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RESEARCH ARTICLE

Benign Diseases Masquerading as Cholangiocarcinoma: Can we Differentiate before Surgery?

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Abstract

Background: Cholangiocarcinoma (CCA) is a potentially lethal disease that requires surgical treatment. There are many benign conditions, those that do not require surgical treatment, displaying imaging characteristics that resemble CCA, leading to therapeutic misadventures. This study aimed to evaluate the proportion of benign conditions that underwent hepatic resection for presumed CCA, and explore the differences between the characteristics of these two entities stratified by primary imaging features of the lesions. **Methods:** This retrospective study ran between January 2004 and December 2011. We reviewed the pathological records of all 1,402 patients who underwent curative-intent hepatic resection for preoperatively diagnosed CCA. All clinical and pathological parameters were analyzed. **Results:** The proportion of benign conditions that underwent hepatic resection was 3.78% (53/1,402). For mass-forming lesions, CCA was associated with higher age, alkaline phosphatase, tumor markers, neutrophil to lymphocyte ratio, and mass size. The patients with mass-forming benign conditions were more associated with diabetes mellitus. For lesions with bile duct dilatation, intraductal tumor, including CCA, had higher CA19-9 level and NLR with statistical significance. For cystic lesions, biliary cystic neoplasm had statistical significance in the rate of abdominal pain. **Conclusions:** The proportion of hepatic resection for benign conditions was quite low. There were many characteristic differences used to differentiate benign mass-forming conditions from CCA, whereas only few markers in the setting of cystic lesions and biliary dilatation. We recommend performing standard hepatic resection in every case, regardless of the type of imaging features, if the lesion has a chance of being CCA.

Keywords: Cholangiocarcinoma- benign- hepatic resection- intraductal papillary neoplasm of the bile duct- mimic

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Introduction

Cholangiocarcinoma (CCA) is a potentially lethal disease [1], which exhibits a wide spectrum of imaging findings [2, 3], including mass-forming appearance, thickening along the bile duct, intraductal tumor with bile duct dilatation, cystic lesion, and a combination of the aforementioned features, though with different progression [4]. No matter what CCA displays, it ultimately should be treated by radical surgical resection [3, 5]. However, there are many benign conditions, those that do not require surgical treatment, which display imaging characteristics that resemble CCA [2, 6] (Figure 1). Preoperative histopathological diagnosis of intrahepatic or hilar lesion by biopsy or brush cytology is difficult, due to limitations in the yield of cytology and the risk of tumor seeding, with injury to adjacent structures during the receipt of the tissue. Therefore, patients with imaging features of

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suspected CCA are usually advised to undergo hepatic resection to eliminate the chance of disease progression. It is not surprising that there were a number of patients reported with benign diseases who underwent unnecessary hepatic resection for presumed CCA [7, 8].

So far as we know, there is limited evidence about the proportion of benign conditions that underwent hepatic resection for presumed CCA. Most of them are from western countries, where there is a high incidence of sclerosing cholangitis, inflammatory pseudotumor, and other inflammatory conditions [7, 8]. The reported proportion of benign conditions masquerading as CCA in eastern countries is scarce. Moreover, the head-to-head comparison of characteristics between benign conditions and CCA stratified by primary imaging features has not been reported.

To achieve a better understanding of the benign conditions masquerading as CCA, the aim of this study was to ascertain the proportion of benign conditions that underwent hepatic resection for presumed CCA. In particular, we analyzed the differences between characteristics between benign conditions and CCA stratified by the primary imaging features of the lesions.

Materials and Methods

This retrospective study ran between January 2004 and December 2011. We reviewed the pathological records of all of the patients from Srinagarind Hospital, Khon Kaen University, who underwent curative-intent hepatic resection for preoperatively diagnosed CCA. The medical and pathological records of all pathologically proven benign conditions in the same period were also reviewed. We found that a total of 1,402 patients underwent surgical operations for preoperatively diagnosed CCA. After exclusion of the patients with intraoperatively found advanced disease, precluding hepatic resection, 53 patients with pathologically proven benign conditions underwent hepatic resection for some reason.

Regarding the management protocol for the patients with CCA at our center, all patients were diagnosed at least by cross-sectional imaging (CT or MRI). In the study period, there was no hepatocyte-specific contrast MRI, per-oral cholangioscopy, and laparoscopic hepatic resection at our center. Patients with cross-sectional imaging character compatible with CCA would undergo open exploratory laparotomy; after diagnosis and the resectability of CCA being confirmed intraoperatively, the patients would receive hepatic resection. All hepatic resections were planned to achieve at least gross tumor removal. All surgical specimens were sent to the Department of Pathology for pathological diagnosis and final staging.

Ethical considerations

This study was approved by the Institutional Review Board (IRB), Office of Human Research Ethics, Khon Kaen University (HE601131)

Outcome variables. The primary outcome of this study was the proportion of benign conditions among the patients with preoperatively diagnosed CCA who underwent hepatic resection. We additionally evaluated the differences in characteristics between patients with benign conditions and those with CCA that underwent hepatic resection in the same period, stratified by dominant features on cross-sectional imaging. For the CCA group, we selected only patients with single prominent imaging features (i.e., mass-forming lesion, intrahepatic duct dilatation and cystic lesion), excluding those with combined features.

Statistical analysis. The data are presented as medians (min: max), or as counts and percentages. Survival analysis was presented using the Kaplan–Meier analysis. Comparisons among groups were analyzed using a log-rank test. Patients who had perioperative death (defined as death within 30 days after surgery) were censored from the analysis. A P-value of less than 0.05 was considered to be statistically significant. All statistical analyses were performed using STATA version 13.

Results

Among 1,402 patients who underwent operations for preoperative diagnoses of cholangiocarcinoma, 53 patients (3.78%) were found to have benign conditions at postoperative pathological diagnosis. During the study period, the number of patients with benign conditions who underwent hepatic resection, for all of diagnosis, was 75 patients. Of these, cholangiocarcinoma, therefore, was the most common preoperative diagnosis (n=53; 70%), followed by corrected diagnosis of benign conditions (15%), hepatocellular carcinoma (10%), and liver metastasis (5%). Among the 53 patients who had benign conditions who underwent hepatic resection for preoperatively diagnosed CCA, the most common pathological results were non-specific inflammation (n=33; 44%), parasitic infection (n=7; 9%), hemangioma (n=6; 8%), intrahepatic duct stone (n=4; 5%) and simple cyst (n=3; 4%) (Figure 2). Most of these were male (56.6%) with the mean age of 53.9 (+/- 9.1) years.

Survival of patients with a benign condition. With median follow up time of 4,121 days, the respective 1-, 3- and 5-year survival was 100%, 86.79% (74.3-93.5), and 84.91% (72.1-92.2). There was no death of patients with hemangioma and simple cyst; those had a significantly higher survival rate than the remaining three conditions (Figure 3). The median survival was not reached in all groups. The respective 3- and 5-year survival rates for IHD stone, parasitic infection and non-specific inflammation were: 3-year 75% (12.8-96.1), 85.7% (33.4-97.9), 84.9% (67.4-93.4) and 5-year 75% (12.8-96.1), 71.4% (25.8-91.9), 84.9% (67.4-93.4).

Comparison of characteristics between benign conditions and CCA. For mass-forming lesions, CCA was associated with higher age (58.4 vs 51.9), ALP (228.2 vs 100.9), CA19-9 level (507.8 vs 17.8), CEA (59.1 vs 2.6), AFP (54.2 vs 2.5), neutrophil to lymphocyte ratio: NLR (4.1 vs 2.5) and mass size (8.1 vs 4.3 cm). The patients with mass-forming benign conditions were more associated with diabetes mellitus (28% vs 3.23%) (Table 1). For

Table 1. Comparison of Characteristics between Mass-forming Benign Conditions and Mass-forming CCA

Characteristics	Benign (N =25)	MF-CCA (N=73)	Mean/ proportion difference	p-value
History				
Age (Mean, years)	51.88	58.35	6.47 [2.58 -10.37]	0.0014
Symptom duration (Mean, weeks)	20.39	12.49	7.90 [-2.38, 18.18]	0.1267
Sex [Male] %	13 [52%]	42 [57.5%]	0.04 [-0.13, 0.21]	0.648
DM	7 [28%]	2 [3.23%]	0.54 [0.25, 0.83]	0.001
HBV infection	1 [4%]	0 [0%]	0.72 [0.62, 0.81]	0.113
Clinical manifestations				
Weight loss	11 [44%]	28 [38.57%]	0.04 [-0.13, 0.22]	0.63
Abdominal pain	22 [88%]	59 [81.69%]	0.08 [-0.12, 0.30]	0.466
Laboratory results				
AST [IU/L]	30.36	45.67	15.31 [1.40, 29.22]	0.0314
ALT [IU/L]	30.52	52.8	22.28 [7.66, 36.89]	0.0033
ALP [IU/L]	100.84	228.2	127.33 [70.31, 184.36]	0
Total bilirubin [mg/dL]	0.64	0.93	-0.28 [-1.03, 0.46]	0.4456
CA19-9 [U/ml]	17.86	507.83	489.96 [353.56, 626.37]	0
CEA [ng/ml]	2.61	59.09	56.49 [17.61, 95.36]	0.0053
AFP [IU/ml]	2.52	54.15	51.63 [4.22, 99.03]	0.0335
Hematocrit (%)	38.26	39.95	-1.68 [-10.71, 7.34]	0.7106
Eosinophil count	320.6	426.25	392.89 [308.29, 477.48]	0.1552
NLR	2.5	4.12	1.61 [0.59, 2.62]	0.0022
PLR	149.12	181.44	171.23 [144.10, 198.38]	0.1652
Imaging finding				
Location Left Lobe N,%	5 [20%]	11 [15.49%]	0.62 [-0.18, 0.30]	0.603
Maximum mass size (cm)	4.34	8.09	3.74 [2.54, 4.94]	<0.001
Multiple masses	2 [8%]	4 [5.48 %]	0.08 [-0.30, 0.47]	0.65

lesions with intrahepatic bile duct dilatation, intraductal tumor, including CCA, had a statistically significant higher CA19-9 level (130.5 vs 43.7) and NLR (3.81 vs 2.08) (Table 2). For cystic lesions, biliary cystic neoplasm had a statistically significant rate of abdominal pain (76.5 vs 0%) and seems likely to be associated with higher CA19-9 level (208.5 vs 7.3). All patients with benign cystic lesions were male; none of them had abdominal pain at diagnosis. Hematocrit was higher in this group (40.75% vs 33.95%) (Table 3).

Discussion

Previous studies have reported a number of patients with benign conditions who underwent hepatic resection for presumed malignancy, especially CCA. We found that only 3.78% of all presumed CCA patients who underwent hepatic resection had benign conditions, confirmed by pathological report, which was quite lower than previous reports, which found about 7.2-15% [7-9]. This might be due to differences in the nature of the benign conditions among various regions. However, among the presumed malignant diagnoses, CCA was the most common preoperative diagnosis in the patients with pathologically proven benign conditions in all reports. The reason that may account for this is that CCA has various non-specific radiological manifestations [10], which are difficult to differentiate from some benign conditions by cross-sectional imaging alone [2]. Until now, there has been no study investigating the different characteristics between benign conditions and CCA stratified by primary imaging features of the lesions.

In general, outcomes of hepatic resection for benign conditions are very good [11]. The previous reports have shown improvement of the patients' symptoms after hepatic resection for benign disease [11, 12]. Our study found that the survival outcome after hepatic resection for benign conditions for presumed CCA was very good, especially in patients with non-inflammatory conditions (i.e., hemangioma, simple cyst). We found that inflammatory-related benign conditions worsened the survival rate. Intrahepatic duct stone requires not only hepatic resection but also good biliary drainage. Recurrent intrahepatic duct stone in the liver remnant is usually difficult to treat. Recurrent cholangitis of the liver remnant, which cannot be further resected, might lead to patient fatality. Hepatic resection is actually considered a non-definite treatment for parasitic liver disease. If the patient does not receive a proper anti-parasitic drug, the disease would recur at the liver remnant. As with aforementioned inflammatory

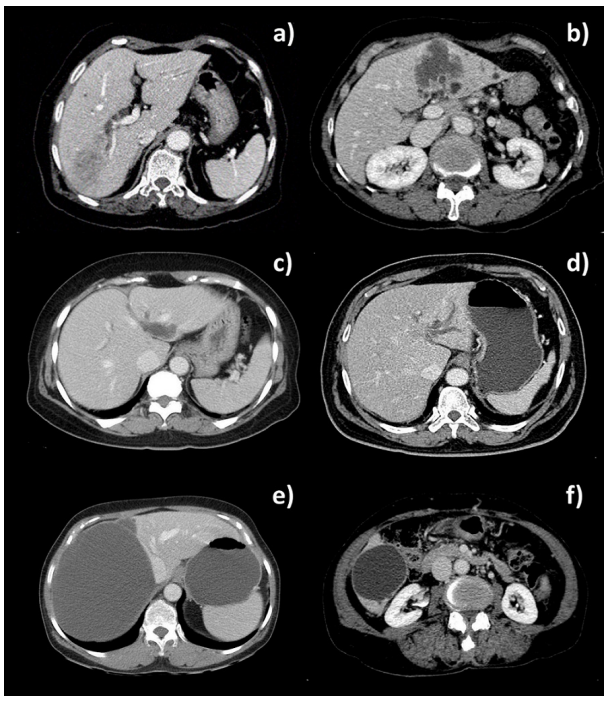


Figure 1. Comparison of CT Scan Findings of Benign Conditions (a, c, e) and CCA (b, d, f). a) Inflammatory Pseudo-tumor. b) mass-forming CCA. c) post-traumatic benign stricture causing S2 bile duct dilatation. d) micro-papillary IPNB at S2 bile duct. e) Simple liver cyst. f) cystic-variant IPNB.

conditions, non-specific inflammatory conditions had no specific definite treatment, leading to uncontrolled conditions [13]. We thus recommend determining the definite diagnosis of inflammatory benign conditions extensively after hepatic resection, in order to administrate appropriate further treatment for patients, not just hepatic resection for symptom relief.

We also summarize the differences of characteristics between benign conditions and CCA stratified by imaging appearances, including mass formation, bile duct dilatation, and cystic lesions (Figure 4). The first one had the highest number of characteristic differences between benign conditions and CCA. Malignant mass of bile duct, of course, causes some degree of biliary obstruction, and sometimes liver parenchymal injury, resulting in a higher level of all types of liver enzymes. Common hepatobiliary-tumor markers (i.e., CEA, CA19-9, AFP), size of the tumor, a simple inflammatory marker, NLR, predicted the chance of malignant mass lesion very well. These findings were quite straight forward. Our previous study reported that CA19-9 level was associated with the level of invasiveness of bile duct tumors and predicted prognosis of the patients very well [3], since non-specific inflammation accounts for most mass-forming benign conditions, and patients with diabetes mellitus, who are immunocompromised, are prone to all types of infection, whether bacterial or parasitic. Diabetes mellitus was thus found to be associated with benign conditions. We unexpectedly found that eosinophil count was unable to differentiate benign lesions from CCA. We had hypothesized that a common parasitic inflammatory CCA-mimicking lesion, a Fasciolar liver abscess, might be associated with higher levels of eosinophil count. Actually, CCA in our region is also related to another kind of parasitic infection, Opisthorchis viverrini, therefore an elevated eosinophil count could not be used as a marker of benign conditions [14, 15]. There were no differences

Table 2. Comparison of Characteristics between Benign Conditions with Intrahepatic Duct Dilatation and Intraductal Tumor

Characteristics	Benign (N =26)	CCA [N=65]	Mean/ proportion difference	p-value
History				
Age (Mean, years)	55.53	57.44	-1.90 [-6.13, 2.31]	0.3721
Sex [Male] %	15 [57.69%]	41 [63.08%]	0.04 [-0.14, 0.23]	0.6334
Clinical manifestations				
Weight loss	9 [34.6%]	21 [31.75%]	0.02 [-0.17, 0.23]	0. 7928
Abdominal pain	25 [96.15%]	55 [84.13%]	0.22 [0.03, 0.42]	0. 1170
Laboratory results				
AST [IU/L]	59.4	57.35	2.04 [-30.05, 34.14]	0.8995
ALT [IU/L]	53.6	69.81	-16.21 [-63.76, 31.32]	0.4993
ALP [IU/L]	158.76	200.11	-41.35 [-120.65, 37.93]	0.3026
Total bilirubin [mg/dL]	1.86	1.84	0.01 [-2.05, 2.08]	0.9873
CA19-9 [U/ml]	43.72	130.58	86.85 [0.19, 173.51]	0.0495
CEA [ng/ml]	2.79	5.86	-3.07 [-6.47, 0.33]	0.0763
AFP [IU/ml]	2.22	7.49	-5.27 [-15.12, 4.58]	0.2865
NLR	2.08	3.81	1.72 [0.49, 2.96]	0.0069
PLR	134.96	188.66	-53.70 [-108.34, 0.93]	0.0539
Imaging finding				
Location Left Lobe N,%	18 [68.18%]	29 [44.44%]	0.18 [0.00, 0.36]	0.0552

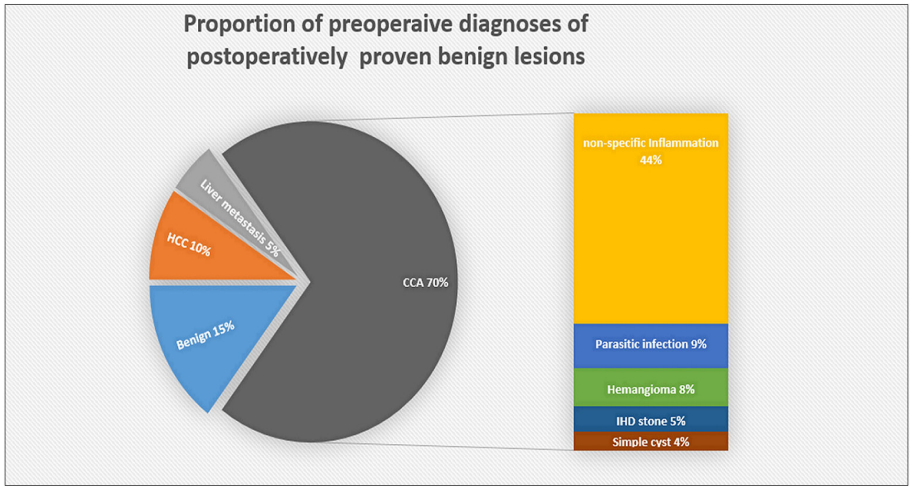


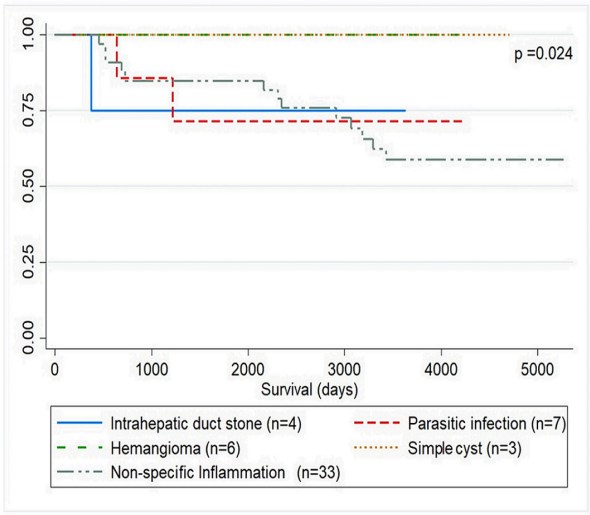
Figure 2. Proportion of Preoperative Diagnoses of Postoperatively Proven Benign Lesions. The vertical bar chart represents the proportion of benign diseases masquerading as CCA.

in the rate of abdominal pain and weight loss between benign conditions and CCA, after undergoing hepatic resection. An explanation for this was that the patients with symptomatic benign conditions would eventually undergo hepatic resection, regardless of their imaging findings. When considering hepatic resection for asymptomatic benign-suspected conditions, especially for the diabetes mellitus patients, the risk of postoperative liver failure and benefit of resection of benign lesions should be carefully weighed. We suggest that preoperative diagnosis should be as accurate as possible before hepatic resection. Owing to the simplicity of the percutaneous biopsy of mass-forming lesions, the young patients with small (<5 cm) mass with normal tumor markers level, those with high risk of postoperative liver failure, should undergo either extensively workup to rule out benign conditions or closely follow up, rather than hepatectomy. On the other hand, older patients with larger masses and rising tumor markers should be treated as having malignancies, until proven otherwise [16,17].

Bile duct tumor, including cholangiocarcinoma, can be manifested as an unexplained biliary dilatation or

Table 3. Comparison of Characteristics between Cystic Benign Conditions and Biliary Cystic Neoplasm

Characteristics	Benign [N =2]	Cystic neoplasm [N=21]	Mean/ proportion difference	p-value
History				
Age (Mean, years)	58.5	57.95	0.54 [-12.77, 13.86]	0.9327
Symptom duration (Mean, weeks)	3	20.5	-17.5 [-62.63, 27.63]	0.4147
Sex [Male] %	2 [100%]	6 [28.57%]	-0.25 [-0.55, 0.05]	0.0427
Clinical manifestations				
Weight loss	2 [100%]	7 [35.29%]	0.25 [-0.05, 0.55]	0.0796
Abdominal pain	0 [0%]	16 [76.47%]	-0.33 [-0.71, 0.04]	0.0278
Laboratory results				
AST [IU/L]	26	41.64	-15.64 [-58.71, 27.42]	0.4539
ALT [IU/L]	26	49.17	-23.17 [-101.07, 54.72]	0.5385
ALP [IU/L]	58.5	159.47	-100.97 [-252.15, 50.20]	0.1768
Total bilirubin [mg/dL]	0.55	0.85	-0.30 [-2.28, 1.67]	0.7508
CA19-9 [U/ml]	7.37	208.45	-201.07 [-406.37, 4.22]	0.0542
CEA [ng/ml]	3.77	110.75	110.75 [-266.35, 52.38]	0.1707
AFP [IU/ml]	2.18	6.71	-4.53 [-10.72,1.64]	0.1292
Hematocrit (%)	40.75	33.95	6.8 [0.13, 13.46]	0.0463
NLR	2.53	4.07	-1.54 [-6.32, 3.22]	0.5037
PLR	130.37	179.74	-49.37 [-300.84, 202.10]	0.6839
Imaging finding				
Location Left Lobe N,%	1 [50%]	6 [28.57%]	0.14 [-0.36, 0.20]	0.5291
Maximum mass size (cm)	4.7	11.11	-6.41 [-17.73, 4.89]	0.2514



Pathology	1-year survival	3-year survival	5-year survival
IHD stones	100%	75% (12.79 - 96.05)	75% (12.79 - 96.05)
Parasitic infection	100%	85.71% (33.41 -97.86)	71.43% (25.82- 91.98)
Hemangioma	100%	100%	100%
Simple cyst	100%	100%	100%
Non-specific inflammation	100%	84.85% (67.36 -93.40)	84.85% (67.36 -93.40)

Figure 3. Kaplan–Meier Survival Curve of Patients with Benign Conditions Treated by Hepatic Resection Stratified by Pathological Diagnosis

cystic lesion [10, 15]. We found that NLR and CA19-9 level predicted the chance of malignancy very well. This finding is consistent with our previous report that NLR was a likely candidate for predicting malignancy, lymph node involvement, and survival of bile duct tumor, especially in patients with micro-papillary lesions, which are difficult to differentiate from benign conditions [18]. Having only a few markers able to differentiate benign from malignant biliary dilatation, we thus suggest that unexplained biliary dilatation should be extensively searched for the actual diagnosis, especially in a region that has a high incidence of CCA. Cholangioscopy, either per-orally or intraoperatively, is the best way to determine the actual cause of biliary dilatation. Eventually, if the chance of CCA was not fully eliminated after the patient being fully investigated, hepatic resection is an acceptable option [7, 9].

We found that neoplastic cysts tended to be of larger size, with more abdominal pain. The reason for this is the slow-growing nature of non-neoplastic cysts, which would distend the liver capsule gradually, compared with a more rapid enlargement of a neoplastic cyst. This is in line with the findings from a previous study that there was a correlation between lesion size and symptom intensity [11]. The small number of patients with benign cystic lesions in our series may account for a higher level of CA19-9 and CEA in neoplastic cyst, which was not statistically significant. Benign cystic lesions rarely mimic neoplastic cysts, eventually leading to therapeutic misadventures with undergoing hepatic resection, because these lesions are usually clearly described on cross-sectional imaging. Treatment for hepatic cystic lesions is different between neoplastic and non-neoplastic cysts. Neoplastic cysts, including cystic-IPNB and hepatic mucinous cystic neoplasm (hMCN), require formal hepatic resection [10], whereas non-neoplastic cysts require de-roofing only when the patient has symptoms. The breaking of neoplastic cysts, either by cyst de-roofing or aspiration, may lead to dissemination of the tumor cells, resulting in worsening of the patient survival. Selection of the operative procedure for the patient with cystic lesions usually relies mainly on imaging, because percutaneous biopsy and cholangioscopy are unable to be performed in this setting. We therefore recommend that standard hepatic resection, rather than de-roofing, should be performed if the chance of neoplastic cyst is not fully eliminated.

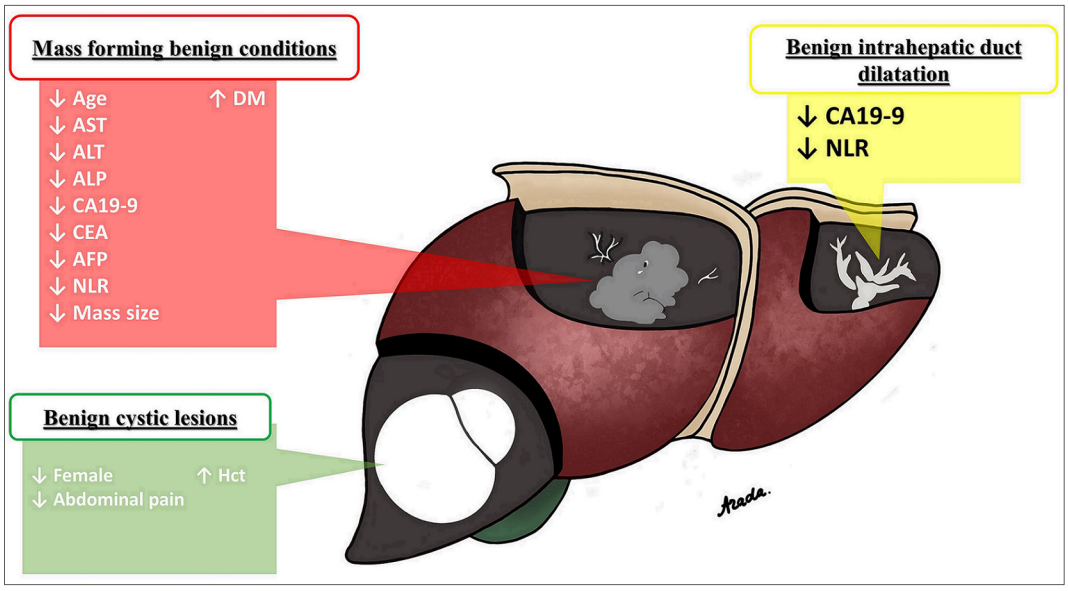


Figure 4 Schematic Illustration Summarizing the Characteristic Differences between Benign Conditions and CCA, According to Imaging Appearances

To the best of our knowledge this is the first and the largest study demonstrating the differences between benign conditions and CCA. The stratification according to main imaging finding is practical for the real-life situation. Moreover, we followed up the patients long enough to assure long-term outcomes of benign conditions. We intended to conduct this study over the period when our center performed all hepatic resection by open surgery, which allowed the surgeon to re-evaluate the lesions intraoperatively before performing hepatic resection. This simulated a real-life situation in most low to middle income countries. However, this study had some limitations. First, the retrospective nature from a single center may introduce some selective biases. Second, we were unable to obtain actual pathological diagnoses in the patients with non-specific inflammation. Lastly, during the study period, there was no uniform treatment protocol at our center, so the decisions regarding operative procedure were subjective. Moreover, most recent imaging technologies and interventions, allowing surgeons to make more accurate diagnoses, were not available at that time.

In conclusion, this study provides a view of benign conditions mimicking CCA. We found that the proportion of hepatic resection for these conditions was quite low, only 3.78%. There were many characteristic differences used to differentiate benign mass-forming conditions from CCA. We recommend to perform biopsy in young patients with small (<5 cm) mass, especially those with normal liver functions and tumor markers. However, only a few markers were able to differentiate benign from CCA in the setting of cystic lesions and biliary dilatation. We recommend that standard hepatic resection be performed in every case, regardless of the type of imaging features, if the lesion has a chance of being CCA.

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Conflict of Interests

All authors disclose that there was no conflict of interests for this article.

Statement of Informed Consent

If identifying information about participants is available in the article Informed consent: Additional informed consent was obtained from all individual participants for whom identifying information is included in this article.

Authors' contributions

All authors contributed to the study conception and design. Material preparation, data collection and analyses were performed by Thitiporn Wannasri and Vor Luvira. The first draft of the manuscript was written by Vor Luvira, Thitiporn Wannasri and Arada Wongwattanachai, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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