Optimizing Distal Biliary Stricture Diagnosis: Endoscopic Ultrasonography for Undetected Masses on Cross-Sectional Imaging

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Background and study aim: Biliary strictures (BS), especially when associated with undetected masses on magnetic resonance imaging (MRI) or computed tomography (CT), present diagnostic challenges. Termed indeterminate biliary strictures (IBS), these cases necessitate accurate differentiation between benign and malignant causes. Endoscopic ultrasonography (EUS) is an advanced imaging modality with diagnostic and interventional capabilities that can help in better identification of IBS. This study aims to evaluate the accuracy of EUS in identifying the underlying causes of indeterminate biliary strictures (IBS). **Patients and Methods:** The study included 36 patients with distal common bile duct strictures and undetected masses on CT or MRI. EUS was employed to differentiate between benign and malignant strictures, and the final diagnosis was confirmed through histological examination. **Results:** EUS demonstrated a sensitivity of 90% and specificity of 71.4% in accurately identifying DBS without a tumor. After six months of follow-up, EUS maintained sensitivity and specificity rates of 87% and 100%, respectively. Malignant strictures were associated with significant weight loss and elevated levels of aspartate aminotransferase (AST), alanine transaminase (ALT), direct bilirubin, cancer antigen 19-9 (CA 19-9), and carcinoembryonic antigen (CEA).**Conclusion:** In summary, EUS emerged as a dependable diagnostic tool for patients with DBS and undetected masses on cross-sectional imaging, revealing small irregular hypoechogenic masses disrupting duodenal and bile duct layers, potentially indicative of malignancy.

INTRODUCTION

Biliary strictures [BS] pose a prevalent difficulty in gastrointestinal clinical practice. The most relevant and crucial distinction lies in classifying etiology as benign or malignant. Distinguishing between these two conditions frequently presents considerable difficulty in diagnosis and treatment, often necessitating thorough investigation[1]. Nevertheless, this distinction can provide substantial challenges in situations where no detectable mass on magnetic resonance imaging (MRI) or computed tomography (CT) could cause the stricture. In addition, when individuals with a detectable mass on MRI or CT are not considered, the benign strictures percentage is approximately 30%–50%[2]. Previously, the choice to perform surgery was typically made by considering the clinical history of the patient and stricture appearance on cholangiography. In some cases, it was necessary to surgically remove the stricture without prior confirmation of its nature to distinguish benign and malignant strictures[3]. However, identifying the underlying etiology of stricture using morphologic characteristics and brush cytology is undependable[4.[

For individuals with jaundice, endoscopic retrograde cholangiopancreatography (ERCP) represents the recommended initial procedure for both diagnosing and treating the condition.

To prevent complications associated with ERCP, magnetic resonance cholangiopancreatography [MRCP] has become a diagnostic alternative to ERCP[5]. Because endoscopic ultrasound (EUS) is now the preferred method for detecting undetected small pancreatic tumors using other imaging techniques and lacks the risk of complications associated with ERCP, it is necessary to explore further its effectiveness in distinguishing between malignant and benign biliary strictures[6]. Endoscopic ultrasonography (EUS) allows for detecting an undetected mass lesion using other imaging techniques and provides detailed imaging of the stricture morphology. Furthermore, it aids in staging by evaluating the vascular involvement and regional lymphadenopathy. In addition, EUS-guided fine-needle aspiration (EUS-FNA) can be employed for tissue acquisition[7.[

Accordingly, we aim to utilize EUS to improve distal biliary stricture (DBS) diagnosis in cases with an undetected mass on cross-sectional imaging.

PATIENTS AND METHODS

Patients

This study included a cohort of 36 patients who sought medical care at the outpatient clinics or were admitted to the Tropical Medicine Department, Endoscopy Unit, Zagazig University Hospitals in Sharkia, Egypt, spanning the period from October 2020 to October 2022. The demographic distribution comprised 16 males and 20 females with ages ranging from 40 to 75 years. Approval for the study was obtained from the Institutional Review Board (IRB) and the Tropical Medicine Department at Zagazig University. All participants provided informed consent before participation in the study. The inclusion criteria included the following: patients with [1] indeterminate DBS who were recruited based on elevated alkaline phosphatase (ALP) and gamma-glutamyl transferase (GGT) with or without jaundice as well as abdominal pain; [2] strictures in the distal half of biliary duct that ERCP or MRCP detected; [3] unidentifiable mass lesion that caused the stricture on CT or MRI[8]. Meanwhile, the exclusion criteria included patients with [1] ERCP or MRCP-detected strictures in the biliary tract along with CT or MRI-identifiable mass lesion causing the stricture; [2] strictures at the proximal bile duct due to the already established lower accuracy of EUS for such strictures; [3] any contraindications for EUS (Figure 1).

A comprehensive evaluation of all enrolled patients encompassed meticulous history-taking, focusing on significant medical habits, and eliciting information about comorbidities such as diabetes, hypertension, liver disease, biliary disease, pancreatic disease, malabsorption, or steatorrhea. Additionally, a thorough examination of the patient's clinical history included an inquiry into any family history of pancreatic and biliary malignancy. The clinical examination was conducted with careful attention to the presence of jaundice, abdominal findings, and the identification of any organomegaly.

Laboratory investigation

Blood samples were systematically collected from all participants for a comprehensive analysis, encompassing a complete blood count (CBC) utilizing the XKX21 system (Roche Diagnosis). The CBC included assessments of white blood count [WBC], hemoglobin concentration, and platelet count.

Moreover, various biochemical tests were conducted to evaluate liver function, coagulation profile, and renal function. Liver function was assessed through measurements of aspartate aminotransferase (AST), alanine transaminase (ALT), albumin, and bilirubin [total and direct] using the Dimension RXL Auto-analyser (Siemens, Dimension RXL). The coagulation profile, including prothrombin time (PT) and international normalized ratio (INR), was also determined.

Renal function was assessed through the measurement of serum creatinine. Additionally, biochemical markers such as alkaline phosphatase (ALP) and gamma-glutamyl transferase (GGT) were analyzed using the Dimension RXL Auto-analyser.

Furthermore, tumor markers, including carcinoembryonic antigen (CEA) and cancer antigen 19-9 (CA 19-9), were evaluated by spectrophotometry to indicate the potential presence of malignancy.

Endoscopic ultrasound examination

A single endosonographer skillfully conducted all examinations using a Pentax linear array EUS machine (EG-3870-UTK; HOYA Corporation, PENTAX Lifecare Division, Showanomori Technology Center, Tokyo, Japan) connected to a Hitachi EUB-7000 HV ultrasound unit (Hitachi Medical Systems, Tokyo, Japan). The patients underwent intravenous sedation with propofol during the EUS examination. The procedural approach involved systematic steps at four primary stations: the initial step included positioning the scope below the papilla to visualize the uncinate process, located to the right of the aorta after clockwise rotation. Following this, the scope was directed towards the papilla, and the tip was deflected upwards to visualize bile and pancreatic ducts as cross-sections, resembling snake eyes, enabling observation of the pancreatic head in a crescent shape. Subsequently, gentle deflection of the scope upwards and counterclockwise rotation allowed observation of the duodenal bulb apex, facilitating visualization of the entire pancreatic head and the portal vein confluence.

Finally, rotating the scope clockwise at the gastroesophageal junction allowed observation of the aorta, tracing it until reaching the celiac artery origin. Further advancement and gentle deflection of the scope downwards brought the pancreatic body into view, and additional clockwise rotation and withdrawal of the scope facilitated visualization of the pancreatic tail.

The Cook needle 22G (Echotip®; Wilson-Cook, Winston Salem, NC, United States) was utilized for EUS-FNA biopsies. The final diagnosis was determined through cytopathological evaluation of the acquired tissues, which a single pathologist performed. The EUS evaluation identified the following points: [1] a mass that could cause external compression at the stricture location, influencing its form and echogenicity; [2] disturbance of the usual two or three sonographic layers of the bile duct wall and muscularis propria layer of the duodenum; [3] extension of the mass into neighboring structures; [4] lymph node (LN) enlargement. The identified benign strictures on EUS were characterized by the intact sonographic bile duct wall layers, regardless of a mass lesion. Nevertheless, each mass had a biopsy to validate its initial endosonographic diagnosis; other restrictions were deemed malignant. The diagnosis of fibrotic inflammatory strictures was determined using data obtained from the EUS examination. The EUS examination revealed no masses in the ampulla and clearly defined swelling of the papilla, which did not affect the duodenum muscularis propria layer or cause any damage to the distal common bile duct (CBD) wall layers. A histological examination was conducted on the swelling using EUS-FNA. Chronic pancreatitis (CP) strictures were diagnosed based on EUS Rosemont criteria [Tables 1–2][9], with undetected pancreatic focal lesions on endosonographic view. Autoimmune pancreatitis [AIP] strictures were diagnosed by EUS features: a large bulky sausage-shaped pancreas with stictured MPD, diffuse wall thickening of the CBD [sandwich-like], and cytopathological examination with + IG4 stain[10]. Type 1 Autoimmune Pancreatitis [AIP] is histologically distinguished by lymphoplasmacytic sclerosing pancreatitis, which is characterized by [1] a significant amount of lymphoplasmacytic infiltration with more than 10 IgG4-positive cells/high power field [HPF]; [2] the presence of storiform fibrosis; [3] obliterative phlebitis. The presence of infiltrating granulocytes usually does not result in damaging alterations to the ducts and acini[11]. The conclusive diagnosis of an underlying stricture was determined to be malignant, based on histological evaluation of either the biopsy or the surgically excised tissues. Patients diagnosed with benign strictures underwent follow-up for six months. This follow-up included clinical examination, laboratory evaluations, and imaging techniques: abdominal CT, MRCP, and EUS if necessary. The findings from these evaluations were documented and reported. The occurrence of any proven malignancy during the follow-up was considered the follow-up endpoint for this specific case.

Statistical Analysis

The statistical analyses were performed through IBM SPSS Statistics for Windows (Version 23.0. Armonk, NY: IBM Corp). Quantitative data are presented as mean ± standard deviation [SD] and median [range], while qualitative data are presented as numbers and percentages. The Mann-Whitney

U-test was employed to compare two groups of non-normally distributed variables while utilizing the T-test to compare two groups of normally distributed variables. The Chi-square or Fisher Exact tests were utilized to compare the percentages of categorical variables. All tests were two-sided; $P < 0.05$ indicated statistical significance, while $P \geq 0.05$ was considered statistically insignificant. The optimal cut-offs for the receiver operating characteristic (ROC) were established by employing the Youden index. Subsequently, the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy were calculated.

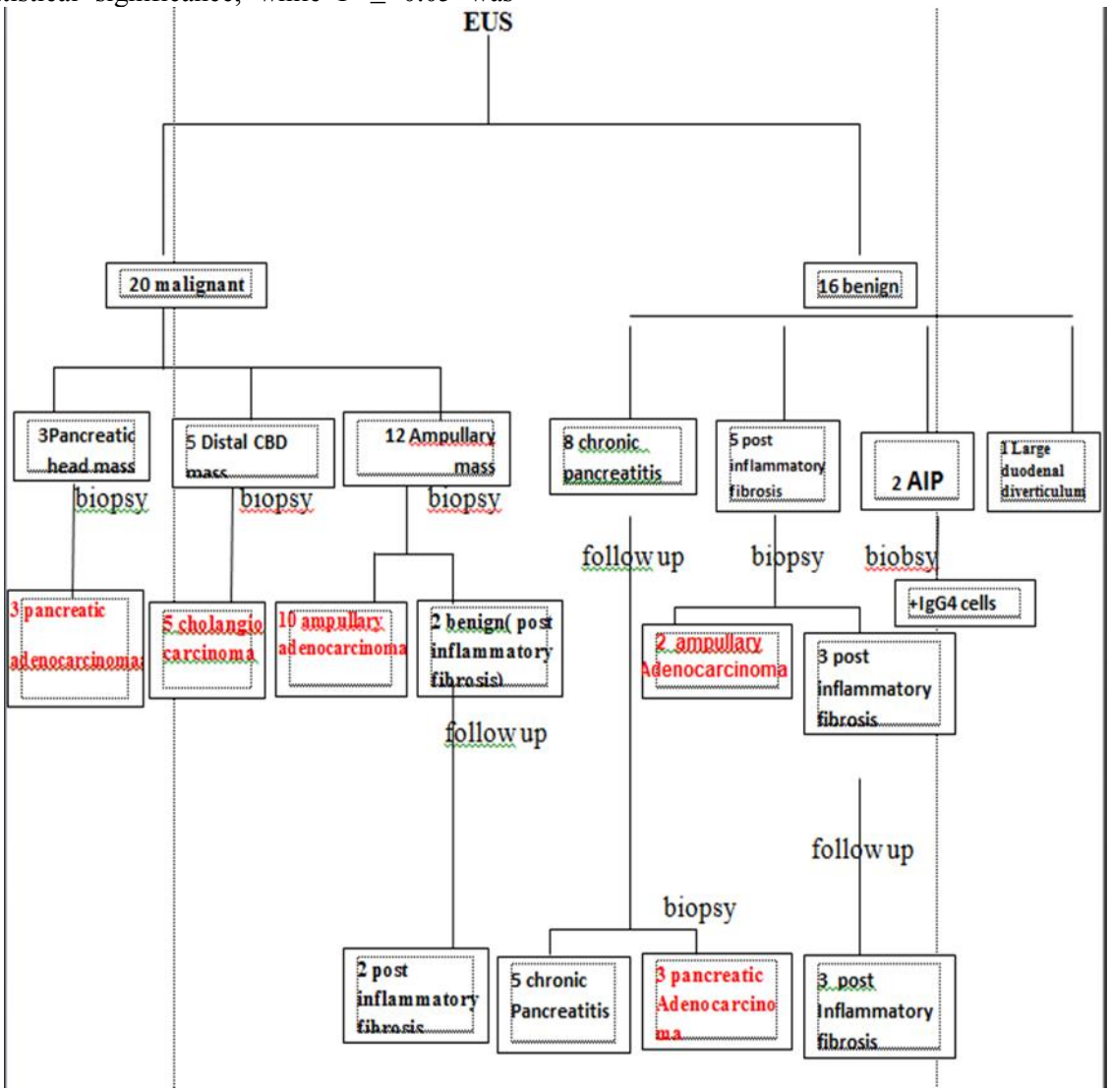

Figure 1. Schematic diagram.

Table 1. Consensus-based parenchymal and ductal features of chronic pancreatitis per the new Rosemont classification[9]

Feature	Definition	Major criteria	Minor criteria
Hyperechoic foci with shadowing	Echogenic structures ≥ 2 mm in length and width that shadow	Major A	
Lobularity	Well-circumscribed, ≥ 5 mm structures with enhancing rim and relatively echo-poor center		
A. With honeycombing	Contiguous ≥ 3 lobules	Major B	
B. Without honeycombing	Noncontiguous lobules		**Yes**
Hyperechoic foci without shadowing	Echogenic structures ≥ 2 mm in both length and width with no shadowing		**Yes**
Cysts	Anechoic, rounded/elliptical structures with or without septations		**Yes**
Stranding	Hyperechoic lines of ≥ 3 mm in length in at least two different directions for the imaged plane		**Yes**
MPD calculi	Echogenic structure[s] within MPD with acoustic shadowing	Major A	
Irregular MPD contour	Uneven or irregular outline and ecstatic course		**Yes**
Dilated sidebranches	3 or more tubular anechoic structures, each measuring ≥ 1 mm in width, budding from the MPD		**Yes**
MPD dilation	≥ 3.5 mm body or ≥ 1.5 mm tail		**Yes**
Hyperechoic MPDmargin	**Echogenic, distinct structure greater than 50% of entire MPD in the bodyand tail**		**Yes**

MPD: Main pancreatic duct

Table 2. EUS diagnosis of chronic pancreatitis [CP] based on Rosemont consensus[9]

I. Consistent with CP	A. 1 major A feature [+] ≥ 3 minor features B. 1 major A feature [+] major B feature C. 2 major A features
II. Suggestive of CP	A. 1 major A feature [+] < 3 minor features B. 1 major B feature [+] ≥ 3 minor features C. ≥ 5 minor features [any]
III. Indeterminate for CP	A. 3–4 minor features, no major features B. Major B feature alone or with < 3 minor features
IV. Normal	≤ 2 minor features, no major features

Results

Patients

A total of 36 patients, with a mean age of 56.6 ± 9.6 years, were enrolled in the study, all presenting with biliary duct distal half strictures in the absence of detectable masses. ERCP successfully identified 30 cases, while the remaining six individuals were detected through MRCP. Among the clinical presentations, jaundice was prevalent in the majority of patients (83.3%), abdominal pain was reported in over two-thirds of cases (66.7%), and 36.1% of the patients experienced weight loss.

Laboratory investigation

Table 3. Laboratory findings of the studied patients [n = 36].

Variables	Mean ± SD	Median [Range]
WBCs [x10^3 cells/mm^3]	6.95 ± 3.2	6.65 [3–13]
HB [g/dL]	10.98 ± 1.4	11 [8–15.1]
PLTs [x10^3cells/mm^3]	210 ± 89	180 [110–1.32]
INR %	1.01± 0.22	1 [0.5–1.32]
ALT [U/L]	65.1 ± 39.2	50 [23–180]
AST [U/L]	70.8 ± 31.1	60 [20–150]
Total bilirubin [mg/dL]	4.7 ± 2.7	4.2 [0.66–11.2]
Direct bilirubin[mg/dL]	3.1 ± 2.3	2.65 [0.19–9]
Albumin [g/dL]	3.6 ± 0.39	3.6 [2.9–4.8]
ALP [IU/L]	338.7 ± 72.7	310 [245–600]
GGT [IU/L]	401.9 ± 96.9	400 [280–700]
CEA [ng\mL]	941.1 ± 1158.9	475 [20–5000]
CA 19- 9 [ng\mL]	1483.8 ± 1934.6	750 [23–8000]

WBCs: white blood count; HB: hemoglobin; PLTs: platelets; INR: international normalized ratio; ALT: alanine transaminase; AST: aspartate aminotransferase; ALP: alkaline phosphatase, its normal reference = 40–150 IU/L; GGT: gamma-glutamyl transferase, its normal reference =10–55 IU/L; CEA: carcinoembryonic antigen, its normal reference = 0–5 ng\mL; CA 19-9: cancer antigen 19-9, its normal reference = 0–35 ng\mL

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Endoscopic ultrasound examination

The EUS examination findings of the study participants revealed 20 cases with malignant strictures and 16 with benign strictures. Among the malignant strictures, 12 cases were associated with an ampullary mass, 3 with a pancreatic head mass, and 5 with a distal common bile duct (CBD) mass. The benign strictures included 8 cases of chronic pancreatitis (CP), 5 cases of post-inflammatory fibrosis strictures, 2 cases of autoimmune pancreatitis (AIP), and 1 case with a large duodenal periampullary diverticulum (PAD). **Table 4** illustrates that the most prevalent characteristics of malignant masses causing stricture were the disruption of bile duct layers [100%], followed by the extension of the mass into adjacent tissues, hypoechogenicity, and irregularity of the masses [90%], with the least frequent characteristic being lymph node enlargement (85%).

Malignant and benign stricture with EUS characters exhibited a statistically significant difference in all studied parameters except LN swelling [Table 5].

Table 4. EUS characteristics of malignant and benign strictures.

Type of strictures			**n [%]**
Malignant n = 20 [55.6%]	Ampullary mass [12]	Mass size in cm [3 ± 0.67]	12 [100]
		Hypoechogenecity	10 [83.3]
		Irregular shape	10 [83.3]
		LN enlargement	11 [91.6]
		Continuation into adjacent tissues	10 [83.3]
		Disruption of bile duct layers	12 [100]
	pancreatic headmass [3]	Mass size in cm [2.6 ± 0.55]	3 [100]
		Hypoechogenecity	3 [100]
		Irregular shape	3 [100]
		LN swelling	2 [66.6]
		Continuation into adjacent tissues	3 [100]
		disruption of bile duct layers	3 [100]
	Distal CBD mass [5]	Mass size [3.1 ± 0.42]	5 [100]
		Hypoechogenecity	5 [100]
		Irregular shape	5 [100]
		LN enlargement	4 [80]
		Continuation into adjacent tissues	5 [100]
		Disruption of bile duct layers	5 [100]
Benign n = 16 [44.4%]	CP [Rosemont criteria] [n = 8]	Honey combing\lobularity\hyperechoic strands\reactive LN, normal layered structure of bile duct	8 [100]
	Inflammatory fibrotic [n = 5]	The normal layered structure of bile duct\enlarged hyperechoic round papillae\reactive LN	5 [100]

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	AIP [bulkysausage-shaped pancreas] [n = 2]	Bulky sausage-shaped pancreas without a definite focal lesion with parenchymallobularity, honeycombing normal CBD layered structure	2 [100]
	Large duodenal PAD [n = 1]	Large PAD	1 [100]

LN: lymph node; CBD: common bile duct; CP: chronic pancreatitis; AIP: autoimmune pancreatitis; PAD: periampullary diverticulum

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Table 5. Comparison between EUS characters of malignant and benign stricture.

	Malignant stricture n = 20 n [%]	Benign stricture n = 16 n [%]	P-value
Mass ^			
Present	20 [100]	5 [31.2]	0.0001*
Absent	0.0	11[68.8]	
Size [cm]			
Mean ± SD	2.9 ± 0.59	1.1 ± 0.22	0.0001*
Range	2–4	1–1.5	
Echogenicity ^			
Hypo echogenic	18 [90.0]	0 [0.0]	0.0001*
Hyper echogenic	2 [10]	5 [31.2]	
Shape ^			
Round	2 [10]	5 [31.2]	0.0001*
Irregular	18 [90]	0.0	
Lymph node swelling ^			
Yes	17 [85.0]	10 [62.5]	0.15
No	3 [15.0]	6 [37.5]	
Continuation into adjacent tissues ^			
Yes	18 [90.0]	2 [12.5]	0.0001*
No	2 [10]	14 [87.5]	
Disruption of bile duct ^			
Yes	20 [100.0]	0 [0.0]	0.0001*
No	0 [0.0]	16 [100]	

^ ; *

Histopathological examination results for the 20 patients [74.1%] diagnosed as malignant strictures by EUS indicated 10 cases with ampullary adenocarcinoma, 3 with pancreatic adenocarcinoma, and 5 with cholangiocarcinoma (distal CBD mass), while 2 cases from the 12 ampullary masses [initially diagnosed as malignant by EUS] were proved to be negative for malignancy on biopsy and were diagnosed post-inflammatory fibrosis. However, in the seven patients (25.9%) diagnosed with benign strictures by EUS (5 as post-inflammatory fibrosis and 2 as autoimmune pancreatitis), histopathological findings revealed ampullary adenocarcinoma in two cases from the 5 cases initially diagnosed as benign post-inflammatory fibrosis by EUS. The remaining five patients were confirmed to have benign post-inflammatory fibrosis strictures [three patients] and autoimmune pancreatitis (AIP) (two patients). During the follow-up period, ten benign cases remained unchanged, while three cases of chronic pancreatitis (CP) developed a malignant pancreatic head mass after six months; one was detected by CT, and two were

identified by EUS. The final diagnosis of the studied patients revealed 23 malignant strictures (12 ampullary adenocarcinomas, 6 pancreatic adenocarcinomas, 5 cholangiocarcinomas) and 13 benign strictures (5 post-inflammatory fibrosis, 5 CP, 2 AIP, and 1 large periampullary diverticulum) **(Table 6)**

Table 6. Histopathological diagnosis of the studied patients [n=27]

	EUS finding	Biopsy result	Studied patients [n. 27]	
			n.	%
Malignant n=20 [74.1%]	[12] Ampullay mass	Adenocarcinoma	10	50
		negative for malignancy	2	10
	[5] Distal CBD mass	Cholangiocarcinoma	5	25
	[3] Pancreatic head mass	Adenocarcinoma	3	15
Benign n=7 [25.9%]	[5] Post- inflammatory fibrosis	Negative for malignancy	3	42
		Ampullary adenocarcinoma	2	28
	[2]Autoimmune pancreatitis	IgG4 cells	2	28

NB: Biopsy was not taken from 8 patients with chronic pancreatitis and 1 patient with a large duodenal periampullary diverticulum as their diagnosis was based on the EUS picture.

Ten benign cases remained without change during the follow-up period, while three cases of chronic pancreatitis developed malignant pancreatic head mass after 6 months of follow-up; one of them was detected by CT, and 2 cases were detected by EUS **(Table 7)**.

Table 7. Follow-up of the cases with benign stricture [n=13]

Before follow up	After follow up	Studied patients [n= 13]	
		n.	%
Chronic pancreatitis [n=8]	Chronic pancreatitis	5	38.4
	Pancreatic head mass	3	23
Post-inflammatory fibrosis [n=5]	Post-inflammatory fibrosis	5	38.4

NB: The benign strictures which were diagnosed as autoimmune pancreatitis and large duodenal diverticulum compressing the distal part of CBD were not followed up.

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Final diagnosis of the studied patients revealed that, there were 23 malignant strictures (12 ampullary adenocarcinoma, 6 pancreatic adenocarcinoma, and 5 cholangiocarcinoma, and 13 benign stricture (5 post inflammatory fibrosis, 5 chronic pancreatitis, 2 AIP, and 1 large periampullary diverticulum) **(Table 8)**.

Table 8. The final diagnosis of the studied patients after 6 months of follow-up

	Studied patients [n=36]	
	n.	**%**
Malignant	23	63.9
Benign	13	36.1

The validity of EUS in diagnosing DBS without mass versus the biopsy pathology revealed a sensitivity, specificity, and accuracy of 90%, 71.4%, and 91.7%, respectively. The AUC was 0.81, indicating that EUS is good for diagnosing DBS without mass (**Figure 2**).

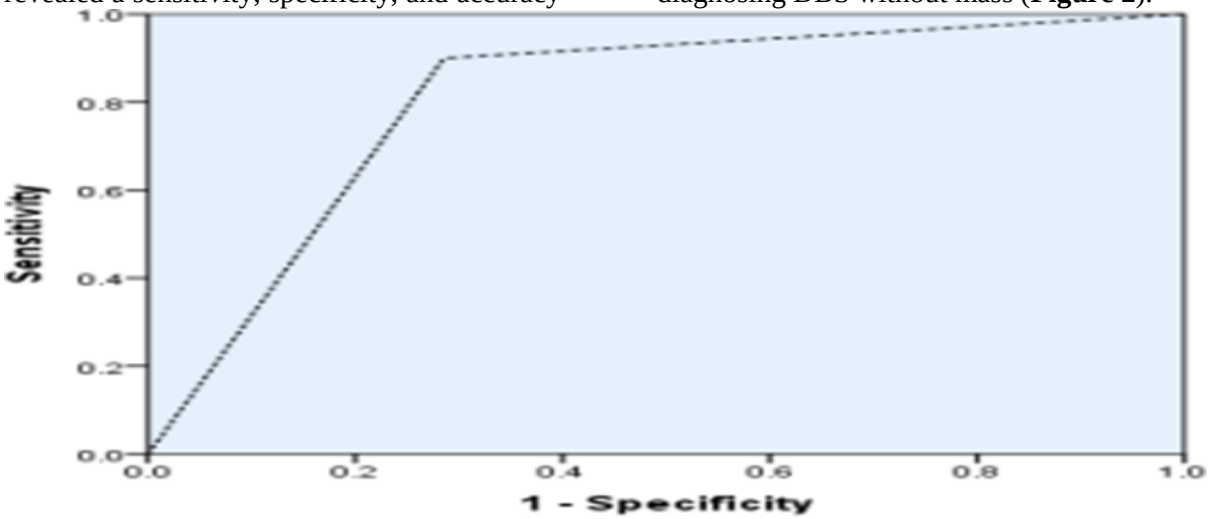

Figure 2. ROC curve comparing the validity of EUS in diagnosing distal biliary stricture without mass versus biopsy pathology.

After six months of follow-up, the validity of EUS in diagnosing distal biliary strictures (DBS) without a mass showed a sensitivity of 87%, specificity of 100%, and accuracy of 91.7%. The area under the curve (AUC) was 0.93, indicating that EUS is highly effective in diagnosing DBS without a mass (**Figure 3**).

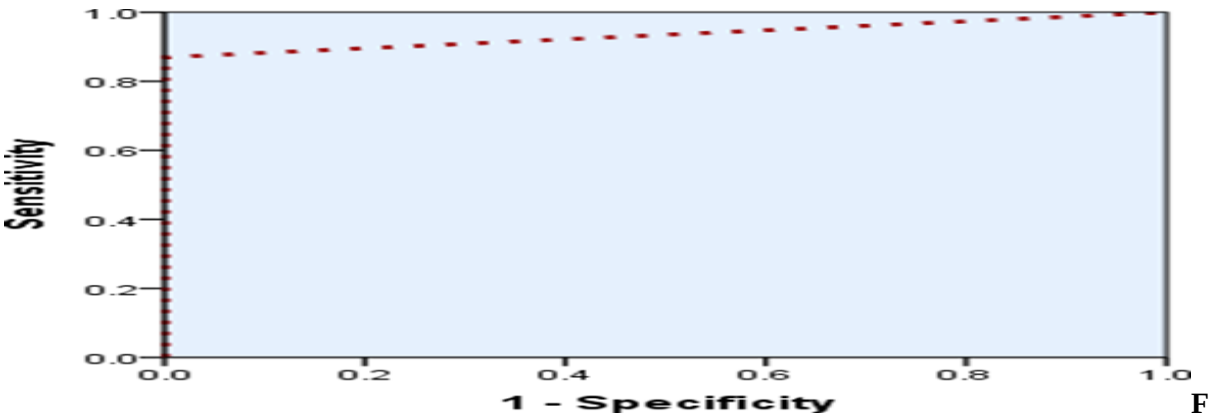

Figure 3. ROC curve comparing the validity of EUS in diagnosing distal biliary stricture without mass versus outcome after six months of follow-up.

The CEA at a cutoff value of ≥ 55 demonstrates excellent discrimination between malignant and benign DBS without a mass, with a sensitivity, specificity, and accuracy of 100.0%, 76.9%, and 91.7%, respectively. At a cutoff value of ≥ 82.5, the CEA achieves sensitivity, specificity, and accuracy of 95.7%, 84.6%, and 91.7%, respectively. This indicates that a CEA value ≥ 82.5 is optimal for diagnosing DBS without a mass, highlighting the effectiveness of the CEA tumor marker in distinguishing between malignant and benign cases of DBS without a mass (**Figure 4**).

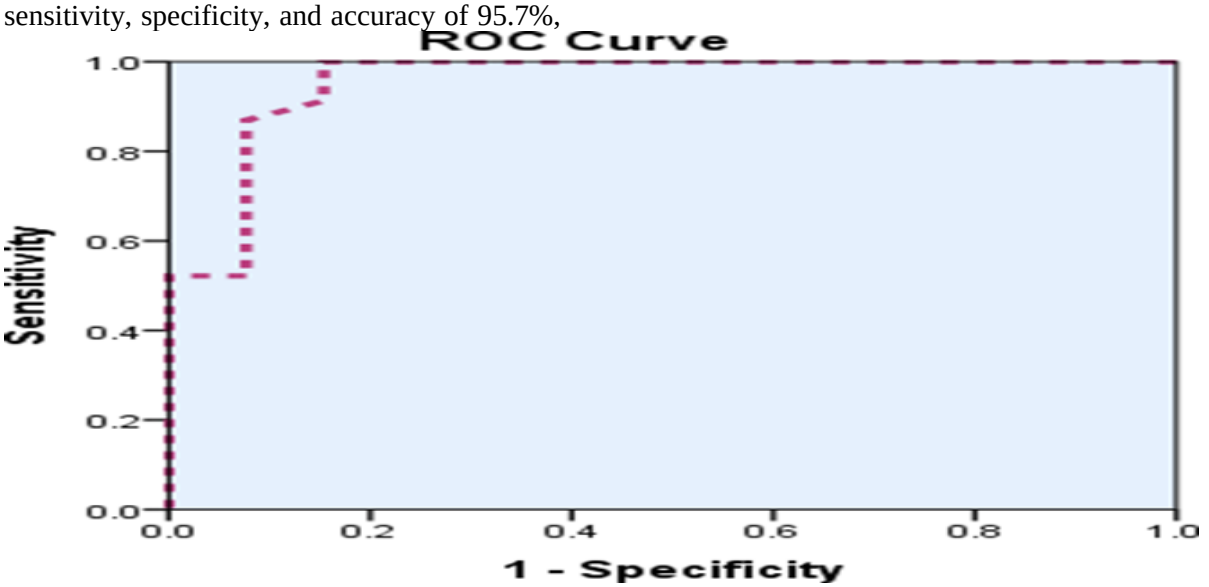

Figure 4. ROC curve defining the role of CEA in diagnosing distal biliary stricture without mass after six months of follow-up. The area under the curve (AUC = 0.955) with (95% CI 0.88–1) P = 0.0001.

The cancer antigen 19-9 (CA 19-9) at a cutoff value of ≥ 75 exhibits robust discrimination between malignant and benign distal biliary strictures (DBS) without a mass, with a sensitivity, specificity, and accuracy of 100.0%, 76.9%, and 91.7%, respectively. At a cutoff value of ≥ 125, the CA 19-9 achieves sensitivity, specificity, and accuracy of 95.7%, 84.6%, and 91.7%, respectively. The optimal cutoff value for the diagnosis of DBS without a mass is ≥ 125, underscoring the effectiveness of CA 19-9 as a tumor marker in distinguishing between malignant and benign cases of DBS without a mass (**Figure 5**).

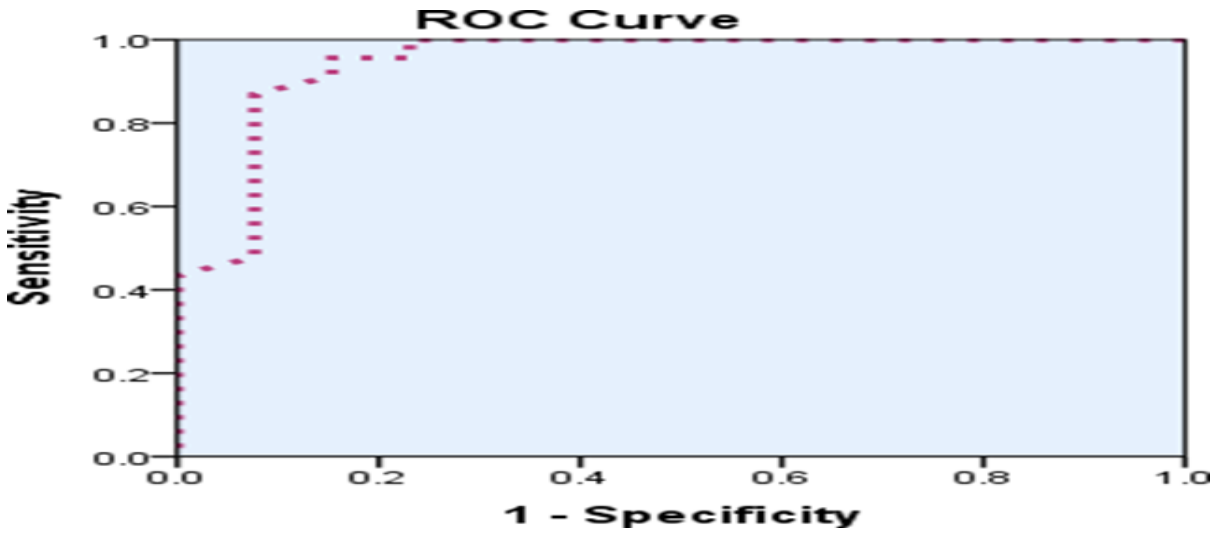

Figure 5. ROC curve defining the role of CA 19-9 tumor marker in diagnosing distal biliary stricture without mass after six months of follow-up. The area under the curve (AUC = 0.916) with (95%CI 0.86–1) P = 0.0001.

Discussion

The investigation into DBS poses a substantial challenge in clinical practice, particularly when the absence of a detectable mass complicates the distinction between benign and malignant etiologies. Distinguishing between these conditions is pivotal for guiding appropriate therapeutic interventions and optimizing patient outcomes. While conventional diagnostic methods such as ERCP and MRCP have been employed, their limitations in cases without an identified mass underscore the need for alternative approaches. Endoscopic ultrasonography (EUS), as a cutting-edge imaging modality, offers a promising avenue for improved diagnostic accuracy in DBS cases where conventional methods fall short. In this discussion, we delve into the findings of our study, exploring the efficacy of EUS in delineating the nature of DBS without a discernible mass, considering both diagnostic accuracy and the correlation with clinical and laboratory parameters. The nuanced understanding gained from this investigation may contribute to refining the diagnostic algorithm for patients facing the diagnostic conundrum of distal biliary strictures without an evident mass.

The demographics of the 36 participants in our study revealed a male predominance of 55.6%, with an average age of 56.6 years, in line with findings reported by Oppong et al.[12]. Malignant strictures were more prevalent in males, constituting 60.9% of cases with a mean age of 57.5 years. Jaundice was the most common presenting symptom, observed in 83.3% of participants, consistent with Saifuku et al.'s observations [13]. Noteworthy differences emerged when comparing patients with malignant and benign biliary strictures. Those with malignant strictures exhibited significantly elevated liver enzymes (ALT, AST, and ALP) and bilirubin concentrations compared to their benign counterparts. This elevation can be attributed to the complete and prolonged obstruction seen in malignant cases, potentially due to hepatic metastases or infiltration. Furthermore, patients with extra-hepatic malignant obstruction displayed more direct hyperbilirubinemia compared to those with extra-hepatic benign obstruction[14].

In discrimination between malignant and benign strictures, we revealed that the sensitivity, specificity, and accuracy of both CEA at a cutoff value of ≥ 82.5 ng/mL and CA 19-9 at a cutoff value of ≥ 125 ng/mL were 95.7%, 84.6%, and 91.7%, respectively. Both CEA and CA 19-9 may show an increase in patients with malignancies such as cancer head of the pancreas, cholangiocarcinoma, and ampullary carcinoma[15]. Moreover, Tsukada et al.[16] set the cutoff level for CA 19-9 as 37 U/mL and demonstrated a nonsignificant difference between malignant and benign strictures. This is owing to the CA 19-9 level increases in the case of cholestasis, leading to false-positive cases, which caused a decrease

in CA 19-9 specificity to 76.9% when using a cutoff value of 75 ng/mL. Our results manifested that 23 patients had malignant strictures (63.9%) and 13 had benign strictures (36.1%), which aligns with the findings of Abou Bakr et al.[17]. The occurrence of cancer in BS is not negligible in the literature, which justifies the use of surgical exploration as a proactive strategy. Specifically, when obstructive jaundice is present, most BSs are considered to be malignant, and surgical intervention is commonly performed[18]. Nonetheless, we revealed that 69% of benign biliary strictures were accompanied by obstructive jaundice, which was considered quite a high percentage. Therefore, recommending exploratory surgery in all patients may not be justifiable especially since such benign strictures can be managed endoscopically.

Regarding the etiology of strictures, malignant stricture cases were 12 (33.3%) ampullary adenocarcinomas being the most common cause, 6 pancreatic head cancers, and 5 cholangiocarcinomas. Meanwhile, benign stricture cases were five fibrotic inflammatory, five CP, two AIP, and one large PAD. This differed from the results of Abou Bakr et al.[17], who found that pancreatic cancer was the most common cause of malignant strictures (43.5%). This can be attributed to variations in the patient selection process, as their study included 60 patients with obstructive jaundice and CBD dilatation identified through abdominal ultrasonography. Additionally, the variability in the assessment tools they used should be considered. In this case, CT scans were not utilized to determine the cause of obstructive jaundice, which means that patients with a mass that was detected through cross-sectional imaging, which is highly effective in identifying pancreatic cancer cases, were not excluded.

The EUS imaging findings consistently revealed mass lesions as a hallmark feature of malignancy, characterized by hypoechogenicity, irregular shape, and larger size compared to benign masses. In certain cases, these malignant lesions had invaded adjacent tissues, disrupting the bile duct layers and LN affection. All these features were significantly more prevalent in malignant strictures compared to benign strictures, except LN affection, which was also observed in benign strictures without significant differences. These features agree with that of Tamada et al.[19], with a difference in the detection of mass size > 8 mm, which was smaller than our mean mass size (2.9 cm). This is because they used intraductal ultrasound (IDUS) to define malignancy criteria, which is more sensitive than traditional EUS. Furthermore, Menzel et al.[20] reported a mixed echo pattern of malignant masses, and they observed that malignant LNs were hypochogenic, round-shaped, and larger than benign LNs detected by EUS imaging. From these features, Lee and his colleagues[3] found that in diagnosing adenocarcinoma of biliary and pancreatic origin, the presence of pancreatic head mass, irregular bile duct wall, or both had a sensitivity, specificity, PPV, and NPV of 88%, 100%, 100%, and 84%, respectively. In this study, follow-up was performed for 13 benign cases [8 with strictures due to CP and 5 fibrotic inflammatory strictures]. After six months of follow-up, three cases of those who were diagnosed as CP were found to have malignant pancreatic focal lesions. They may have had small pancreatic focal lesions at the initial EUS examination but were missed and enlarged to be detected after six months. Notably, CP is considered a risk factor for pancreatic cancer[21]; accordingly, developing malignant focal lesions alongside the previously diagnosed CP is possible.

Diagnosis of ampullary tumors is usually challenging and needs multiple imaging protocols[22]. This study identified two cases initially diagnosed by EUS as having malignant ampullary lesions [false positives], which histopathologically proved to be benign fibrotic inflammatory strictures. Conversely, two cases diagnosed by EUS as having benign strictures (fibrotic inflammatory strictures; false negatives) were histopathologically confirmed to be ampullary adenocarcinoma. The accuracy of distinguishing between benign and malignant ampullary lesions through sonography, relying on factors like echogenicity, shape irregularity, and disruption of the bile duct wall, may be influenced by the operator's expertise. Moreover, the presence of a bile duct stent can contribute to an increase in wall thickness and irregularity, potentially leading to misdiagnoses of malignancy[3]. In addition, Chen et al.[23] conducted a

comparative analysis of various diagnostic imaging techniques (EUS, ERCP, US, and CT) to identify and determine the stage of primary ampullary tumors. They found that EUS had a sensitivity of 95% for identifying the tumors, 75% for determining the T stage, and 50% for determining the N stage compared to surgical histological findings. They also stated that the presence of no biliary stents might decrease the accuracy of EUS in staging ampullary tumors. Furthermore, Maluf-Filho et al.[24] reported 90% sensitivity of EUS in diagnosing ampullary adenocarcinoma.

Our study highlights the high diagnostic efficacy of EUS in identifying DBS without a mass, surpassing biopsy results, with a sensitivity, specificity, and accuracy of 90%, 71.4%, and 91.7%, respectively. Furthermore, when comparing EUS findings to the outcome after six months of follow-up, the sensitivity, specificity, and accuracy were 87%, 100%, and 91.7%, nearly similar to the results of Saifuku et al.[13]. Compared to the study of Heinzow et al.[25] who compared different diagnostic tools for detecting bile duct malignancy, our results had more accuracy. This may be because their study included a large group of 234 patients, and their follow-up was at least one year and extended to three years in some cases. Moreover, Abou Bakr et al.[17] reported sensitivity and specificity of EUS for detecting malignant obstruction of 100% and 86.36%, respectively, with an overall accuracy of 95%. Their studied patients were cases of obstructive jaundice, and they excluded patients with biliary stones detected by transabdominal ultrasonography only. Consequently, they reported higher sensitivity. In addition, Maluf-Filho et al.[24] showed that the sensitivity and specificity values for pancreatic adenocarcinoma detected by EUS were 96.6% and 90.6%, respectively, with an accuracy of 93.4%. These were higher results because they did not use MRCP and ERCP to exclude diagnosed cases.

Ultimately, the sonographic presentation on EUS demonstrates significant diagnostic potential for extrahepatic BS, particularly when other cross-sectional imaging techniques fail to visualize the underlying lesion. This non-invasive approach allows for avoiding unnecessary invasive procedures like surgical exploration or prolonged follow-up assessments in cases of benign strictures. Moreover, the early detection of malignant strictures through EUS provides patients with very early-stage pancreaticobiliary cancer with a broader spectrum of treatment options. EUS proves to be a highly accurate, minimally invasive diagnostic technique with low risk and high precision for patients with indeterminate distal biliary strictures[26].

Limitations and Future Directions

The study has several limitations that warrant consideration. Firstly, the study is constrained by a limited sample size, which may impact the generalizability of the findings. Larger and more diverse cohorts in future studies could strengthen the robustness of the results. Additionally, the operator-dependent nature of EUS introduces variability, emphasizing the need for standardized procedures and the inclusion of multiple operators to mitigate this limitation.

Notably, discrepancies between EUS diagnoses and histopathological results resulted in false positives and negatives. Further investigation into the factors contributing to these discrepancies is crucial for refining diagnostic accuracy. The specificity of CEA and CA 19-9, while effective, may be influenced by other factors, prompting the exploration of additional biomarkers for improved specificity.

In terms of future directions, larger prospective studies with extended follow-up periods could offer more comprehensive insights into the diagnostic accuracy and predictive value of EUS for biliary strictures. Implementing standardized training programs for EUS operators and assessing their impact on diagnostic accuracy could enhance consistency across practitioners. Exploring the integration of advanced imaging techniques, such as artificial intelligence or machine learning algorithms, with EUS represents a promising avenue for improving diagnostic precision and reducing operator dependency. Collaboration with multiple centers is encouraged to facilitate the recruitment of larger and more diverse patient populations, contributing to a broader understanding of biliary strictures and the utility of EUS.

Finally, the evaluation of emerging biomarkers, in addition to CEA and CA 19-9, holds the potential for enhancing the specificity of diagnostic markers in distinguishing between benign and malignant biliary strictures. Addressing these limitations

and pursuing these future directions is essential for advancing the field, leading to more reliable diagnostic methods and improved patient outcomes.

Conclusion

This study highlights the value of EUS as a minimally invasive and effective diagnostic tool for evaluating biliary strictures, particularly when no mass is visible on imaging. EUS plays a key role in early detection and differentiation of malignant from benign strictures, supporting timely and appropriate management.

Institutional Review Board Statement: This research study has been ethically reviewed and approved by the Institutional Review Board (IRB) at the Faculty of Medicine, Zagazig University, Egypt [6249-5-7-2020]. The IRB has carefully examined the study's protocol, methodologies, and ethical considerations, ensuring alignment with the principles outlined in the Declaration of Helsinki.

Informed Consent Statement: Written informed consent was obtained from each participant, signifying their voluntary agreement to take part in the study.

Data Availability Statement: The datasets generated and analyzed during the current study are available from the corresponding author upon reasonable request.

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HIGHLIGHTS

- Endoscopic Ultrasound (EUS) is a valuable and minimally invasive tool for diagnosing biliary strictures, especially when no mass is detected on conventional imaging.
- EUS facilitates early detection of malignant biliary strictures, enabling earlier intervention and expanding treatment options.
- Tumor markers CEA and CA 19-9 assist in differentiating malignant from benign biliary strictures, supporting accurate diagnosis and clinical decision-making.

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