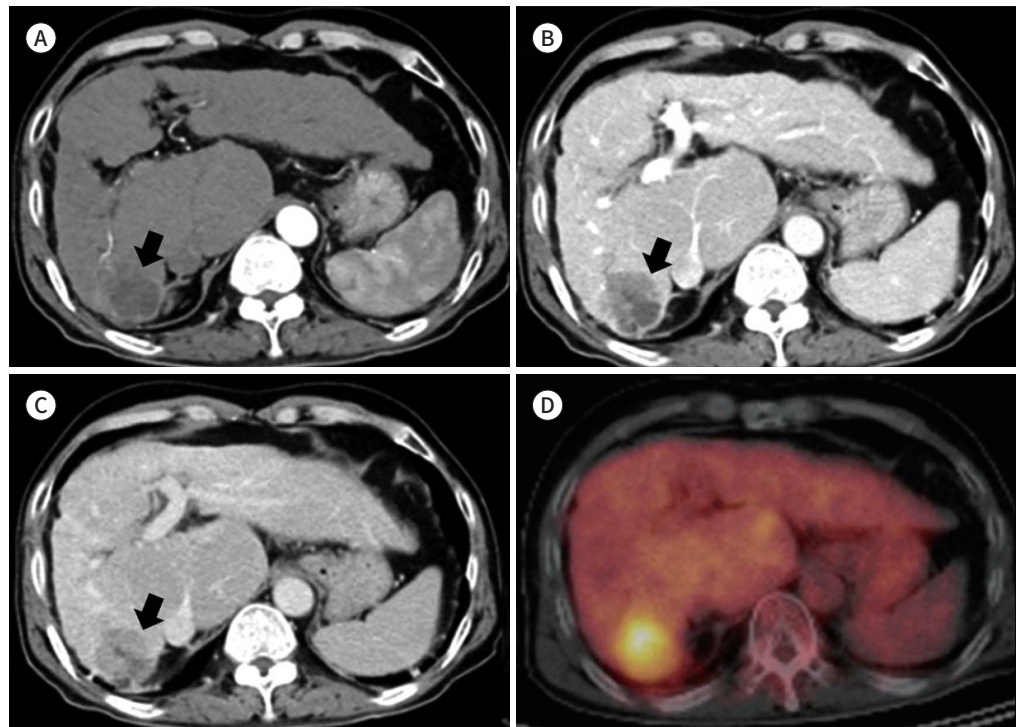
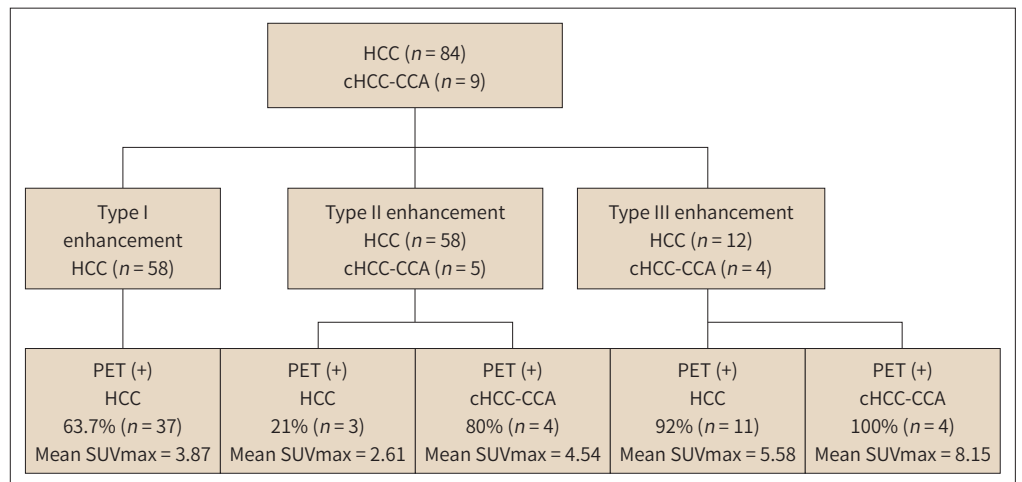


Fig. 5. Distribution of enhancement pattern and fluorodeoxyglucose uptake in 84 HCC and 9 cHCC-CCA cases.



cHCC-CCA = combined hepatocellular carcinoma-cholangiocarcinoma, HCC = hepatocellular carcinoma, SUV = standardized uptake value

modalities of multiphase liver CT and MRI (19). HCC can often be diagnosed with noninvasive image modalities such as multiphase liver CT and liver MRI. However, some cases of intrahepatic CCA and cHCC-CCA show marked enhancement on the arterial-phase of multiphase CT that resembles the typical radiologic findings of HCC (9-12).

cHCC-CCA is an important differential diagnosis for other primary liver tumors, although it is rarely encountered clinically. Substantial effort has been invested in improving the preoperative performance of radiological findings to differentiate cHCC-CCA from HCC. The correct diagnosis of this tumor on multiphase liver CT will contribute to the selection of the appropriate therapeutic methods, such as transcatheter arterial chemoembolization, RFA, or radical resection. The type I enhancement pattern is highly specific for HCC in patients with cirrhosis or other HCC risk factors (20-22). However, the type II enhancement pattern is nonspecific, as it can also be observed in those with dysplastic nodules, HCC, and non-HCC malignancies such as intrahepatic CCA and cHCC-CCA (11, 12, 23). In this study, the type I enhancement pattern was seen in only HCCs (58 cases, 69.05% of HCC) and the type II enhancement pattern was observed in both HCC (17%) and cHCC-CCA (56%).

An awareness of the different imaging characteristics of HCC and other liver cancers is important for pre-study planning. An understanding of their features on cross-sectional imaging would provide great value in determining the most appropriate treatment plan and the prediction of the prognosis of each patient. However, the role of ^{18}F -FDG in the diagnosis of HCC is controversial (24). This limited sensitivity is due to variable tumor FDG uptake and high background metabolic activity in the normal liver (25, 26). In particular, well-differentiated and early HCC might remain undetected using FDG PET. Indeed, the overall sensitivity for detection of primary HCC is reported to be only 50% to 65% (14, 15). On the other hand, the sensitivity of ^{18}F -FDG PET/CT for detecting CCA is higher than that for detecting HCC (84-94%) (16, 17). Moreover, mass-forming intrahepatic CCA shows intense FDG uptake, whereas hilar CCA shows only mild uptake (27). Only one report describes the ^{18}F -FDG PET/CT findings of cHCC-CCA (15). The report revealed that ^{18}F -FDG PET/CT shows high FDG uptake for cHCC-CCA. Whether FDG PET/CT can be used for differential diagnosis of cHCC-CCA and HCC is uncertain. The aim of this study was to evaluate multiphase CT and ^{18}F -FDG PET/CT findings for differential diagnosis of combined cHCC-CCA from HCC.

In our study, cHCC-CCAs had a significantly higher PET-positive rate ($p = 0.020$) than did HCCs only in cases with a type II enhancement pattern. No significant difference was observed in the PET-positive rates for nodules with type III enhancement pattern. Our results revealed that FDG PET/CT could contribute to differential diagnosis between HCCs and cHCC-CCAs with type II enhancement pattern. Ijichi et al. (28) reported that the PET-positive rate differed significantly according to enhancement pattern and tumor size. They proposed that the sensitivity of FDG PET for detecting HCCs was significantly associated with tumor differentiation, tumor size, and microvascular invasion. In our study, the HCCs with type II enhancement pattern had a lower positive rate of PET than did those with type I/II enhancement pattern ($p = 0.008$). We surmise that HCCs with type II enhancement pattern were well-differentiated for early HCCs, although we did not evaluate tumor differentiation.

Significant differences were also shown for the capsule appearance between HCC and cHCC-CCA ($p = 0.006$). The presence of a fibrous capsule is a characteristic finding of classic HCC (29).

This characteristic histologic finding demonstrated a good correlation with the capsule appearance on multiphase liver CT (30). The capsule appearance is a reliable indicator in the diagnosis of HCC (20). This result suggests that capsule appearance can be a diagnostic clue for differentiating between HCC and cHCC-CCA.

This study had several limitations. First, it was retrospective, which may have limited the data quality. However, because cHCC-CCA is rare, prospective studies may be difficult. Second, the sample size was relatively small and drawn from a single facility. Moreover, the proportion of cHCC-CCAs was small. However, our study evaluated pathologically confirmed HCC and cHCC-CCA on contrast-enhanced multiphase CT and ^{18}F -FDG PET/CT. Additional studies using a larger patient sample size will be necessary to verify our conclusions.

In conclusion, In this study, the PET-positive rate of cHCC-CCA was significantly higher than that of HCC in lesions with type II enhancement pattern. The ^{18}F -FDG PET/CT can be used as a clue for the differentiation of cHCC-CCA from HCC in lesions with early arterial enhancement without delayed washout on multiphase CT. Therefore, if there are no typical imaging features of HCC or CCA on multiphase CT and FDG uptake is visible on ^{18}F -FDG PET/CT, histologic confirmation is recommended.

Author Contributions

Conceptualization, P.J.G., J.G.; data curation, P.J.G., P.J.C.; formal analysis, P.J.G., P.J.C.; investigation, P.J.C.; methodology, P.J.G., P.J.C., J.S.; project administration, P.J.G.; resources, P.J.G., J.S.; supervision, J.S., P.J.G.; validation, P.J.G.; visualization, K.H., P.J.C.; writing—original draft, P.J.C., P.J.G.; and writing—review & editing, all authors.

Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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간세포암종과 혼합성 간세포암종-담관암종에서 다위상 전산단층촬영술 소견과 ^{18}F -FDG PET/CT에서 섭취율 차이에 대한 분석

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목적 간세포암종과 혼합성 간세포암종-담관암종의 다위상 전산단층촬영술 소견과 ^{18}F -fluorodeoxyglucose 양전자방출단층촬영(이하 FDG PET/CT)에서 섭취율 차이를 연구하여 이들의 감별 진단에 유용성이 있는지를 알아보고자 하였다.

대상과 방법 2007년 1월에서 2016년 4월까지 조직학적으로 간세포성 암종으로 진단된 84명과 혼합성 간세포암종-담관암종으로 진단된 9명의 환자를 대상으로 하였다. 조영증강 양상은 유형 I (동맥기 조영증강과 지연기 조영유실), 유형 II (지연기 조영유실이 없는 동맥기 조영증강), 유형 III (저혈관성 병변, 침투성 양상 혹은 변연부 조영증강)로 구분하였고, PET/CT 소견은 FDG 섭취 여부에 따라서 양성과 음성으로 분류하였다.

결과 혼합성 간세포암종-담관암종(89%)은 간세포암종(61%)보다 PET/CT 섭취 양성률이 높았으나 통계적으로 유의한 차이는 보이지 않았다($p = 0.095$). 유형 I 조영증강양상을 보이는 58개의 간세포암종 중 37예(64%)가 PET/CT에서 양성이었다. 유형 II 조영증강양상을 보이는 19예 중 간세포암종 3예(21%)에서 PET/CT에서 양성을 보였고 혼합 간세포암종-담관암종 4예(80%)에서 PET/CT 양성을 보였다. 유형 II 조영증강양상을 보이는 경우 혼합 간세포암종-담관암종이 간세포암종보다 PET/CT 양성률이 유의하게 높았다($p = 0.020$). 유형 III 조영증강 양상을 보이는 16예 중 간세포암 11예(91.6%), 혼합 간세포암-담관암종 4예(100%)에서 PET/CT 양성을 보였다. 유형 III 조영증강양상을 보이는 경우 간세포암과 혼합 간세포암-담관암종의 PET/CT 양성률의 유의한 차이는 보이지 않았다.

결론 유형 II 조영증강 양상을 보이는 경우 간세포암종과 혼합성 간세포암종-담관암종의 감별진단에 전산단층촬영술과 병행하는 ^{18}F -FDG PET/CT가 도움이 될 것으로 보인다.

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