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Clinical and Imaging Features of a Focal Intrahepatic Biliary Stricture Visualized Only as Duct Dilatation

영상검사에서 폐쇄성 종괴 및 벽 비후가 없는 국소간내담관협착 환자의 병리적-영상의학적 관계

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Purpose We assessed the proportion of patients with a focal intrahepatic stricture (FIHS) that was a precursor lesion or malignancy and visualized only as a duct dilatation.

Materials and Methods This retrospective study assessed patients who underwent surgery or biopsy for an FIHS on CT or MRI between January 2010 and March 2022. The number and proportion of non-precursor benign lesions, precursors, and malignancies were calculated. Clinical variables and imaging features were compared between non-premalignant benign and premalignant/malignant FIHSs.

Results Twenty-eight patients with confirmed histopathological diagnoses were identified, including 15 men (54.0%) and 13 women (46.0%). The median age of all patients at the first imaging diagnosis was 65 ± 9.54 (range, 43–78) years. Of the 28 patients with FIHSs, 9 (32%) were diagnosed with cholangiocarcinoma and 7 (25%) were diagnosed with precursor lesions, which included six intraductal papillary neoplasms of the bile duct and one biliary intraepithelial neoplasm. Accordingly, 16 (57%) patients had malignant or precursor lesions, and 12 (43%) were diagnosed with non-precursor benign lesions. None of the clinical variables and imaging features used for analysis showed a statistically significant difference between the non-premalignant benign and premalignant/malignant FIHS groups ($p > 0.05$).

Conclusion FIHSs visualized only as duct dilatation can harbor malignant or precursor lesions.

Index terms Bile Duct; Biliary Stricture; Malignancy; Cholangiocarcinoma; Magnetic Resonance Imaging

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INTRODUCTION

Biliary strictures refer to luminal narrowing of intrahepatic or extrahepatic bile ducts. When the bile duct narrows, bile flow is impeded, resulting in clinical symptoms and biochemical evidence of bile duct obstruction (1). However, focal intrahepatic strictures (FIHSs) involving the small and medium intrahepatic bile ducts are often asymptomatic (2). They are often incidentally detected on imaging studies performed for other reasons (3). In recent decades, as the number of CT and magnetic resonance imaging (MRI) scans has increased, interest in FIHSs without radiographically demonstrable bile duct abnormalities but only visualized as duct dilatation on imaging studies is increasing. However, the percentage of FIHS cases that can harbor precursor lesions or malignancies is currently unknown. Moreover, it is unknown whether there is a variable to differentiate malignant or precursor lesions from non-precursor benign lesions.

In the last 20 years, pathologists have identified two types of premalignant lesions that are considered precursors of cholangiocarcinoma (CCA): biliary intraepithelial neoplasm (BilIN) and intraductal papillary neoplasm (IPNB) (4). Lesions in BilIN are flat, less than 2–3 mm in length, and microscopically epithelial lesions. Therefore, they cannot be detected via imaging studies (5). Further, up to 10 percent of IPNBs may not be detectable on imaging studies (6). Therefore, diagnosis completely depends on pathologic studies, and the two types of lesions can be visualized as FIHSs without a visible mass on imaging study. As interest in the precursors of CCA is increasing, concerns regarding FIHSs are also increasing.

Although several previous studies have reported on the pathology of FIHSs, they are studies with small cohorts or that did not include MRI data. There is no report as to the proportion of precursor lesions that are present in FIHSs (3, 7-14). Therefore, we studied the proportion of FIHSs without radiographically demonstrable bile duct abnormalities, but only visualized as duct dilatation, that were precursor lesions or malignancies. Additionally, we evaluated the clinical variables and imaging features of these patients to discriminate between non-premalignant benign and premalignant/malignant FIHSs.

MATERIALS AND METHODS

This retrospective observational study was approved by our institutional research ethics board, which waived the requirement for informed consent (IRB No. 2022-06-014).

STUDY POPULATION

Electronic health records (BESTCare, version 2.0, ezCaretech) were used to search for patients who underwent surgery or biopsy for intrahepatic bile duct strictures on CT or MRI between January 2010 and March 2022. Among these patients, those meeting the following criteria were excluded: 1) stricture involving primary biliary confluence, 2) radiological intrahepatic bile duct abnormality, 3) clinical, biochemical, or histological diagnosis of primary or secondary sclerosing cholangitis, 4) extrahepatic imaging abnormalities, including lymphadenopathy, and 5) any history of suspected malignancy. Radiological intrahepatic bile duct abnormality was defined as no visible bile duct wall thickening, hyper-/hypo-enhancement,

or attenuation/signal change in the area with the stricture on CT or MRI phases and sequences, including diffusion weighted images.

DATA COLLECTION AND IMAGING ANALYSIS

Two radiologists (each with 6 or more years of clinical experience in abdominal radiology) reviewed all patient images. The reviewers were blinded to the clinical features and pathological diagnoses. Patient CT or MRI scans without radiological intrahepatic bile duct abnormality, except bile duct dilatation, were evaluated for imaging features including the number of involved hepatic segments and lobes, presence, or absence of visible hepatolithiasis, transient hepatic attenuation difference, lobar/segmental hepatic atrophy, and abscesses. When there was a difference in interpretation between the two reviewers, they re-evaluated the images together and reached a consensus.

IMAGING TECHNIQUE

CT was performed using a 64- and 128-detector row CT scanner (Somatom Definition Somatom Definition AS and Somatom Definition Edge; Siemens Healthcare). CT images were obtained using the breath-hold technique at end-expiration and included non-enhanced, arterial, and portal venous phase images with a 3–5 mm slice thickness for all patients. The total volume of non-ionic iodinated contrast medium was stratified according to each patient's body weight (approximate rate, 2 mL/kg; maximum 150 mL), and an automatic power injector was used to deliver the agent intravenously (3 mL/s). Arterial phase images were obtained using a 10–15 s delay after aortic attenuation had reached 100 Hounsfield units. Portal venous phase images were obtained using a fixed 75 s delay. CT images were acquired at 100–120 kVp and reconstructed using filtered back projection with a 3 mm slice thickness.

MRI and MR cholangiopancreatography (MRCP) were performed using 1.5- and 3-T scanners (Magnetom Avanto and Magenetom Vida; Siemens Healthcare), respectively. Axial dual-echo T1-weighted breath-hold gradient-echo sequence for acquisition of in-phase and out-of-phase images, half-Fourier acquisition singe-shot turbo spine-echo T2-weighter axial and coronal images, diffusion-weighted images with a respiratory-triggered single-shot echo-planar imaging sequence with b values of 0, 50, 500, and 900 s/mm^2, and axial fat saturated T1-weighted gradient echo before and after administration of gadoxetic acid (Primovist; Bayer Schering Pharma, Berlin, Germany) were acquired. Contrast material was administered as a bolus at a dose of 0.025 mmol/kg body weight at a rate of 1 mL/s via a 22-gauge intravenous cubital line, followed by a 10-mL saline flush at the same flow rate, delivered using a power injector. Images in the arterial phase were obtained 5 s after the peak time determined using a test bolus technique, and portal venous phase, transitional phase, and hepatobiliary phase images were obtained 50 s, 3 min, and 20 min, respectively, after contrast material injection. Images were acquired in the transverse plane with a section thickness of 3–4 mm without any gaps that subsequently develop in the oblique-coronal plane. MRCP sequences were acquired prior to intravenous contrast injection, and respiratory-triggered and breath-hold 3D MRCP images were obtained.

JOURNAL of THE KOREAN SOCIETY of RADIOLOGY

STATISTICAL ANALYSIS

First, to determine the proportion of FIHSs that were precursors or malignancies, the number and proportion of non-precursor benign lesions, precursors, and malignancies were calculated.

Additionally, to evaluate the clinical variables and imaging features to discriminate between non-precursor benign and premalignant/malignant FIHSs, continuous data were calculated as the mean and standard deviation, and categorical data were reported as frequency and percentage. Continuous data were compared as the mean difference between the two groups by the independent *t*-test, and categorical data were compared as the proportional difference between the two groups using the chi-squared test. The variables included clinical variables (age, sex, white blood cell count, and total bilirubin, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, and carbohydrate antigen 19-9 [CA 19-9] levels) and imaging variables (number of involved hepatic segments and lobes, hepatolithiasis, transient hepatic attenuation difference, lobar/segmental atrophy, and hepatic abscess). All statistical analyses were performed using SPSS version 21.0 (IBM Corp., Armonk, NY, USA).

RESULTS

PARTICIPANT CHARACTERISTICS

A total of 262 patients who underwent surgery or biopsy for bile duct strictures were identified in the initial search. Among these patients, 234 with radiographically demonstrable bile duct obstructive masses were excluded. Within the cohort of patients exhibiting focal intrahepatic strictures, this study finally incorporated 28 individuals who pursued surgical intervention due to escalating bile duct dilatation or the manifestation of symptoms such as uncontrolled fever and pain (Fig. 1).

The demographic and clinical characteristics of the patients are summarized in Table 1. The study included 15 men (54.0%) and 13 women (46.0%). The median age of all the patients at the

Fig. 1. Flow diagram of patient selection.

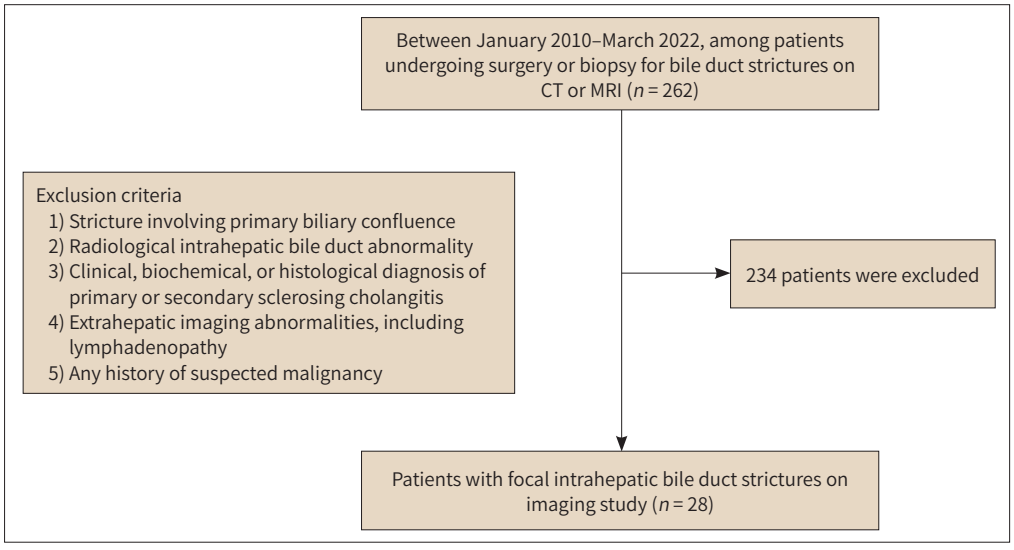

Table 1. Demographic and Clinical Characteristics of the Study Patients

Characteristics	Value
No. of patients	28
Age, median (range), years	65 (43–78)
Sex, no. (%)	
Male	15 (54)
Female	13 (46)
Underlying liver disease, no. (%)	
Hepatitis B	2 (7)
Hepatitis C	2 (7)
Clonorchis sinensis	1 (13)
None	23 (82)
Laboratory findings	
White blood cell count, median (range), $\times 10^3/mm^3$	7.595 (2.98–19.16)
Total bilirubin, median (range), mg/dL	0.755 (0.2–7.9)
Alkaline phosphatase, median (range), IU/L	232.5 (58–642)
Aspartate aminotransferase, median (range), IU/L	31 (16–317)
Alanine aminotransferase, median (range), IU/L	30 (9–158)
Cancer antigen 19-9, U/mL	18.91 (7.21–393.17)
Imaging modality, %	
CT	2 (7)
MRI	2 (7)
CT and MRI	24 (86)

Table 2. Histopathologic Diagnoses of the Study Patients

Histopathologic Diagnoses	*n* = 28 (%)		
Non-precursor benign lesion	12 (43)		
Precursor lesion			16 (57)
IPNB	6 (21)	7 (25)	
BilIN	1 (4)		
Cholangiocarcinoma	9 (32)		

BilIN = biliary intraepithelial neoplasm, IPNB = intraductal papillary neoplasm of the bile duct

first imaging diagnosis was 65 ± 9.54 years (range, 43–78 years). One patient received a preoperative diagnosis of malignancy through CT-guided biopsy, another experienced progressive bile duct dilatation after a 6-month interval, while surgical intervention was necessary for 26 patients who presented with symptomatic fever and pain (Supplementary Table 1). The imaging modalities used were CT and MRI in 24 (86%) patients, CT only in 2 (7%), and MRI only in 2 (7%) patients.

HISTOPATHOLOGIC DIAGNOSIS AND CLINICAL AND IMAGING VARIABLES FOR DIFFERENTIATING MALIGNANCY/PRECURSOR AND NON-PREMALIGNANT BENIGN FIHSS

The histopathological diagnoses of the study patients are summarized in Table 2. Of the 28

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patients with FIHSs, 9 (32%) were diagnosed with cholangiocarcinoma and 7 (25%) were diagnosed with precursor lesions. Among the precursor lesions, six were IPNBs, and 1 was BilIN. Therefore, 16 (57%) patients had malignant or premalignant lesions. Twelve (43%) patients were diagnosed with non-precursor benign lesions (Fig. 2).

No clinical variable or imaging feature used for analysis showed statistically significant differences between the non-premalignant benign and premalignant/malignant FIHS groups ($p > 0.05$), and these data are summarized in Table 3.

Further details of the histopathologic diagnosis and included variables are provided in Supplementary Table 1.

Fig. 2. Four different pathologic diagnoses in four different patients of focal intrahepatic strictures, visualized only as duct dilatation at the left lateral section.
A. A 78-year-old man with a non-premalignant benign lesion.
B. A 68-year-old woman with an intraductal papillary neoplasm with low grade dysplasia.
C. A 60-year-old man with high grade biliary intraepithelial dysplasia.
D. A 66-year-old man with a cholangiocarcinoma.

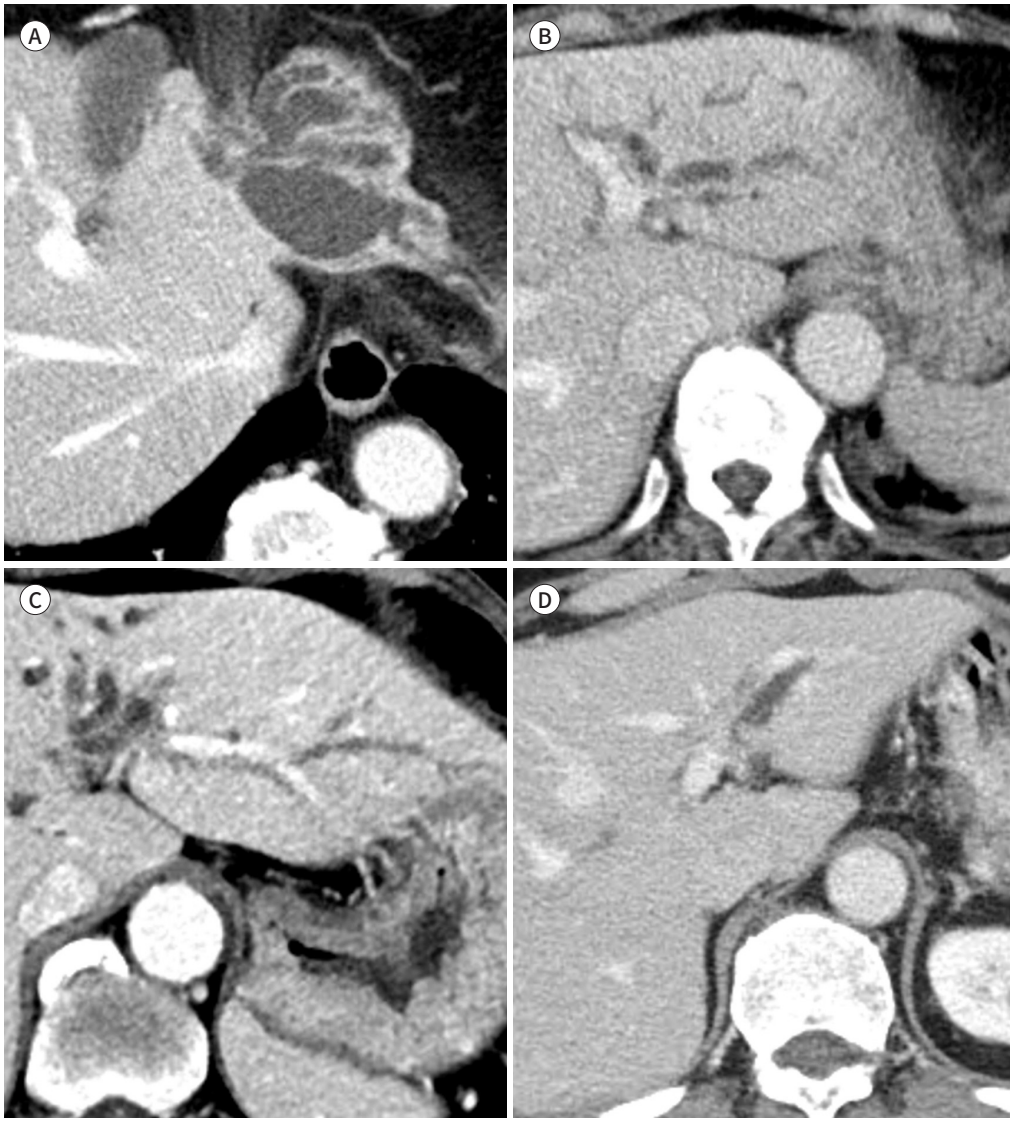

Table 3. Clinical and Imaging Features of Non-Premalignant Benign and Premalignant/Malignant Focal Intrahepatic Strictures

Variable	Non-Premalignant Benign (*n* = 12)	Premalignant/Malignant (*n* = 16)	*p*-Value
Clinical variables			
Age, years	64.0 ± 11.1	64.9 ± 9.3	0.834
Sex, no, (%)			0.165
Male	4 (33.3)	11 (68.8)	
Female	8 (66.7)	5 (31.3)	
WBC count	8.6 ± 4.5	9.5 ± 5.3	0.649
Total bilirubin	12.2 ± 36.5	6.4 ± 17.5	0.648
ALP	243.6 ± 96.2	255.5 ± 175.3	0.847
AST	60.5 ± 92.4	42.7 ± 32.2	0.571
ALT	38.3 ± 44.5	40.3 ± 30.6	0.893
CA 19-9	63.3 ± 97.0	63.4 ± 104.6	0.998
Imaging feature			
Number of involved hepatic segments, no. (%)			0.198
One	5 (41.7)	10 (62.5)	
Two	4 (33.3)	5 (31.3)	
Three	3 (25.0)	1 (6.3)	
Number of involved hepatic lobes, no. (%)			0.255
Right	5 (41.7)	13 (81.3)	
Left	7 (58.3)	3 (18.8)	
Hepatolithiasis, no. (%)	7 (58.3)	4 (25.0)	0.255
THAD, no. (%)	8 (66.7)	13 (81.3)	0.524
Lobar/segmental atrophy, no. (%)	4 (33.3)	3 (18.8)	0.924
Abscess, no. (%)	1 (8.3)	2 (12.5)	0.652

Data are presented as mean ± standard deviation, unless mentioned otherwise. To evaluate the clinical variables and MRI features to discriminate between non-premalignant benign and premalignant/malignant FIHSs, independent *t*-tests and chi-squared tests were used for continuous and categorical variables, respectively. A significance level of 0.05 was used.
ALP = alkaline phosphatase, ALT = alanine aminotransferase, AST = aspartate aminotransferase, CA = carbohydrate antigen, THAD = transient hepatic attenuation difference, WBC = white blood cell

DISCUSSION

In our study, we found that 57% of FIHSs visualized only as duct dilatation were precursor or malignant lesions, and 25% were IPNBs or BilINs, which are premalignant diseases. These values were lower than the malignant proportion reported in previous studies, which were 50.0% and 70.6%, respectively (3, 9). These earlier studies included patients with radiologically demonstrable bile duct abnormality or no described radiological feature. Therefore, malignancy should be included in more studies. Some studies reported imaging features of IPNBs (11-13) and classified them into four morphological subtypes (11): intraductal mass with only proximal duct dilatation, disproportionate duct dilatation without visible mass, intraductal mass with both proximal and distal duct dilatation, and focal aneurysmal ductal dilatation containing intraductal mass. However, these studies did not mention that FIHSs were visualized only as duct dilatation. Our study focused on FIHSs without radiologically demonstrable bile duct abnormalities and potentially included both IPNBs and BilINs. Moreover, there have

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been no reports on the proportion of FIHSs that are premalignant lesions.

It is generally accepted that CCA develops through a multistep carcinogenesis sequence, originating from transformed biliary epithelial cells or stem cells (15), similar to the tumorigenesis of colorectal cancer. Most cancers are considered to develop from preceding benign adenoma. Presently, the pathophysiology of cholangicarcinogenesis is poorly understood; however, chronic inflammation, bile flow obstruction, and bile duct injury are recognized as the main contributors to malignant transformation (16). In the last two decades, pathologists have identified two main precursors of invasive cholangiocarcinoma, BilINs and IPNBs, both of which were included in the 2019 WHO classification of tumors of the digestive system (4). However, there have been no studies on the proportion of precursors found in FIHSs. In the context of our investigation, a considerable proportion of FIHSs revealed imperceptible precursors, thereby imparting clinical significance to our findings in guiding treatment modalities and justifying early surgical intervention as a preventive measure against malignant transformations in patients with an extended life expectancy. Conventionally, in the absence of malignancy evidence amidst FIHS, a vigilant follow-up ensued. Should stability persist, affirming the benign nature of the stricture, surgical intervention is deemed unnecessary.

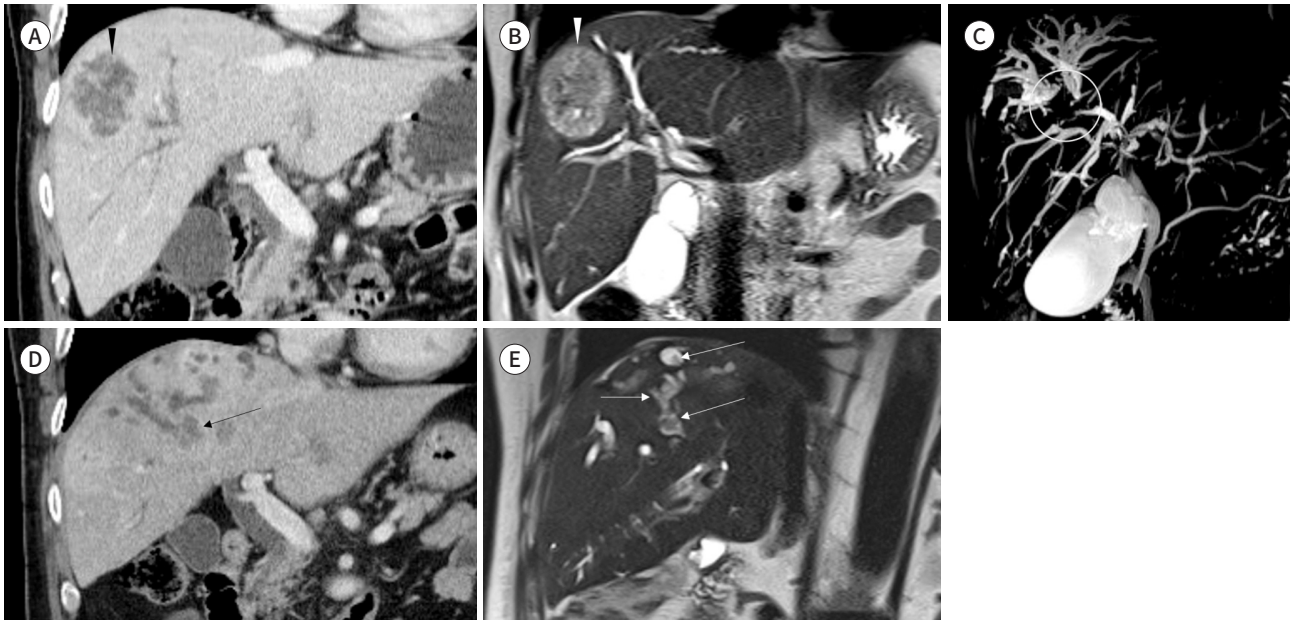
In our study, there were no clinical factors or significant secondary imaging findings for predicting malignant or premalignant lesions in FIHSs visualized only as duct dilatation. As previously reported, serum CA19-9 level is an effective tumor marker for the diagnosis of CCA (17). However, our study did not show a significant result. In FIHSs visualized only as duct dilatation, the tumor burden may be insufficient to increase the level of tumor markers, and biliary obstruction and cholangitis might serve as confounding factors (18). Furthermore, Kim et al. (3) suggested that wall thickening ≥5 mm and enlargement of lymph nodes ≥1 cm on CT were significant differential diagnostic markers for malignancy. However, in our study, demonstrable bile duct wall abnormalities and lymphadenopathy cases were excluded, and only secondary imaging features, such as hemodynamic change, hepatolithiasis, parenchymal atrophy, and involved hepatic lobe and segment number were included in the analysis, which differs from their study.

CCA is the most common malignancy of the biliary tract and has a poor prognosis. Surgery is the only potentially curative treatment option; therefore, early diagnosis is very important. Pathologic diagnosis is based on the accessibility and location of the biliary stricture. Various transluminal techniques for acquiring tissue from biliary tumors are used with endoscopic retrograde cholangiopancreatography (ERCP) and percutaneous transhepatic biliary drainage. Transluminal forceps biopsy is a widely used technique, in addition to brush cytology (19), and the reported sensitivity for malignant biliary stricture biopsy is 29%–81% (20) and 55.8%–93.3% (21) on ERCP and percutaneous transhepatic approaches, respectively. Unfortunately, no study of FIHSs visualized only as duct dilatation on imaging exists, and the sensitivity may be less than that reported, because of low tumor burden and desmoplastic reaction. For the reasons mentioned earlier, false-negative results may delay treatment, and the patient may lose the opportunity to receive potentially curative treatment. Although the natural course of FIHSs is unknown, in our study, more than half of FIHSs visualized only as duct dilatation had premalignant or malignant lesions. In one case in our study, imaging-guided biopsy was performed on an FIHS visualized only as duct dilatation with abscess, three at a

time, twice in total, and the pathologic results were fibroinflammatory lesions without tumors (Fig. 3A, B, C). The patient recovered and was discharged after treatment for hepatic abscess. However, six years later, the patient revisited our hospital for fever and jaundice, and the disease progressed. The patient was pathologically diagnosed with mass-forming intraductal cholangiocarcinoma at the FIHS site (Fig. 3D, E). Therefore, a continuous follow-up imaging study is required. In addition, because of the undefined possibility of an FIHS harboring a precursor or malignancy, surgical resection should be considered whenever malignancy is suspected during the diagnostic work-up and follow-up imaging study. Yeo et al. (22) proposed an interesting diagnostic and treatment algorithm for FIHSs. In this review, after a two-level diagnostic work-up, based on non-invasive and invasive diagnostic tools, cholangioscopy with or without biopsy should be performed in case of supposed benign stricture; if a benign stricture is confirmed, treatment should be reserved only for symptomatic patients and could be surgical or non-surgical. In one study, after performing 10 laparoscopic anatomic liver resections for FIHSs, Dagher et al. (7) maintained that laparoscopic treatment of FIHSs is safe. Although most of the patients in our study were of older age, surgery can be considered for patients with a greater life expectancy. This is especially recommended for easily accessible left lateral section lesions, considering more than half of FIHSs were premalignant or malignant lesions in our study.

There were several limitations to our study. The main limitation of our study is its retrospective design, and we only included pathologically diagnosed FIHSs. In addition, we excluded

Fig. 3. Progression to a cholangiocarcinoma, initially pathologically diagnosed as a non-precursor benign FIHS. The patient is a 76-year-old woman with an FIHS visualized only as duct dilatation.
A-C. Initial portal phase coronal CT and T2-weighed MRI show VII segmental bile duct dilatation with parenchymal abscess (arrowheads). Imaging-guided biopsy for stricture was performed, and the patient was pathologically diagnosed with a fibroinflammatory lesion without a tumor. Her symptoms improved after abscess drainage and antibiotic treatment, and she was discharged.
D, E. Six years later, the patient revisited for fever and jaundice, and a new intraductal mass (arrows) is evident on CT and MRI, and intraductal cholangiocarcinoma was pathologically diagnosed at the FIHS site.
FIHS = focal intrahepatic stricture



cases of subjectively recognizable radiological intrahepatic bile duct abnormality, which could have led to a selection bias. However, we aimed to investigate the pathological diagnosis of FIHSs visualized only as duct dilatation; therefore, this potential bias could not be avoided. Additionally, a relatively small number of patients were included. However, FIHSs are not commonly encountered in practice, and the largest numbers of pathological cases reported to date were enrolled. In the future, a prospective study to determine the natural course of FIHSs in a large cohort is needed.

In conclusion, FIHSs visualized only as duct dilatation can harbor malignant or precursor lesions. In addition, there were no predictive values for clinical and imaging parameters. Therefore, a more active strategy for diagnosis and follow-up imaging should be considered.

Supplementary Materials

The Supplement is available with this article at http://doi.org/10.3348/jksr.2023.0096.

Availability of Data and Material

The datasets generated or analyzed during the study are available from the corresponding author on reasonable request.

Author Contributions

Conceptualization, K.K.J., K.B.J.; data curation, K.M.J., L.H.W.; formal analysis, Y.J.H.; investigation, Y.J.H.; methodology, Y.J.H., P.C.H.; resources, P.J.H., P.C.H.; software, P.J.H., P.C.H.; supervision, K.B.J., P.J.H.; validation, L.H.W., L.G.; visualization, K.M.J., L.H.W.; writing—original draft, K.B.J., K.M.S.; and writing—review & editing, K.B.J.

Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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영상검사에서 폐쇄성 종괴 및 벽 비후가 없는 국소간 내담관협착 환자의 병리적-영상의학적 관계

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목적 본 연구는 영상검사에서 폐쇄성 종괴 및 벽 비후가 없는 국소간내담관협착 환자의 병리적 결과를 평가하기위해 설계되었다.

대상과 방법 2010년 1월부터 2022년 3월까지 국소간내담관협착으로 진단받고 수술적 치료 및 병리학적 진단을 받은 환자 중 담관 확장 외 폐쇄성 종괴 및 벽 비후가 없는 환자를 대상으로 하였다. 병리 결과와 임상적-영상의학적 연관성을 분석하였다.

결과 28명의 환자가 포함되었고 이 중 9명(32%)가 담관암종으로 진단되었고 7명(25%)이 전구체로 진단되었다. 전암성 병변 중 6명은 담관관내유두종양으로 진단되었고 1명은 담관상피내신생물로 진단되었다. 유의한 임상적-영상의학적 소견은 보이지 않았다.

결론 후향적 심전도 동기화 방법으로 촬영된 관상동맥전산화단층 영상을 이용하여 얻은 좌심실의 포괄적 기능 수치는 심초음파와 비교하여 신뢰할만한 결과를 얻을 수 있다.

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