RESEARCH ARTICLE

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Characteristics of Previously Undetected or Newly Emerging Cholangiocarcinoma Detected by Ultrasound Surveillance in an Endemic Area

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Abstract

Background and Aim: Cholangiocarcinoma (CCA) is an aggressive biliary malignancy with poor prognosis, largely due to delayed diagnosis. In endemic regions, abdominal ultrasonography is a rapid, inexpensive, and widely available surveillance tool that may support earlier detection. However, some lesions are missed at initial screening and detected only on follow-up. This study aimed to characterize the sonographic features and anatomical distribution of previously undetected or newly identified CCAs detected through an ultrasound-based surveillance program. **Methods:** We retrospectively reviewed patients diagnosed with CCA through an abdominal ultrasound surveillance program in Nan Province, Thailand, between 2011 and 2017. Ultrasound findings and lesion locations were analyzed. All patients underwent confirmatory computed tomography or magnetic resonance imaging at Chulabhorn Hospital, with pathological confirmation of CCA. Descriptive and comparative analyses were performed. **Results:** Thirty-nine patients with 41 lesions were identified after a negative ultrasound examination 6 months earlier. Sonographic patterns included isolated hepatic masses, hepatic masses with bile duct dilatation, focal segmental bile duct dilatation, diffuse bile duct dilatation, and intraductal nodules. The most common presentations were isolated liver masses, liver masses with bile duct dilatation, and focal peripheral bile duct dilatation. Lesions were predominantly located in the peripheral intrahepatic bile ducts, especially second-order branches in hepatic segments VI and VII. **Conclusions:** Previously undetected or newly identified CCAs during ultrasound surveillance most commonly appear as small hepatic nodules or focal bile duct abnormalities arising from peripheral and second-order intrahepatic bile ducts, particularly in posterior right hepatic segments VI-VII. These patterns may reflect both liver fluke-associated cholangiocarcinogenesis and technical limitations of ultrasonography in hepatic blind areas. Careful evaluation of these high-risk regions and awareness of subtle signs, including small hyperechoic nodules and focal ductal dilatation, may improve early detection and optimize surveillance in endemic populations.

Keywords: Cholangiocarcinoma, Liver Fluke, Ultrasound characteristics of Cholangiocarcinoma

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Introduction

Cholangiocarcinoma (CCA) is an aggressive malignancy of the biliary epithelium and is associated with a poor prognosis. Most patients present for diagnosis and treatment at an advanced stage of disease, at which point curative surgical resection is often not feasible [1]. Clinically, the most common presenting manifestations include obstructive jaundice and scleral icterus caused by biliary tract obstruction, which frequently prompt further evaluation with abdominal ultrasonography.

The incidence of CCA is particularly high in the northern and northeastern regions of Thailand, where it constitutes a significant public health burden and contributes substantially to regional mortality rates [2-4]. A major etiological factor in these endemic areas is chronic infection with liver flukes acquired through the consumption of undercooked or raw freshwater fish. The International Agency for Research on Cancer has identified Opisthorchis viverrini as a Group 1 carcinogen, with strong evidence supporting its causal role in the development of CCA in humans, particularly in Southeast Asian countries where infection are prevalent [3, 5, 6].

Within Thailand, Nan Province has been reported to have a higher incidence of liver cancer, including CCA, compared with surrounding regions [7]. In

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response to this disease burden, Chulabhorn Hospital initiated an abdominal ultrasound–based surveillance program for early detection of CCA among the local population of Ban Luang District, Nan Province. Findings from this surveillance program demonstrated that ultrasonography provides a rapid method for identifying hepatobiliary abnormalities at an early stage, enabling earlier intervention and potentially improving patient survival [2, 8]. Consequently, ultrasonography has become the primary imaging modality for CCA surveillance in endemic areas [2, 3].

Ultrasound examination is a cost-effective [9], safe, and non-invasive technique that serves as a first-line imaging modality for the evaluation of abdominal organs [10]. Despite its clinical importance, ultrasonography has inherent limitations that may result in inaccurate characterization or failure to detect lesions. These limitations include operator dependency and variable experience, unfavorable tumor location, acoustic artifacts caused by bowel gas or adjacent lung tissue, obscuration of small lesions by ribs or other osseous structures, and suboptimal image quality related to equipment performance [11, 12]. Typical sonographic manifestations of CCA include focal or diffuse bile duct dilatation, hepatic nodules with associated biliary dilatation, and intraductal lesions [2]. During longitudinal surveillance, a substantial number of new CCA cases were identified at each follow-up interval, representing either newly developed malignancies or pre-existing lesions that were not detected during prior ultrasound examinations.

This study aimed to investigate the sonographic characteristics and anatomical locations of CCAs that were either newly developed or previously undetected during ultrasound-based surveillance. The findings are expected to provide valuable insights to improve recognition of disease patterns and high-risk lesion locations, thereby enhancing the effectiveness of future ultrasonographic surveillance programs for CCA in endemic regions.

Materials and Methods

Study Design and Population

This study was a retrospective observational study of participants enrolled in an ultrasound-based screening program for cholangiocarcinoma (CCA) surveillance conducted in northern Thailand. The surveillance cohort comprised 4,225 participants aged 30–60 years residing in Ban Luang District, Nan Province. All participants underwent abdominal ultrasound examinations at six-month intervals over a five-year period.

Ultrasound Examination Protocol

All ultrasound examinations were performed using a curved-array transducer with a frequency range of 2–5 MHz. Standardized abdominal ultrasound protocols were applied in all examinations. Image acquisition and interpretation were conducted by experienced radiologists with specialized expertise in abdominal and hepatobiliary imaging.

Diagnostic Confirmation

When ultrasound findings were suspicious for malignancy, participants were referred to Chulabhorn Hospital, Bangkok, for further diagnostic evaluation using contrast-enhanced computed tomography (CT) and/or magnetic resonance imaging (MRI). Definitive diagnosis of CCA was established by histopathological examination of tissue samples obtained through percutaneous core needle biopsy or surgical resection, performed at Chulabhorn Hospital.

Case Selection and Inclusion Criteria

During the five-year surveillance period, a total of 63 participants were diagnosed with CCA [2]. Lesions detected at the initial (baseline) screening examination were excluded from the present analysis to ensure inclusion of only lesions that were previously undetected. Eligible cases met all of the following criteria:

1. The lesion was first identified on an ultrasound examination after a prior ultrasound performed six months earlier showed no detectable abnormality.
2. Findings on CT or MRI were consistent with a diagnosis of CCA.
3. Histopathological analysis confirmed the diagnosis of CCA.

Ultrasound Image Analysis and Lesion Classification

A review of established ultrasound characteristics of CCA and related premalignant lesions revealed a spectrum of sonographic appearances, including focal or diffuse bile duct dilatation, hepatic masses with associated bile duct dilatation, and intraductal nodular lesions. Based on these features, detected lesions were classified into two main groups according to the presence or absence of a detectable tumor mass on ultrasound.

Group 1: Lesions Presenting as Nodules

Lesions presenting as nodules (mass-forming lesions) were characterized according to their sonographic echogenicity and classified as hypoechoic, hyperechoic, isoechoic, or heterogeneous. These nodular lesions were further subclassified based on their association with bile duct dilatation into the following categories:

- Nodular lesion without bile duct dilatation
- Nodular lesion with bile duct dilatation
- Intraductal nodular lesion with bile duct dilatation

The anatomical location of each nodular lesion was documented according to hepatic lobe and Couinaud segmental anatomy as follows: left lobe (segments II, III, IVa, and IVb), right lobe (segments V, VI, VII, and VIII), or segment I (caudate lobe).

Group 2: Lesions Without a Detectable Nodule

Lesions without a detectable nodular component on ultrasound were characterized by the presence of bile duct abnormalities, including focal segmental or diffuse bile duct dilatation. For these lesions, the involved biliary branches were documented with respect to their anatomical location and hierarchical ductal order as follows:

- First-order intrahepatic bile ducts: right and left main hepatic ducts, including the biliary confluence

• Second-order intrahepatic bile ducts: segmental branches arising from the first-order ducts (right anterior and posterior segmental branches; left medial and lateral segmental branches)

• Peripheral intrahepatic bile ducts: small biliary duct branches within individual liver segments [13]

• Extrahepatic bile ducts: including the common hepatic duct (CHD) and common bile duct (CBD)

Data Analysis

Ultrasound characteristics and anatomical locations of CCA lesions were recorded in a dedicated database. Comparative analyses were performed between the two lesion groups to evaluate differences in imaging features and lesion distribution. The ultrasound features assessed in each group are summarized in Table 1.

Results

The ultrasound surveillance program enrolled 4,225 adult participants between 2011 and 2017. During the five-year follow-up period, 63 participants were diagnosed with cholangiocarcinoma (CCA). Retrospective analysis demonstrated that clinical or imaging data were incomplete for 11 patients. Consequently, 52 patients had complete datasets available for evaluation. Among these, 13 patients were diagnosed with CCA at the initial (baseline) ultrasound examination and were therefore excluded from further analysis. A total of 39 patients met the study inclusion criteria and were included in the final analysis (Figure 1).

The final dataset comprised 41 CCA lesions identified in 39 patients. Of these lesions, 25 (61.0%) presented as nodular lesions, while 16 (39.0%) did not demonstrate a discrete mass. Among the lesions presenting as nodules, 18 (72.0%) measured less than 3 cm in maximum diameter, whereas 7 (28.0%) measured 3 cm or greater. Two patients exhibited two distinct lesion patterns concurrently, consisting of focal segmental bile duct dilatation and diffuse bile duct dilatation (Table 1).

The sonographic characteristics of the 41 CCA lesions were categorized as follows: nodular lesion without bile duct dilatation in 13 lesions (31.70%); nodular lesion with bile duct dilatation in 11 lesions (26.83%); focal segmental bile duct dilatation without a detectable mass in 11 lesions (26.83%); diffuse bile duct dilatation in 5 lesions (12.20%); and intraductal lesion in 1 lesion (2.44%). The distribution of echogenicity patterns is summarized in Table 2 and was comparable between nodular lesions with and without associated bile duct dilatation.

Regarding anatomical distribution, the majority of lesions (77.1%) were located in the right hepatic lobe (Figure 2). Most of these were situated in the right posterior segments, with an approximately equal

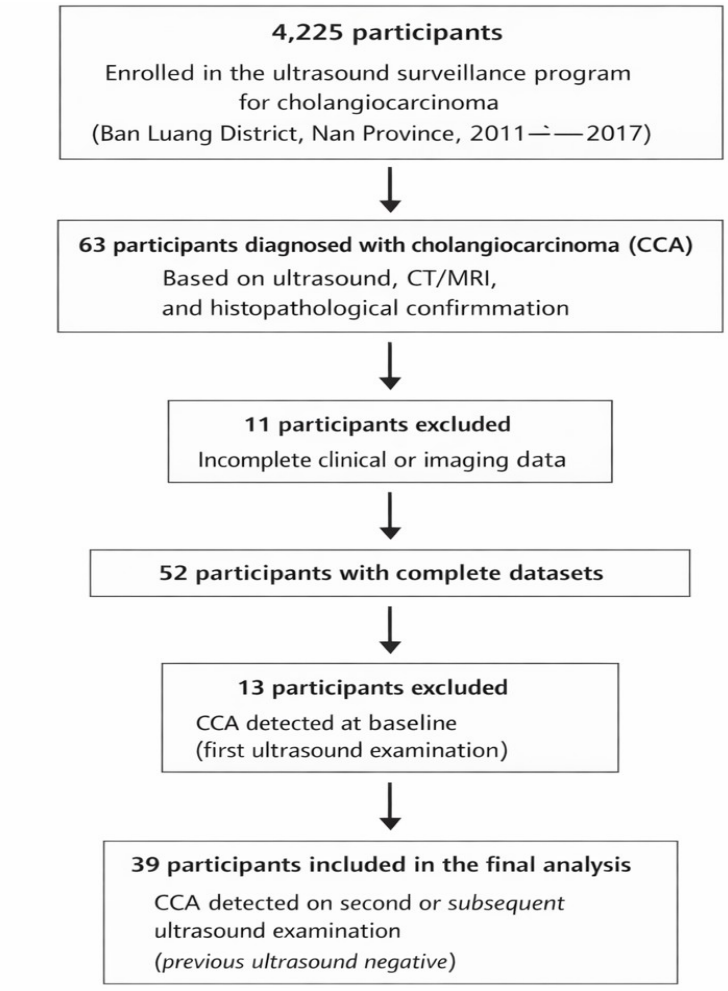

Figure 1. Flow Diagram of Subject Selection for Analysis

Table 1. Basic Information on CCA Patients (39 Patients, 41 Lesions)

Variable	
Gender	Number (%)
Female	20 (51.30%)
Male	19 (48.70%)
Mean age	Years (+ SD)
Female	53.5±4.66
Male	51.89±7.14
Total	52.72±5.97
Size of mass	Number (%)
< 3 cm	18 (72.00%)
≥ 3 cm	7 (28.00%)
Lesions per person	Number (%)
1 lesion	37 (94.87%)
2 lesions	2 (5.13%)
Total	41

Table 2. Characteristics of CCA Lesions on Ultrasound Images in Relation to CT/MRI in 41 Lesions (39 Patients)

Characteristics of lesions on ultrasound images	Number (%) of lesions
Isolated Liver nodule (n = 13)	
Hyperechoic	7 (53.80%)
Hypoechoic	3 (23.10%)
Isoechoic	0 (0%)
Heterogeneous	3 (23.10%)
Liver nodule with bile duct dilatation (n = 11)	
Hyperechoic	6 (54.54%)
Hypoechoic	2 (18.18%)
Isoechoic	1 (9.10%)
Heterogeneous	2 (18.18%)
Intraductal nodule	1 (2.44%)
Focal segmental bile duct dilatation	11 (26.83%)
Diffuse bile duct dilatation	5 (12.20%)

distribution between segments VI and VII. One lesion was located outside the liver, involving the common bile duct.

Among the 41 lesions, 28 resulted in either focal or diffuse bile duct dilatation. Of these, 11 lesions involved second-order intrahepatic bile duct branches, and 7 involved small peripheral intrahepatic bile duct branches (Figure 3). The majority of ductal abnormalities were located in the right hepatic lobe, particularly within the posterior segmental regions. Only one case of bile duct dilatation attributable to CCA was observed in an extrahepatic location (Figure 3).

Discussion

In Thailand, the highest incidence rates of cholangiocarcinoma (CCA) are observed in the northern and northeastern regions, largely attributable to chronic infestation with the liver fluke Opisthorchis viverrini [14, 15]. The pathogenesis of CCA in these endemic areas involves several interrelated mechanisms. First, liver flukes attach to the bile duct epithelium, causing mechanical irritation and chronic inflammation, which in turn stimulates tissue injury and repair processes. These repetitive cycles of injury and regeneration alter the immune microenvironment and promote persistent inflammatory changes within the biliary epithelium. Second, excretory–secretory (ES) products released by the parasites induce epithelial cell alterations, including adenomatous hyperplasia and goblet cell metaplasia. These altered cells secrete various cytokines and mucins, and prolonged stimulation may result in excessive mucus production, leading to biliary obstruction and ductal dilatation. In addition, parasite-induced immune responses promote periportal fibrosis. Third, fibrosis and chronic inflammation stimulate the release of nitric oxide and reactive oxygen species, which can cause DNA damage

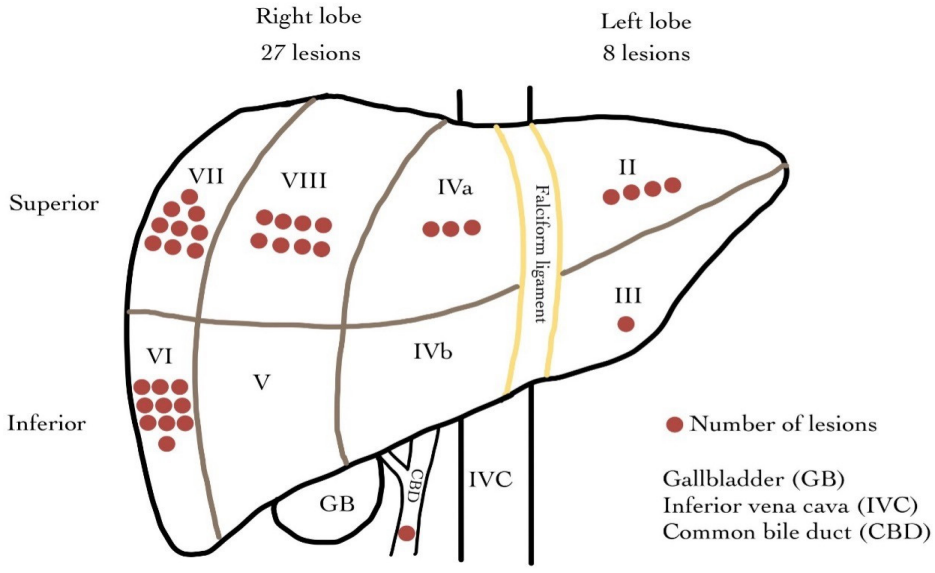

Figure 2. Locations of CCA Lesions Detected by Hepatic Ultrasound based on CT/MRI Images

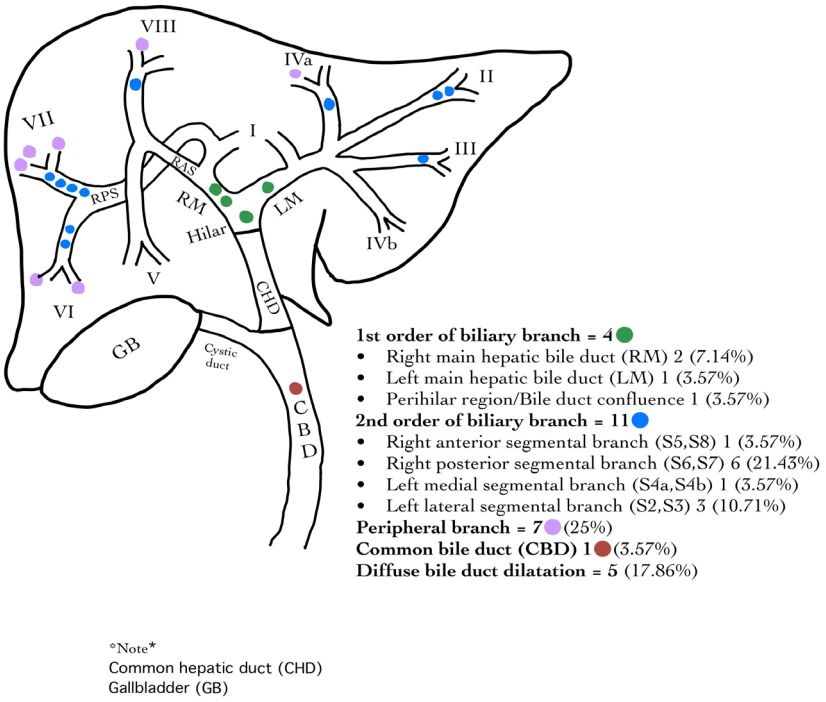

Figure 3. Branch Locations of Bile Duct Dilatations associated with CCA Lesions

to biliary epithelial cells, impair DNA repair mechanisms, and generate oncogenic mutations that ultimately contribute to carcinogenesis [16-18].

The World Health Organization (WHO) classifies CCA-associated premalignant lesions into two main categories: biliary intraepithelial neoplasia (BilIN) and intraductal papillary neoplasm of the bile duct (IPNB).

On ultrasound imaging, biliary intraepithelial neoplasia (BilIN) most commonly presents as focal bile duct dilatation, reflecting its underlying pathology of epithelial thickening and dysplastic change along the bile duct lining. Because BilIN is a microscopic, non–mass-forming lesion confined to the biliary epithelium, it does not produce a discrete intraductal mass. Instead, progressive epithelial thickening and associated periductal inflammation may result in partial luminal narrowing and upstream ductal dilatation, which is often subtle and localized, particularly in peripheral intrahepatic bile duct branches.

In contrast, intraductal papillary neoplasm of the bile duct (IPNB) is characterized by papillary proliferation of biliary epithelial cells with fibrovascular stalks, leading to the formation of macroscopic intraductal tumor nodules and abundant mucin production [19, 20]. Excessive mucin secretion contributes to diffuse, fusiform, or cystic bile duct dilatation, which may involve both intrahepatic and extrahepatic bile ducts. Ultrasonographically, IPNB demonstrates a wide spectrum of appearances, ranging from focal bile duct dilatation with visible intraductal

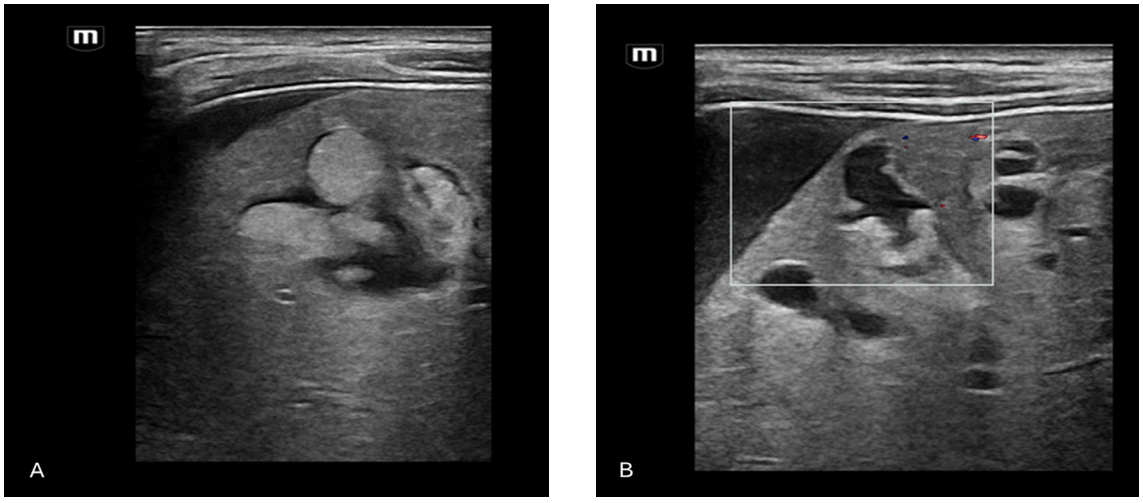

Figure 4. US Images of the Early Cholangiocarcinoma. (A) Gray scale US reveals a hyperechoic intraductal nodule of peripheral intrahepatic duct. (B) Doppler US shows a focal hyperechoic periductal nodule causing focal duct dilatation without vascularity.

nodules to diffuse ductal dilatation with or without identifiable solid components. The intraductal nodules of IPNB are frequently hyperechoic on ultrasound. This echogenicity is attributed to multiple acoustic interfaces created by the papillary tumor surface, mucin, bile fluid, and the bile duct wall, resulting in increased internal reflectivity. In more advanced cases, IPNB may appear as complex cystic lesions that communicate with the biliary tree, further supporting the diagnosis [20-22].

Progression from premalignant lesions to invasive CCA occurs when abnormal epithelial cells breach the basement membrane and infiltrate hepatic parenchyma [23]. The Liver Cancer Study Group of Japan classifies CCA morphologically into three major types: periductal infiltrating, intraductal tumor, and mass-forming types [24]. Periductal infiltrating tumors, commonly associated with BilIN, cause circumferential bile duct wall thickening and luminal narrowing, resulting in upstream bile duct dilatation, particularly in perihilar and distal CCA. In contrast, IPNB-related tumors predominantly grow within dilated bile ducts [21]. With disease progression, both lesion types may enlarge to form visible hepatic nodules accompanied by bile duct dilatation, hepatic atrophy, and capsular retraction [25, 26]. These changes are thought to arise from liver fluke–induced stimulation of cholangiocytes within small bile duct branches and terminal ductules, including the canals of Hering [27]. Importantly, early malignant transformation within the liver may occur without significant bile duct dilatation, rendering such lesions difficult to detect on ultrasound.

This study demonstrated characteristic ultrasonographic features of CCAs that were either previously undetected during surveillance or newly emerged at follow-up. The most frequent sonographic pattern was an isolated liver nodule, which was commonly hyperechoic, followed by liver nodules with bile duct dilatation and focal segmental bile duct dilatation without a detectable mass (Figure 4). Most intrahepatic CCAs in this cohort involved second-order biliary branches or peripheral bile ducts. These findings contrast with reports from East Asian countries such as China, Korea, Japan, and Taiwan, where CCA is more frequently associated with Clonorchis sinensis infection [18, 28, 29]. C. sinensis is larger than O. viverrini, measuring approximately 10–25 mm, whereas O. viverrini typically measures 5–10 mm, with an average length of approximately 7 mm [30, 31]. The smaller size of O. viverrini may allow migration into more distal bile duct branches, resulting in inflammation, cholangitis, and subsequent malignant transformation in peripheral intrahepatic ducts.

In Western countries, the etiology of CCA differs substantially, with primary sclerosing cholangitis identified as a major risk factor. As a result, the imaging characteristics and anatomical distribution of CCA may differ from those observed in parasite-endemic regions. Importantly, early-stage intrahepatic CCA may mimic benign hepatic lesions on ultrasound, particularly hemangiomas. Both lesions may appear as hyperechoic nodules; however, CCA often demonstrates a peripheral hypoechoic halo, irregular margins, or associated bile duct changes. Awareness of this pitfall is essential, as misinterpretation may delay diagnosis and appropriate follow-up.

Interestingly, CCA lesions in this study were most frequently located in the posterior segments of the right hepatic lobe (segments VI and VII). This distribution is consistent with findings from previous studies conducted in Southeast Asian populations, including Thailand and Laos, where liver fluke–associated biliary tract malignancies are endemic [32-34]. These studies similarly demonstrated the predominance of premalignant lesions and cholangiocarcinoma arising from small intrahepatic bile duct branches within the posterior right lobe. In contrast, studies by Kim et al. [35] and Gordon-Weeks et al. [36], which primarily investigated intraductal papillary neoplasm of the bile duct (IPNB) in populations infected with Clonorchis sinensis, reported a higher frequency of lesions involving the left hepatic lobe. Such discrepancies may be attributable to differences in parasite morphology and size, which could influence migration behavior and preferential colonization of bile ducts with larger calibers, such as the left hepatic duct or the perihilar region.

In addition to parasitic factors, anatomical characteristics of the biliary tree may contribute to the observed lesion distribution. The posterior sectoral bile duct courses relatively horizontally and then bends posteriorly before joining the right hepatic duct, a configuration that may facilitate parasite retention or lodging within these branches (Figure 3). Body position and gravitational effects may also play an important role in parasite migration and localization. In the supine position, particularly during prolonged periods such as sleep, the posterior segments of the right hepatic lobe represent a relatively gravity-dependent region within the intrahepatic biliary system. This positional dependency may facilitate passive movement or settling of parasites into the posterior branches of the right intrahepatic bile ducts. Together, these anatomical, gravitational, and parasitic factors may explain the predilection for lesions to arise in the posterior right hepatic segments observed in this and other endemic-area studies.

Detection of lesions in the posterior segments of the right hepatic lobe remains challenging on ultrasound, particularly when lesions are located in the hepatic dome or subcapsular regions that are distant from the transducer and frequently obscured by ribs or adjacent lung tissue. These regions are well recognized as ultrasonographic "blind areas" of the liver [37] and require optimal patient cooperation, including controlled respiration and positional adjustments, as well as meticulous scanning technique to improve visualization. In this ultrasound surveillance study conducted in a cholangiocarcinoma-endemic region, previously undetected or newly emerging CCAs most commonly presented as small hepatic masses or focal bile duct abnormalities involving peripheral and second-order intrahepatic bile ducts, with a marked predilection for segments VI and VII. Awareness of these high-risk anatomical sites, subtle sonographic patterns, and inherent ultrasonographic limitations is therefore essential to minimize missed lesions and enhance the effectiveness of ultrasound-based CCA surveillance in endemic populations.

This study has several limitations. First, the relatively small sample size and the single-center design may limit the generalizability of the findings to other endemic regions or healthcare settings. Although the cohort reflects real-world ultrasound surveillance in a high-risk population, lesion characteristics and anatomical distributions observed in this study require validation in larger, multicenter cohorts with broader demographic and epidemiologic representation. Second, the retrospective nature of image review may be subject to selection and information bias, and inter-operator variability in ultrasound acquisition and interpretation could not be fully controlled. Future multicenter studies are warranted to confirm these findings.

In conclusion, this surveillance study in a cholangiocarcinoma-endemic region shows that CCAs missed at baseline or newly detected during follow-up most often present as small hepatic nodules or subtle bile duct abnormalities arising from peripheral and second-order intrahepatic bile ducts, with a predilection for the posterior right hepatic segments (VI–VII). These patterns may reflect both liver fluke–associated cholangiocarcinogenesis and technical limitations of ultrasound in hepatic blind areas, which may explain why early lesions are overlooked. Focused evaluation of these high-risk regions and increased awareness of subtle sonographic signs, including small hyperechoic nodules and focal ductal dilatation, may improve early detection and refine ultrasound-based surveillance in endemic populations.

Author Contribution Statement

Study concept and design: Nutsurang Promrach and Surachate Siripongsakun. Acquisition of data:Nutsurang Promrach, Saowalak Chonyuen, Jitsupa Sritasan Surachate Siripongsakun. Analysis and interpretation of data: Nutsurang Promrach, Pooriput Waongenngarm, Surachate Siripongsakun. Drafting the manuscript:Nutsurang Promrach, Nannapat Nuangchamnong, Pantajaree Hiranrat, Pooriput Waongenngarm, Surachate Siripongsakun. Critical revision of the manuscript:Nutsurang Promrach, Nannapat Nuangchamnong, Pantajaree Hiranrat, Pooriput Waongenngarm, Surachate Siripongsakun.

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Ethical declaration

The project was approved by the Ethics Committee for human research of Chulabhorn Research Institute (certificate no.016/2566)

Data availability

The data that support the findings of this study are available on request from the corresponding author (SS). The data are not publicly available due to ethical restrictions.

Abbreviations used in this paper

Biliary intraepithelial neoplasm (Bil-IN), Cholangiocarcinoma (CCA), Computed tomography (CT), Excretory-secretory products (ES products), Intraductal papillary neoplasm of the bile duct (IPNB), Magnetic resonance imaging (MRI), Opisthorchis viverrini (O. viverrini), Ultrasonography (US), World Health Organization (WHO).

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