Original Article

# Preoperative Computed Tomography of Intrahepatic Mass-forming Cholangiocarcinomas: Morphologic Features and Enhancement Patterns Correlation with Clinicopathologic Factors and Clinical Outcomes

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## Abstract

**Purpose:** To evaluate preoperative morphologic features and enhancement patterns of intrahepatic mass-forming cholangiocarcinomas (IMCC) on CT and to determine the relationship between CT features, clinicopathologic factors, and clinical outcomes.

**Materials and methods:** Twenty patients with pathologically confirmed IMCC were included. Two radiologists independently evaluated the CT features and then reached consensus decisions. Histopathologic data and clinical outcomes after surgical resection were collected. Statistically significant CT parameters were identified through univariate analyse.

**Results:** Patients with negative preoperative CEA had longer disease free rate (DFR) than those with positive CEA (13.8 vs. 3.5 months; $P = 0.014$). Patients with tumors < 5 cm) had longer DFR than patients with tumors > 5 cm (16.5 vs 4.7 months; $P = 0.006$). Patients with well moderately differentiated tumors demonstrated longer DFR than those with poorly differentiated tumors; $P = 0.007$. IMCC with daughter nodules had more frequent adjacent organ involvement at pathological examination ($P = 0.005$). IMCC with hepatic vein invasion more frequently had margin involvement than those without hepatic vein invasion ($P = 0.018$).

**Conclusion:** Preoperative CEA levels, tumor sizes, daughter nodules, hepatic vein invasion, and pathological grades are significant prognostic factors of clinical outcome after surgical resection of IMCCs. Our results suggest that pre-operative CEA level and morphologic features of IMCC on CT may be useful to predict clinicopathological outcomes.

**Keywords:** Cholangiocarcinoma, Computed tomography, Enhancement pattern

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## Introduction

Cholangiocarcinoma is a malignant tumor arising from the epithelial lining of the biliary tract.[1, 2] It accounts for approximately 10-15% of all primary liver cancers and is the second most common primary hepatic tumor worldwide.[3, 4, 5] Intrahepatic cholangiocarcinomas can be classified into three types according to morphology and growth pattern: mass-forming type, periductal infiltrative type, and intraductal growing type.[6, 7]

Among the three types of cholangiocarcinomas, intrahepatic mass forming cholangiocarcinoma (IMCC) is the most common, accounting for 60% of all intrahepatic cholangiocarcinomas. Hepatic resection is currently the optimal curative treatment for IMCC; however, curative resection is still only possible in less than 50% of patients, and the reported 5-year survival rate in this group has been in the range of 13% - 42%.[8] Preoperative imaging can play a major role in diagnosis, staging, and treatment planning in patients with IMCC. Dynamic computed tomography (CT) or magnetic resonance imaging (MRI) can help distinguish intrahepatic cholangiocarcinoma from hepatocellular carcinoma (HCC) given that surgical resection is the only curative option for IMCC at present.[9, 10, 11, 12]

There is limited data in the literature regarding morphologic features, enhancement patterns of IMCCs on CT and we attempted to define the relationship between CT features and patient prognosis after surgery. Kim et al reported that arterially enhancing IMCCs showed less central fibrous stroma and more frequently had a cholangiolocellular component than did other types of IMCCs at pathologic examination.[13] Arterial enhancement of IMCCs was found to be an independent prognostic factor for longer disease-free survival. In addition, hypovascular IMCCs in the hepatic arterial phase (HAP) on dynamic CT tended to have more malignant potential compared to rim-enhancement and hypervascular IMCC.[14]

Our hypothesis is that preoperative CT findings can predict the prognosis in patients with IMCC. The purpose of this study was to evaluate the pre-operative morphologic features and enhancement patterns of IMCC on MDCT. In addition, this study was designed to determine the relationship between CT features of IMCC, clinicopathologic factors and clinical outcomes.

## Materials and methods

This study was approved by the institutional review board of our institution. The requirement for informed consent was waived for this retrospective review.

### Study population

This retrospective study was approved by the ethics committee at our institution. Between January 2013 and December 2017, 23 patients who had been given a pathologic diagnosis of IMCC after surgical resection were retrospectively identified through a review of the database and records of the department of pathology. Among these patients, the study population was selected by using the following inclusion criteria: (a) patients who underwent preoperative multiphasic enhanced CT (either triphasic or quadriphasic) within 1 month of surgery; (b) optimal hepatic arterial (HAP) and portovenous phase (PVP) images had to be available; (c) patients did not receive preoperative adjuvant treatment.

A total of 20 patients (mean age of 62.7 years; age range 34 - 86 years), consisting of 13 men and 7 women were included. Thus, we evaluated a total of 20 pathological confirm of IMCC in 20 patients.

### CT imaging techniques

CT examinations were performed using a Philips Brilliance ICT 256 slice helical scanner (Philips Healthcare Medical System) or a SOMATOM Definite AS 128 slice helical scanner (Siemens Healthineers) at our institution. After unenhanced CT was performed, each patient received 120 mL of nonionic contrast material ([iopromide] Ultravist 370, Schering). Contrast material was injected at 3 mL/s using an automatic power injector and multiphasic contrast-enhanced CT with a combination of HAP at 35 s, PVP at 80 s, and EP at 180 s after initiation of the contrast injection was performed. The parameters were 2.5-mm detector collimation, 20 mm/s table speed, 3.2-mm slice thickness, and 1.6-mm reconstruction interval.

### Pre-operative imaging interpretation

All CT images were retrospectively and independently reviewed with a picture archiving and communications system (PACS) by two abdominal

radiologists with 9 and 10 years of experience in abdominal imaging. Both reviewers were aware that the patients had been given a histopathologic diagnosis of IMCC but were blinded to all other clinicopathologic factors. Interobserver agreement was evaluated. In case of inconsistencies between evaluations, two radiologists reevaluated to try to reach a consensus.

To assess the morphologic features of the tumor, the observers measured the maximal diameter of the tumor, and attempted to determine the contour (round/ lobulated, or irregular, or diffused infiltrative), and margin (shape or ill-defined). The location of the tumor was classified as peripheral (subcapsular) or central (perihilar). Any accompanying findings (daughter nodules, capsule retraction, hepatic vein invasion, portal vein invasion, portal vein thrombosis, bile duct dilatation, bile duct invasion, calcification, presence of intrahepatic duct stones, and presence of intra-abdominal lymphadenopathy) were also noted. Multifocal tumors were considered to be daughter nodules if they located in the same segment as the dominant mass. Multifocal lesions located in different segments were considered to be multiple tumors.

For analysis of tumor enhancement features, the observers determined the following: (a) the pattern of enhancement on HAP was classified as peripheral rim enhancement or diffused heterogeneous enhancement; (b) the degree of enhancement of the tumor compared with that of normal liver parenchyma during HAP. In terms of relative attenuation, the lesions were classified as hyperattenuating or isoattenuating/ hypoattenuating compared with the surrounding liver parenchyma during unenhanced and enhanced phases. To ensure accurate classification of the relative lesion attenuation, CT numbers were obtained with region-of-interest cursors placed on the lesions and on the liver parenchyma. A difference of more than 10 HU between the tumor and the liver attenuation was considered significant; (c) the hyperattenuating lesions on HAP were further divided into two groups hypervascular (hyperattenuation area measured > 50% of the lesion volume) (Figure 1a) or hypovascular groups (hyperattenuation area measured < 50%) (Figure 1b); (d) pattern of enhancement on PVP and equilibrium phases (EP) was classified into internal progressive enhancement or necrotic-like pattern. The presence of internal progressive enhancement was defined as > 50% of the lesion volume showing contrast enhancement compared with the surrounding liver parenchyma in PVP or EP[14] (Figure 2a). The necrotic-like pattern was defined as a persistent, non-enhancing defect (from arterial to equilibrium phase images) (Figure 2b). In the cases of multiple tumors, the enhancement pattern of the largest lesion was evaluated.

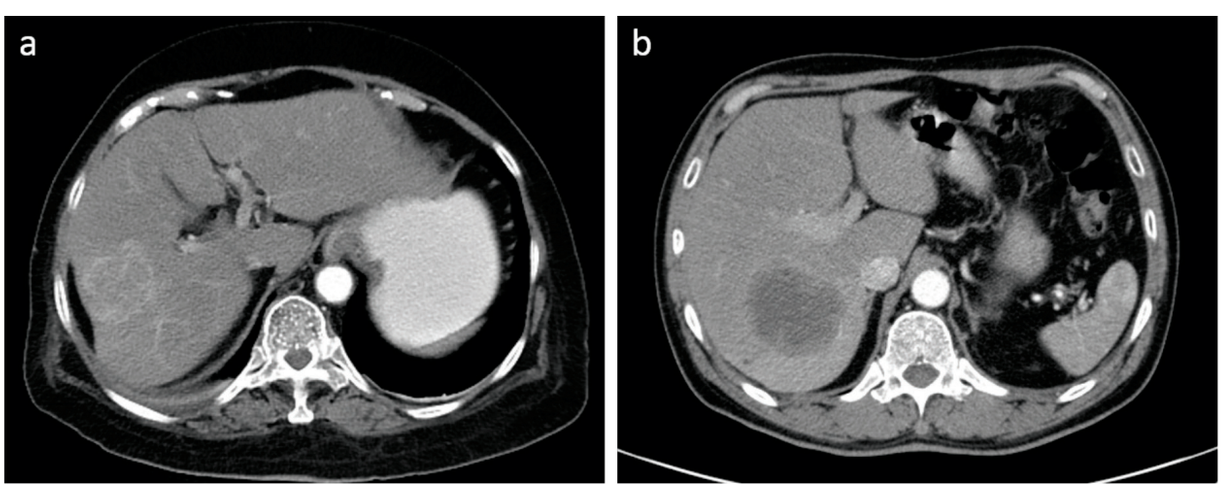


**Figure 1** The illustration shows the degree of enhancement of intrahepatic cholangiocarcinoma compared with the surrounding liver parenchyma on HAP. (a) An 86-year-old-woman with incidental finding of liver mass. Axial contrast enhanced MDCT on HAP showed hypervascular tumor (hyperattenuation area measured more than 50% of the lesion volume). (b) A 59-year-old-man with liver mass. Axial contrast enhanced MDCT on HAP showed hypovascular tumor (hyperattenuation area measured less than 50% of the lesion volume).

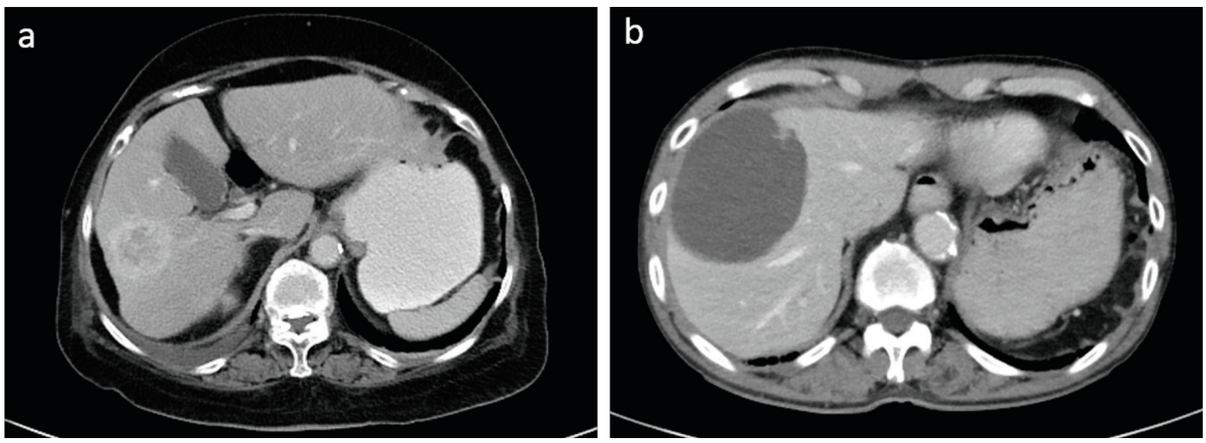


**Figure 2** The illustration shows the degree of enhancement of intrahepatic cholangiocarcinoma compared with the surrounding liver parenchyma on PVP. (a) An 86-year-old-man with liver mass. Axial contrast enhanced MDCT showed liver mass with presence of internal progressive enhancement (more than 50% of the lesion volume showing contrast enhancement compared with the surrounding liver parenchyma). (b) A 72-year-old-man with right upper quadrant abdominal pain and liver mass. Axial contrast enhanced MDCT showed liver mass with necrotic-like pattern.

**Clinicopathologic evaluation**

The following characteristics were recorded from electronic medical records of each patient; age, sex, preoperative serum levels of carbohydrate antigen (CA) 19-9, and carcinoembryonic antigen (CEA). The histopathologic information was acquired from the pathologic reports. We collected the following pathologic parameters; tumor size, tumor number, tumor differentiation, resection margin status, vascular invasion, lymphatic invasion, perineural invasion, biliary invasion, tumoral necrosis, intrahepatic metastasis, and lymph node metastasis.

**Analysis of recurrence and death**

Routine postoperative surveillance at our institution consisted of physical examination, chest radiography and laboratory tests performed 1 month after surgery and then every 3-6 months. All patients underwent radiographic monitoring with ultrasonography or contrast enhanced CT and/ or MRI at 3-6 month interval after surgery. The clinical outcomes included the current status of each patient (dead, alive or lost to follow-up). These data were collected using electronic medical records and follow-up imaging studies until December 31, 2018. We were able to obtain the postoperative data of 17 of the 20 patients who were followed up at our institution. Recurrence was defined as any sign of recurrent tumor, either biopsy-proven or documented progression on serial imaging. The recurrent site was categorized as hepatic only or local and distant recurrence. Time to recurrence was calculated from the date of surgery to the date of tumor recurrence or death. Time to death was defined as the interval between the date of surgery and the date of death.

**Statistical analysis**

We used the Chi-squared tests or Fisher exact test to analyse the relationship between the enhancement pattern and other imaging findings and categorical clinicopathological factors and clinical outcomes. We used the t-test or the Mann–Whitney U-test to analyse the correlations between the enhancement pattern and continuous clinicopathological factors. Statistical analysis was performed using a statistical software package (SPSS for Windows, version 13.0; SPSS, Chicago, IL, USA). The *P* value less than 0.05 indicated a statistically significant difference.

Interobserver agreement was evaluated by using weighted kappa statistics for CT findings. Weighted kappa values of less than 0.20 indicated slight agreement; values of 0.20 - 0.39, fair agreement;

values of 0.40 - 0.59, moderate agreement; values of 0.60 - 0.79, substantial agreement; and values greater than 0.80, outstanding agreement.

## Results

### Baseline characteristics

Clinical and demographic data of patients are listed in Table 1. A total of 7 out of 20 patients had morphologic alteration of liver cirrhosis. The underlying causes of cirrhosis included chronic hepatitis B (n = 3) and alcohol abuse (n = 5). The preoperative serum levels of carbohydrate antigen 19 - 9 and CEA were above the normal value in 10 of 20 patients (median, 72.9 U/mL; range, 0.5 - 1001.0 U/mL) and 11 of 20 patients (median, 10.3 U/mL; range, 0.9 - 221.0 U/mL), respectively. The median diameter of the 20 IMCCs was 5.2 cm (range, 1.7 - 13.9 cm). Among 20 patients, there were 17 patients (85%) with a single tumor and 3 patients (15%) with multiple tumors in the resected specimens. At histopathologic analysis of 20 tumors, 6 (30%) showed perivascular invasion, 6 (30%) showed perineural invasion and 7 (35%) showed lymphatic involvement. A total of 4 of 20 tumors (20%) manifested with necrosis.

**Table 1** Clinical and demographic data of the 20 patients

| | |
|---|---|
| **Sex (male/female)** | 13/7 |
| **Age*** | 62.5 (34 - 86) |
| **CEA (ng/ml)*** | 10.3 (0.89 - 221) |
| **CA 19-9 (U/ml)*** | 72.9 (0.50 - 1001) |
| **Tumor size (cm)*** | 5.2 (1.7 - 13.9) |
| **Disease free rate (month)*** | 5.0 (1 - 32) |

* Data are median and ranges are in parentheses.

### CT findings

The preoperative morphologic features and enhancement patterns of IMCC were summarized in Table 2. The relationship between CT findings and clinicopathologic factors were described in Tables 3 and 4. According to arterial enhancement pattern of IMCCs, the preoperative serum levels of CEA in hypovascular group was higher than in hypervascular group, $P = 0.028$. The preoperative serum levels of CEA in necrotic liked pattern on PVP were higher than in internal progressive enhancement group, $P = 0.002$. The pattern of enhancement differed significantly between solitary and multiple tumors. Solitary tumor showed greater peripheral rim enhancement on HAP than the multiple tumors with a statistical significance of $P$ value = 0.049.

Perivascular, perineural and lymphatic involvement were more frequently observed in hypovascular group on HAP. However, there was no significant difference.

The tumor size of IMCC with malignant portal venous thrombosis (mean size = 13.9 ± 0 cm) was significantly larger than that without portal venous thrombosis (mean size = 5.5 ± 2.65 cm) $P = 0.006$. The tumor size of IMCC with internal hemorrhage (mean size = 10.6 ± 4.67 cm) was significantly larger than did those without hemorrhage (mean size = 5.4 ± 2.68 cm) $P$ value = 0.024. IMCC with daughter nodules had more frequent adjacent organ involvement at pathological examination ($P = 0.005$). IMCC with hepatic vein invasion more frequently had involved parenchymal margin that without hepatic vein invasion ($P = 0.018$).

### Interobserver agreement for CT findings

Interobserver agreement for the pattern of enhancement on HAP was fair (k = 0.308), the degree of enhancement of the tumors compared with that of normal liver parenchyma during HAP was poor (k = 0.077). The interobserver agreement for the pattern of enhancement on PVP and EP was moderate (k = 0.519).

### Risk of death and recurrent rates

The median follow-up was 266 days (range: 38 - 960 days). Among 20 patients, 3 patients showed no recurrence, 14 showed recurrence (local recurrence in 6 and distant recurrence in 8) and 3 deaths. Recurrence within 6 months in 11

patients and more than 6 months in 6 patients were observed. Patients with smaller tumor (size < 5 cm) showed longer disease free rate (DFR) than patients with larger tumors (> 5 cm) (16.5 vs 4.7 months; $P$ = 0.006). In addition, patients with negative preoperative CEA had longer DFR than those with positive CEA (13.8 vs 3.5 months $P$ = 0.014). According to pathological examination, patients with well to moderately differentiated tumors demonstrated longer DFR than those with poorly differentiated tumos ($P$ = 0.007). Table 5 shows relationship of DFR with pathological grade and tumor markers. Patients with hypovascular tumors tended to suffer from recurrence within 6 months more frequently than those with hypervascular tumor in HAP (63.6 vs 36.4 %, $P$ = 0.247). Patients with hypervascular tumors on HAP showed a trend of longer DFR than patients with hypovascular tumors (10.5 vs 5.0 months, $P$ = 0.27). In addition, patients with internal progressive heterogeneous enhancement showed longer DFR than patients with necrotic-like pattern on PVP (9.8 vs 6.8 months, $P$ = 0.56).

**Table 2** The preoperative morphologic features and enhancement patterns of IMCC

| | |
|---|---|
| **Contour** | |
| - Round/lobulated | 16 (80%) |
| - Irregular | 2 (10%) |
| - Diffuse infiltrative | 2 (10%) |
| **Number** | |
| - Solitary | 17 (85%) |
| - Multiple | 3 (15%) |
| **Size** | |
| - < 5cm | 9 (45%) |
| - > 5cm | 11 (55%) |
| **Lobe** | |
| - Right lobe | 17 (85%) |
| - Left lobe | 3 (15%) |
| **Margin** | |
| - Well-defined | 11 (55%) |
| - Ill-defined | 9 (45%) |
| **Location** | |
| - Subcapsular | 14 (70%) |
| - Perihilar | 6 (30%) |
| **Internal calcifications** | |
| - Absence | 18 (90%) |
| - Presence | 2 (10%) |
| **IHD stone** | |
| - Absence | 19 (95%) |
| - Presence | 1 (5%) |
| **Internal hemorrhage** | |
| - Absence | 18 (90%) |
| - Presence | 2 (10%) |
| **Capsular retraction** | |
| - Absence | 9 (45%) |
| - Presence | 11 (55%) |
| **Adjacent bile duct dilatation** | |
| - Absence | 8 (40%) |
| - Presence | 12 (60%) |

**Table 2** The preoperative morphologic features and enhancement patterns of IMCC (Cont.)

| | |
|---|---|
| **Portal vein invasion** | |
| - Absence | 13 (65%) |
| - Presence | 7 (35%) |
| **Hepatic vein invasion** | |
| - Absence | 12 (60%) |
| - Presence | 8 (40%) |
| **Tumor thrombosis** | |
| - Absence | 19 (95%) |
| - Presence | 1 (5%) |
| **Bile duct invasion** | |
| - Absence | 19 (95%) |
| - Presence | 1 (5%) |
| **Daughter nodule** | |
| - Absence | 14 (70%) |
| - Presence | 6 (30%) |
| **Significant LN** | |
| - Absence | 12 (60%) |
| - Presence | 8 (40%) |
| **Imaging of liver cirrhosis** | |
| - Absence | 13 (65%) |
| - Presence | 7 (35%) |
| **Pattern enhancement on HAP** | |
| - Peripheral | 12 (60%) |
| - Diffused heterogeneous enhancement | 8 (40%) |
| **Attenuating area on HAP** | |
| - Hyperattenuating | 11 (55%) |
| - Hypo-isoattenuating | 9 (45%) |
| **Area of enhancement on HAP** | |
| - Hypovascular < 50% | 3 (15%) |
| - Hypervascular > 50% | 8 (40%) |
| **Pattern enhancement on PVP** | |
| - Internal progressive enhancement | 15 (75%) |
| - Necrotic-like | 5 (25%) |

Data are number of patients, with the percentage in parentheses.

**Table 3** Morphologic features and enhancement patterns on HAP correlation with demographic data and biomarker

| Variable | Hypervascular tumors | | Hypovascular tumors | | *P* value[a] |
|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | |
| **CEA (ng/ml)*** | 8.637 | 7.340 | 70.376 | 91.243 | 0.028 |
| **CA 19-9 (U/ml)** | 252.883 | 359.151 | 170.097 | 193.718 | 0.670 |

*Significant difference between patients with hypervascular and hypovascular tumors
[a] *P* value was calculated with an independent-sample *t* test

**Table 4** Morphologic features and enhancement patterns on PVP correlation with demographic data and biomarker

| Variable | Internal progressive enhancement | | Necrotic-like | | *P* value[a] |
|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | |
| **CEA (ng/ml)*** | 9.846 | 8.789 | 105.893 | 108.516 | 0.002 |
| **CA 19-9 (U/ml)** | 157.086 | 275.568 | 481.435 | 386.597 | 0.079 |

*Significant difference between patients with internal progressive and necrotic-like enhancement
[a] *P* value was calculated with an independent-sample *t* test

**Table 5** Disease free rate correlation with pathological grade and tumor marker

| Variable | DFR (month) | | *P* value[a] |
|---|---|---|---|
| | Mean | SD | |
| **Pathological grade** | | | 0.007 |
| Well-differentiated | 32.00 | - | |
| Moderately-differentiated | 6.64 | 6.476 | |
| Poorly-differentiated | 4.00 | - | |
| **CEA** | | | 0.014 |
| Negative | 13.78 | 10.035 | |
| Positive | 3.38 | 3.420 | |
| **CA 19-9** | | | 0.113 |
| Negative | 12.22 | 10.97 | |
| Positive | 5.13 | 4.91 | |

*Significant difference between DFR and pathological findings
[a] *P* value was calculated with an independent-sample *t* test

## Discussion

In our study, most of the IMCCs were arterial peripheral enhancement (60 %) with gradually centripetal progressive enhancement on PVP (75 %) which were similar to results reported by other studies of dynamic CT.[15, 16] These enhancement patterns can be explained histologically. The peripheral portion of ICCs contains abundant viable tumor cells, whereas the central portion is composed of coagulative necrosis with few cancer cells and a varying degree of fibrous stroma. The fibrous stroma in the center of the tumor is known to appear as an area of delayed enhancement on dynamic studies.[17]

Previous studies have found that certain clinical-pathologic factors are related to poor prognosis of IMCC after resection.[8, 12, 18] These factors include older age, large tumor size, vascular invasion, underlying liver cirrhosis, lymph node metastasis, a certain gross type, positive resection margins, and multifocal disease.[12, 18] In our study, we found that the tumor size of IMCCs with malignant portal venous thrombosis was significantly larger than that without portal venous thrombosis. The tumor size of IMCC with internal hemorrhage (mean size = 10.6 cm) was significantly larger than that without hemorrhage (mean size = 5.4 cm, $P = 0.024$). Tumor size may affect vascularity, coagulopathy and hemorrhagic necrosis. Tumor size has been reported to correlate with the prognosis of IMCC in the previous study.[19] Tumor that have daughter nodules have significantly more adjacent organ invasion than those without daughter nodules ($P = 0.005$). IMCCs with hepatic vein invasion more frequently involved parenchymal margin than those without hepatic vein invasion ($P = 0.008$).

Previous studies reported that the differences in enhancement patterns in the HAP would be useful for predicting aggressive behavior of IMCC and patient outcomes.[13-15] It has been demonstrated that hypervascular IMCCs in the HAP showed less

aggressive biological behavior or more favourable outcomes after surgical resection than typical hypovascular IMCCs.[13, 14] The hypovascular group IMCC also showed significantly poorer disease-free survival which could be an independent preoperative prognostic factor for disease-free survival.[14] The result showed that the perivascular, perineural and lymphatic involvement were more frequently observed in the patient with hypovascular IMCC on HAP. However, there was no significant difference in our study. Patients with hypovascular IMCC tended to present with recurrence within 6 months more than those with hypervascular IMCC. Moreover, they tended to have shorter DFR. Despite not statistically significant, it may be extrapolated with caution that hypovascular IMCC behaves more aggressively and may carry worse prognosis in line with previously published studies.

Interestingly, our study demonstrated the patients with elevated preoperative CEA level had shorter DFR than those with negative CEA level ($P$ = 0.014) which corresponds accordingly with a previous study that showed that elevated CEA level was significantly associated with worse survival in patients with hilar cholangiocarcinoma.[20] CEA is also significantly related to the rate of unresectibility of hilar cholangiocarcinoma. CEA is an important tumor marker that is usually used in patients with suspected gastrointestinal malignancy as well as cholangiocarcinoma. It is considered to be an epithelial marker with strong staining in adenocarcinomas.[20] CEA level can be used to monitor disease progression or recurrence. Even though the preoperative CEA and clinicopathological features of this phenomenon have not been clarified, our study confirmed the relationship between CEA level and DFR which cholangiocarcinoma could originate from the same hepatic progenitor stem cells in patients with adenocarcinoma.

To our knowledge, there is no study about the relationship between enhancement pattern of IMCC and CEA level. In our study, patient with hypovascular IMCC on HAP significantly had higher preoperative serum CEA level compared to patients with hypervascular IMCC ($P$ = 0.028). The preoperative serum CEA levels in necrotic-like patterns on PVP were also higher than in internal progressive enhancement as well ($P$ = 0.002).

There were several limitations to our study. Firstly, although we recruited patients who met the inclusion criteria, we cannot rule out selection bias that may have resulted from the retrospective design of our study. Secondly, we had a small population of IMCC patients who underwent hepatectomy in our institution. Therefore, the radiologic-clinicopathologic correlation was possible in only 20 patients. Thirdly, we used qualitative evaluation to determine the enhancement pattern. Interobserver agreement for the pattern of enhancement on HAP was fair at best.

In conclusion, preoperative CEA level, tumor sizes, daughter nodules, hepatic vein invasion and pathological grade are significant prognostic factors and clinical outcome after surgical resection of IMCCs. Pre-operative evaluation of morphologic features and enhancement patterns of IMCC on dynamic MDCT may be useful to predict clinicopathological outcomes.

**Conflict of interest**

The authors declare that there are no conflicts of interest.

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