The CT Appearances for Differentiating of Peripheral, Mass-Forming Cholangiocarcinoma and Liver Meatastases from Colorectal Adenocarcinoma

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Objective: To evaluate the computed tomographic (CT) appearances for differentiating of primary hepatic adenocarcinoma (peripheral, mass-forming cholangiocarcinoma) and secondary hepatic adenocarcinoma (liver metastases from colorectal carcinoma).

Material and Method: Between January 2004 and December 2010, 45 patients with peripheral, mass-forming cholangiocarcinoma (Group 1) and 45 patients with liver metastases from colorectal adenocarcinoma (Group 2) who underwent abdominal CT scan at the authors' institution were included in the present retrospective study. Two experienced, abdominal radiologists blinded to the participants' clinical histories and pathological results, separately reviewed the CT findings of each participant (number of liver mass(es), size, margin, internal calcification, hepatic capsule retraction, vascular invasion, peripheral bile duct dilatation, proximal bile duct enhancement, extrahepatic spreading, nearby lymphadenopathy and nearby organ invasion) and gave the presumed diagnosis of each individual case. Any discrepancies were solved by a consensus review. Finally, the authors conducted a stratified analysis of the patients in both groups based on their CT appearances.

Results: Ninety participants were 35 (38.9%) female, 55 (61.1%) male, age range from 43 to 88 years (mean 63.4 years, SD = 10.7). There were 28.9% vs. 48.9% female with the mean age (SD) of 61.5 (9.4) vs. 65.4 (11.6) years in Group 1 and 2, respectively. The mean size (SD) were 7.4 (3.7) cm vs. 4.0 (2.1) cm, in Group 1 and 2, respectively (p<0.001). The presence of hepatic capsule retraction, vascular invasion, peripheral bile duct dilatation, proximal bile duct enhancement, extrahepatic spreading, nearby lymphadenopathy, and nearby organ invasion were significantly higher in Group 1 than Group 2 (p<0.001). In contrary, the presence of multiple lesions with separated locations, and smooth margin were significantly suggested of Group 2 (p<0.001 and p = 0.007, respectively). By logistic regression analysis, peripheral bile duct dilatation, extrahepatic spreading, and proximal bile duct enhancement were the sole predictors of peripheral, mass-forming cholangiocarcinoma. The interobserver agreement for the presumed diagnosis of liver mass was good (kappa = 0.76).

Conclusion: The presence of peripheral bile duct dilatation, extrahepatic spreading, and proximal bile duct enhancement were highly suggestive of peripheral, mass-forming cholangiocarcinoma.

Keywords: Mass-forming cholangiocarcinoma, Liver metastases, Colorectal adenocarcinoma, CT, Computed tomography

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Cholangiocarcinoma is an adenocarcinoma that arises from the bile duct's epithelium. It is the second most common primary liver cancer after hepatocellular carcinoma. The prevalence of cholangiocarcinoma varies markedly from one geographic region to another, with the highest prevalence in Southeast Asia. Cholangiocarcinoma is classified by location as either intrahepatic or extrahepatic types. Intrahepatic cholangiocarcinoma is further classified as peripheral and hilar types. By

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morphology, cholangiocarcinoma can be categorized as mass-forming, periductal infiltrating, and intraductal types.

The typical computed tomographic (CT) features of a peripheral, mass-forming cholangiocarcinoma are hypovascular lesion with irregular peripheral enhancement on early phase and gradual centripetal enhancement on delayed phase. The presence of peripheral bile duct dilatation, hepatic capsule retraction, satellite nodules, and vascular encasement without the formation of a grossly visible tumor thrombus are common⁽¹⁾.

With unknown clinical history, the diagnosis of a peripheral, mass-forming cholangiocarcinoma based on CT findings is challenging. A wide

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spectrum of liver diseases may show the similar CT appearances⁽²⁾. Liver metastasis from colorectal adenocarcinoma is the most common type of liver metastases that causes biliary dilatation⁽³⁻⁵⁾ and often mimics peripheral cholangiocarcinoma. Liver metastasis from colorectal adenocarcinoma is typically a well-defined hypovascular lesion with peripheral rim enhancement on a post-contrast image. Central low attenuation may be present in the large lesion with central necrosis. Gradual centripetal enhancement and internal calcification may be seen^(6,7). Hepatic capsule retraction⁽⁸⁾ can be found, but sporadically. Even histopathology may be difficult to differentiate these two entities since both are adenocarcinoma. The use of immunohistochemical studies and other specific tests may aid in archiving the correct diagnosis^(9,10).

The purpose of the present study was to conduct a descriptive assessment of CT findings for differentiating peripheral, mass-forming cholangiocarcinoma and liver metastases from colorectal adenocarcinoma.

Material and Method *Patients*

The present study was a single-centered study performed at a 3,000-bed university hospital in central Thailand. The present study was approved by the Hospital Institutional Review Board. Written informed consents were waived due to its retrospective design. Due to vascular invasion is commonly seen in peripheral, mass-forming cholangiocarcinoma, but rarely found in liver metastases, the authors calculated the sample size based on the estimation of the vascular invasion probability in both groups using nQuery Advisor program. A sample size of 45 patients would be required in each group (total 90 participants) to demonstrate the difference in vascular invasion of both groups at the two-sided significant level of 1% with a power of 90%.

The authors searched the list of patients who had contrast-enhanced abdominal CT scans at the authors' institution between January 2004 and December 2010, and selected only the patients with liver masses and had pathological proven either primary hepatic cholangiocarcinoma (Group 1) or colorectal adenocarcinoma (Group 2). In general practice, liver metastases can be presumably diagnosed in patients with primary colorectal adenocarcinoma when their CT studies show newly detected hypovascular liver mass(es) without the necessity of liver biopsy. With this reason, the participants in Group 2 did not have the pathology from their liver masses, but all of them had the pathology of adenocarcinoma from colorectal mass biopsy/surgery with the clinical suspicion of liver metastases. With this limitation, the authors strictly selected only the colorectal carcinoma patients who had hypovascular liver masses seen by abdominal CT scans to be the participants in Group 2. The patients who had more than five liver masses and the patients with colonic mass/colostomy seen on their CT studies were excluded from the study population because these CT findings would suggest the diagnosis of liver metastases from colorectal adenocarcinoma. Hilar and extrahepatic cholangiocarcinoma were not included in the present study because most of these lesions can be easily differentiated from liver metastases. With these selected criteria, 90 participants (45 participants in each group) were recruited as the study population.

CT techniques

The participants' CT examinations were performed on various CT scanners, including a spiral CT scanner (Tomoscan AV1, Philips, Netherlands) and two 64-slice CT scanners (LightSpeed VCT, GE Healthcare, United States; and SOMATOM Definition Dual Source, Siemens, Germany). The slice collimations were 1.25 mm and 1.5 mm for LightSpeed VCT and SOMATOM Definition Dual Source, respectively. For Tomoscan AV1, the slice collimations were 5 mm and 10 mm. All participants received the bolus intravenous injection of 100 ml of nonionic iodinated contrast agent and 20 ml of water by a power injector at a rate of 2-3 ml/second. Due to the retrospective design, there was a variety of postcontrast phases (single vs. dynamic post-contrast phases) and the administration of oral and rectal contrasts.

Image analysis

The CT scans of these 90 participants were retrospectively reviewed by two experienced, abdominal radiologists. Both radiologists knew that the participants were diagnosed as one of the two possibilities (primary hepatic cholangiocarcinoma or liver metastases from colorectal adenocarcinoma), but they were blinded to the participants' final diagnosis and clinical data. They separately evaluated the CT findings of each participant and the discrepancies between both readers were solved by a consensus review. The details of image analysis included:

Number of liver mass(es)

The number of liver mass(es) of each participant was classified as single or multiple. In case of multiple liver masses, each radiologist would define further as separated nodules and satellite nodules. "Separated nodules" were defined in case of multiple liver masses that had about the same diameter, scattered in the liver. "Satellite nodules" were defined in case of multiple small nodules surrounding the large liver mass (Fig. 1). Participants who had combined separated and satellite nodules were categorized in the satellite nodules group.

Size

The longest diameter of each liver mass was measured in centimeters. In participants with multiple liver masses, only the largest mass was selected as a representative.

Margin

The margin of the each liver mass was categorized as smooth (grade 1), irregular (grade 2), or ill-defined (grade 3) margin. In participants with multiple liver masses with different appearances of their margins, the more aggressive appearance (higher grade) was selected as a representative.

Internal calcification

The presence of internal calcification within each liver mass was defined on pre-contrast CT images. In participants with multiple liver masses, the presence of internal calcification within only one mass would be sufficient.

Hepatic capsule retraction (Fig. 2)

The presence of hepatic capsule retraction by liver mass was defined only in the participants whose masses adhered with liver capsules. In participants with multiple liver masses, the presence of hepatic capsule retraction by only one mass would be sufficient.

Vascular invasion (Fig. 3)

The presence of vascular invasion by liver mass was defined only in the participants whose masses adhered with the main hepatic vasculature (main/right/left portal veins, or right/middle/left hepatic veins). Vascular invasion by liver mass was considered in participants with clearly visualized tumor thrombus in main hepatic vasculature, or non-visualized main hepatic vasculature obliterated by nearby liver mass. In participants with multiple liver masses, the presence of vascular invasion by only one mass would be sufficient.

Peripheral bile duct dilatation

The presence of bile duct dilatation periphery to each liver mass was defined. In participants with multiple liver masses, the presence of bile duct dilatation periphery to only one mass would be sufficient. Bile duct dilatation with other identified causes (e.g. stone) was excluded.

Proximal bile duct enhancement (Fig. 4)

The presence of proximal bile duct (common hepatic duct or common bile duct) enhancement was defined in each participant. Proximal bile duct



Fig. 1 Axial, post-contrast CT scans show the difference between "separated nodules" and "satellite nodules".A) Separated nodules represent multiple liver masses which had about the same diameter, scattered in the liver.B) Satellite nodules represent multiple small nodules surrounding the large liver mass.



Fig. 2 Axial, post-contrast CT scans show the difference between liver masses without hepatic capsule retraction (A) and with hepatic capsule retraction (B).



Fig. 3 Axial, post-contrast CT scan shows vascular invasion by nearby liver mass. Notice the dilated right portal vein with tumor thrombus inside.

enhancement with other causes (e.g. cholangitis) was excluded.

Extrahepatic spreading

The presence of extrahepatic spreading by liver mass was defined in each participant. Extrahepatic spreading by liver mass was considered in participants with nearby peritoneal nodules/fat stranding.

Nearby lymphadenopathy

The presence of nearby lymphadenopathy was defined in each participant. Lymphadenopathy was considered in participants with an enlarged lymph node (diameter more than 1.0 cm in short axis) or a group of multiple smaller lymph nodes.



Fig. 4 Axial, post-contrast CT scans show the difference between participants with no proximal bile duct enhancement (A) and with proximal bile duct enhancement (B).

Nearby organ invasion

The presence of nearby organ invasion (e.g. right adrenal invasion) by each liver mass was defined. In participants with multiple liver masses, the presence of nearby organ invasion by only one mass would be sufficient.

Finally, each reader gave the presumed diagnosis of each individual case (peripheral, massforming cholangiocarcinoma vs. liver metastases from colorectal adenocarcinoma vs. equivocal case).

Statistical analysis

The Chi-square test and Fisher's exact test were used to compare the CT findings between both groups. The significant CT findings for differentiating these two groups in univariate analysis were entered into the forward, stepwise logistic regression analysis. The kappa statistic was calculated to assess the interobserver agreement for the presumed diagnosis of liver masses. A kappa of less than 0.20 indicated poor agreement; kappa of 0.21 to 0.40 indicated fair agreement; kappa of 0.41 to 0.60 indicated moderate agreement; kappa of 0.61 to 0.80 indicated good agreement; and kappa of 0.81 to 1.00 indicated excellent agreement.

All statistical data analyses were performed by using PASW Statistics 18 (SPSS Inc., Chicago, Illinois, United States). A 2-sided *p*-value of less than 0.05 was considered as a statistical significance.

Results

Patients

Ninety participants in the present study were 35 (38.9%) female, 55 (61.1%) male, with the age range between 43 and 88 years (mean 63.4 years, SD = 10.7). There were 28.9% vs. 48.9% female with the mean age (SD) of 61.5 (9.4) vs. 65.4 (11.6) years in Group 1 and 2, respectively.

CT techniques

Of the 90 CT studies, 88 (43 in Group 1 and 45 in Group 2) studies were performed with one of the two 64-slice CT scanners (LightSpeed VCT, GE Healthcare, United States; or SOMATOM Definition Dual Source, Siemens, Germany) with the slice collimations of 1.25-1.5 mm. Only 2 CT studies in Group 1 were performed with a single slice CT scanner (Tomoscan AV1, Philips, Netherlands) with slice collimations of 5 mm (n = 1) and 10 mm (n = 1).

Image analysis (Table 1) Number of liver mass(es)

A single liver mass was found in 18 (40%) and 23 (51.1%) participants in Group 1 and 2, respectively. In participants with multiple liver masses, there were 0/27 (0%) and 17/22 (77.3%) participants with separated nodules in Group 1 and 2, respectively (p < 0.001).

Size

The mean size \pm SD (range) of liver mass were 7.4 \pm 3.7 cm (1.8-16.1 cm) and 4.0 \pm 2.1 cm (1.4-10.4 cm) in Group 1 and 2, respectively (p<0.001).

Margin

None of Group 1 had liver mass with smooth margin, while seven (15.6%) participants in Group 2 had masses with smooth margin (p = 0.007).

Internal calcification

The presence of internal calcification was found in 20.0% vs. 33.3% in Group 1 and 2, respectively (p = 0.153).

Hepatic capsule retraction

Forty-one participants in Group 1 and 34 participants in Group 2 had liver masses adhered with liver capsule and these liver masses were evaluated for nearby hepatic capsule retraction. The presence of hepatic capsule retraction was significantly higher in Group 1 than Group 2 (80.5% vs. 41.2%, p<0.001).

Vascular invasion

Thirty-six participants in Group 1 and 26 participants in Group 2 had liver masses adhered with the main hepatic vasculature. These liver masses were evaluated for nearby vascular invasion. The presence of vascular invasion was significantly higher in Group 1 than Group 2 (61.1% vs. 3.8%, p<0.001).

Peripheral bile duct dilatation

The presence of bile duct dilatation periphery to liver mass was significantly higher in Group 1 than Group 2 (95.6% vs. 31.1%, p < 0.001).

Proximal bile duct enhancement

The presence of proximal bile duct enhancement was significantly higher in Group 1 than Group 2 (46.7% vs. 2.2%, p<0.001).

CT findings	Group 1	Group 2	<i>p</i> -value
Number of liver mass(es)			< 0.001
Single	18/45 (40.0%)	23/45 (51.1%)	
Multiple	27/45 (60.0%)	22/45 (48.9%)	
Separated nodules	0/27 (0%)	17/22 (77.3%)	
Satellite nodules	27/27 (100%)	5/22 (22.7%)	
Size of liver mass (cm), mean \pm SD	7.4±3.7	4.0±2.1	< 0.001
Margin			0.007
Smooth	0/45 (0%)	7/45 (15.6%)	
Irregular	24/45 (53.3%)	14/45 (31.1%)	
Illdefined	21/45 (46.7%)	24/45 (53.3%)	
Internal calcification	9/45 (20.0%)	15/45 (33.3%)	0.153
Hepatic capsule retraction	33/41 (80.5%)	14/34 (41.2%)	< 0.001
Vascular invasion	22/36 (61.1%)	1/26 (3.8%)	< 0.001
Peripheral bile duct dilatation	43/45 (95.6%)	14/45 (31.1%)	< 0.001
Proximal bile duct enhancement	21/45 (46.7%)	1/45 (2.2%)	< 0.001
Extrahepatic spreading	30/45 (66.7%)	7/45 (15.6%)	< 0.001
Nearby lymphadenopathy	32/45 (71.1%)	9/45 (20.0%)	< 0.001
Nearby organ invasion	26/45 (57.8%)	3/45 (6.7%)	< 0.001

 Table 1. Comparison of the CT appearances between peripheral, mass-forming cholangiocarcinoma (Group 1) and liver metastases from colorectal adenocarcinoma (Group 2)

CT = computed tomographic

Extrahepatic spreading

The presence of extrahepatic spreading was significantly higher in Group 1 than Group 2 (66.7% vs. 15.6%, p<0.001).

Nearby lymphadenopathy

The presence of nearby lymphadenopathy was significantly higher in Group 1 than Group 2 (71.1% vs. 20.0%, p<0.001).

Nearby organ invasion

The presence of nearby organ invasion was significantly higher in Group 1 than Group 2 (57.8% vs. 6.7%, p<0.001).

By logistic regression analysis, peripheral bile duct dilatation (p<0.001), extrahepatic spreading (p = 0.001), and proximal bile duct enhancement (p = 0.042) were the sole predictors of peripheral, mass-forming cholangiocarcinoma with odd ratio (95% CI) of 36.8 (5.5, 246.1), 14.0 (2.8, 71.4), and 10.0 (1.1, 92.5), respectively.

The presumed diagnosis of peripheral, massforming cholangiocarcionoma vs. liver metastases from colorectal adenocarcinoma vs. equivocal cases were 60.0% vs. 38.9% vs. 1.1% by reader 1 and 57.8% vs. 36.7% vs. 5.6% by reader 2. The interobserver agreement for the presumed diagnosis of liver mass was good (kappa = 0.76).

Discussion

In the present study, the authors analyzed the CT features for differentiating peripheral, massforming cholangiocarcinoma and liver metastases from colorectal adenocarcinoma. At the beginning, the authors assumed that vascular invasion would be the CT finding that helping in the differentiation between both entities since it was frequently found in peripheral, mass-forming cholangiocarcinoma but rarely visualized in any liver metastases. As the authors expected, the presence of vascular invasion was significantly higher in the peripheral, mass-forming cholangiocarcinoma group by univariate analysis. However, this CT feature could not be entered into the logistic regression analysis because the number of participants evaluated for vascular invasion was less than those for other CT features (62 vs. 90). For evaluation of vascular invasion, only the participants whose masses adhered to the main hepatic vasculature were selected.

Prior studies⁽²⁻⁸⁾ reported that liver metastases from colorectal adenocarcinoma had many CT features similar to cholangiocarcinoma. The present study also confirmed that there were similar CT findings found in both groups. However, several aggressive CT findings were significantly more common in cholangiocarcinoma than liver metastases and would suggest the diagnosis of cholangiocarcinoma. These included the presence of hepatic capsule retraction, vascular invasion, peripheral bile duct dilatation, proximal bile duct enhancement, extrahepatic spreading, nearby lymphadenopathy, and nearby organ invasion. The mean size of hepatic masses caused by cholangiocarcinoma was also larger than by liver metastases. By logistic regression analysis, peripheral bile duct dilatation, extrahepatic spreading, and proximal bile duct enhancement were the sole predictors of peripheral, mass-forming cholangiocarcinoma.

Although the number of liver masses (single vs. multiple lesions) was not a helpful indicator to differentiate these two entities, the pattern of satellite nodules and separated nodules would suggest of cholangiocarcinoma and liver metastases, respectively. The smooth margin pattern would remind the radiologist to think of other diagnoses, not cholangiocarcinoma. Internal calcification was more commonly seen in liver metastases group, but this did not reach statistical significance and could not be the indicator for differentiation of these two entities.

There were two major limitations of the present study. First, the participants in Group 2 (liver metastases from colorectal cancer) did not have the pathology from their liver masses. This could be explained because in general practice, liver metastases can be presumably diagnosed in patients with primary colorectal adenocarcinoma when their CT studies show newly detected liver mass(es) without the necessity of liver biopsy. The authors were aware of this limitation, therefore the authors selected only the patients with hypovascular liver masses to be the participants in group 2; however, the authors still could not guarantee that these masses were solely liver metastases from colorectal adenocarcinoma. This is possibly why there have been no prior studies focused on the CT features to differentiate these two entities. Further study with the pathology proven of adenocarcinoma metastases should be designed to acquire more reliable data. Second, most participants in Group 2 had pre- and single post-contrast phase CT studies (portal venous phase) while most participants in Group 1 had pre- and dynamic post-contrast phase studies (arterial, portal venous, and 5-minute delayed phases). Hence, the authors could not compare the enhancement pattern between these two groups.

The present study had more limitations. There were inherent biases to the retrospective study design as related to the variability in CT scanners and the CT protocols. It also had small sample size, and focused only on peripheral, mass-forming cholangiocarcinoma and liver metastases from colorectal carcinoma. Furthermore, with the study design, both readers inevitably knew that all participants had the diagnosis as one of these two groups, although they did not know the final diagnosis. Lastly, the presence of surgical materials or surgical scars from prior colorectal surgery on CT images would suggest the diagnosis of liver metastases from colorectal carcinoma.

In conclusion, the presence of three significant CT features included peripheral bile duct dilatation, extrahepatic spreading, and proximal bile duct enhancement would suggest the diagnosis of peripheral, mass-forming cholangiocarcinoma.

Potential conflicts of interest

None.

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ลักษณะทางเอกซเรย์คอมพิวเตอร์ที่ช่วยแยกก้อนมะเร็งท่อน้ำดีในตับและก้อนมะเร็งตับที่แพร่กระจายมาจาก มะเร็งลำใส้ใหญ่

ปียาภรณ์ อภิสารธนรักษ์, ชโลธร พันธุ์ศรี, กอบกุล เมืองสมบูรณ์, สมราช ธรรมธรวัฒน์

วัตถุประสงค์: เพื่อศึกษาลักษณะทางเอกซเรย์คอมพิวเตอร์ที่ช่วยแยกระหว่างก้อนมะเร็งท่อน้ำดีในดับและก้อนมะเร็งตับที่แพร่กระจาย มาจากมะเร็งลำใส้ใหญ่

วัสดุและวิธีการ: ในช่วงเดือนมกราคม พ.ศ. 2547 ถึง เดือนธันวาคม พ.ศ. 2553 ผู้ป่วยที่มีก้อนมะเร็งท่อน้ำดีในตับ 45 ราย (กลุ่ม 1) และผู้ป่วยที่มีก้อนมะเร็งตับที่แพร่กระจายมาจากมะเร็งลำใส้ใหญ่ 45 ราย (กลุ่ม 2) ที่ได้รับการตรวจเอกซเรย์คอมพิวเตอร์ ของช่องท้องเข้าร่วมการศึกษานี้ ภาพเอกซเรย์คอมพิวเตอร์ของผู้ป่วยทั้ง 90 ราย ได้รับการประเมินย้อนหลังโดยรังสีแพทย์ 2 คน เพื่อหาลักษณะทางเอกซเรย์คอมพิวเตอร์ที่ช่วยแยกก้อนในตับ 2 ชนิดนี้

ผลการศึกษา: พบว่าขนาดของก้อนในผู้ป่วยกลุ่ม 1 มีขนาดใหญ่กว่ากลุ่ม 2 (7.4 เซนติเมตร และ 4.0 เซนติเมตร ตามลำดับ) นอกจากนั้นลักษณะการดึงรั้งขอบตับ การลุกลามเข้าหลอดเลือด การอุดตันท่อน้ำดีในตับ การพบท่อน้ำดีขั้วตับมีลักษณะขาวขึ้น หลังฉีดสารทีบรังสี การแพร่กระจายออกนอกตับ การแพร่กระจายไปยังต่อมน้ำเหลืองข้างเคียง และการลุกลามไปยังอวัยวะใกล้เคียง เป็นลักษณะที่พบในผู้ป่วยกลุ่ม 1 มากกว่ากลุ่ม 2 อย่างมีนัยสำคัญทางสถิติ ส่วนลักษณะที่พบก้อนมะเร็งหลาย ๆ ก้อน ที่มีขนาด ใกล้เคียงกันกระจายอยู่ในเนื้อตับ และลักษณะขอบก้อนเรียบจะพบในผู้ป่วยกลุ่ม 2 มากกว่า เมื่อใช้ logistic regression analysis พบว่าการอุดตันท่อน้ำดีในตับ การแพร่กระจายออกนอกตับ และการพบท่อน้ำดีขั้วตับมีลักษณะขาวขึ้นหลังฉีดสารทึบรังสี เป็นลักษณะที่ช่วยบ่งชี้ถึงก้อนมะเร็งท่อน้ำดีในตับ

สรุป: การอุดตันท่อน้ำดีในตับ การแพร่กระจายออกนอกตับ และการพบท่อน้ำดีขั้วตับมีลักษณะขาวขึ้นหลังฉีดสารทึบรังสี และเป็นลักษณะที่ช่วยบ่งชี้ถึงก้อนมะเร็งท่อน้ำดีในตับ