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Role of Endoscopic Ultrasound in Diagnosis of Unexplained Distal Common Bile Duct Stricture

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ABSTRACT

Background: Determining the etiology of distal biliary strictures lacking a recognizable cause on imaging is crucial for appropriate therapy. **Objective:** This study aimed to evaluate the efficacy of endoscopic ultrasound (EUS) in diagnosing distal biliary strictures that were not diagnosed by cross-sectional imaging modalities like computed tomography or magnetic resonance imaging. **Patients and Methods:** Prospective study included 80 patients with unexplained distal biliary strictures diagnosed using Magnetic Resonance Cholangiopancreatography (MRCP), Endoscopic Retrograde Cholangiopancreatography (ERCP), CT, or MRI done EUS.

Results: 80 patients (50 males mean age 57.9 ± 9.8 years) were studied. Based on EUS findings, 51 patients were diagnosed with malignant strictures (63.75%) (21 distal cholangiocarcinomas, 17 pancreatic head masses, 11 ampullary mass lesions, and 2 intraductal papillary mucinous neoplasms), and the remaining patients were diagnosed as benign strictures (36.25%). Receiver Operating Characteristic (ROC) analysis between malignant and benign strictures for distal Common Bile Duct (CBD) wall thickness showed a cut-off value of > 3.2 (Sensitivity of 80.39%, specificity of 89.66%, positive predictive value (PPV) of 93.2% negative predictive value (NPV) of 72.2% and accuracy of 85.7%).

Conclusion: EUS is a promising investigational procedure for patients with challenging distal CBD strictures, and can predict the nature of the strictures whether benign or malignant.

Keywords: Common bile duct, Distal biliary stricture, Endoscopic retrograde cholangiopancreatography, Endoscopic ultrasound.

INTRODUCTION

Endoscopic Ultrasound (EUS) has progressed since its introduction and is now a widely accepted irreplaceable assessment tool that makes previously unreachable anatomical areas visible and has the ability to acquire tissue for diagnosis [1]. Over the past ten years, significant developments in imaging techniques and the emergence of new ways for tissue differentiation based on vascular structure and tissue stiffness have led to enhancements in diagnostic EUS [2]. EUS has grown to be a key tool in assessing biliary disorders. In addition to offering vital diagnostic data on biliary anatomy, it also gives a chance to take a sample of the tissue or lesion for histological diagnosis [3].

Diagnostic challenges frequently arise from intrahepatic and/or extrahepatic biliary strictures in those with a cholestatic clinical scenario. Proper diagnosis is crucial to prevent missing cancer in strictures that seem benign or performing needless surgery to investigate benign conditions that resemble malignancy [4].

With its excellent sensitivity and accuracy in identifying the malignant origin of distal biliary obstruction, endoscopic ultrasonography has emerged as the preferred imaging modality for those patients [5]. Sensitivities ranging from 40% to 90% have been recorded in many trials, with the majority displaying a sensitivity >70% [6].

This study aimed to assess the ability of EUS to diagnose distal biliary strictures in which cross-sectional imaging modalities such as computed tomography (CT) and magnetic resonance imaging (MRI) cannot detect a causative mass or bile duct thickening.

PATIENTS AND METHODS

A prospective study was conducted on 80 patients who underwent EUS at the National Liver Institute, Menoufia University for the evaluation of distal biliary strictures. Patients with distal biliary strictures were diagnosed using other imaging modalities, such as magnetic resonance cholangiopancreatography (MRCP), endoscopic retrograde cholangiopancreatography (ERCP) and CT, or MRI, were included in the study.

Exclusion criteria: Patients under 18 years of age, unfit for EUS due to other severe comorbidities, refusal to participate in this study, identifiable mass lesions causing biliary strictures, and proximal bile duct strictures.

The patients were studied for their full history, physical examination, and laboratory and imaging investigations.

EUS was performed to evaluate the presence of masses that could result in disintegration of the typical 2-3 layers and extrinsic pressure at the CBD stricture site [7]. The EUS procedure was performed in the same manner as the standard endoscopic examinations. Most procedures were performed on an outpatient basis under intravenous sedation [8].

In the present study, EUS images were evaluated to detect extrinsic pressure at the stricture location

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without any prior knowledge of the definite diagnosis. The following were the assessment points: (1) the stricture site is surrounded by a mass that might cause extrinsic compression, (2) the bile duct wall's typical two or three sonographic layers were disrupted or not [9] and (3) the extension of a mass into nearby structures [10].

Ethical approval: This study was approved by The Ethics and Scientific Board of the National Liver Institute (NLI IRB 00014014). Written informed consent was obtained from each patient before inclusion in the study. The Helsinki Declaration was followed throughout the study's conduct.

Statistical analysis

Data were collected and inputted into a computer using (Inc.'s Chicago, Illinois) Statistical Package for the Social Sciences (SPSS) version 13 application for statistical analysis. There were two different types of statistics performed: descriptive statistics, including quantitative data shown as mean ± standard deviation (SD), and range. Qualitative data expressed as frequency and percentage. Analytical statistics including the Chi-square test, Student's t-test, Receiver Operating Characteristic (ROC) curve, and calculations had been performed for sensitivity, specificity, positive and negative predictive values, and diagnostic accuracy. When the P-value ≤ 0.05, it was regarded as statistically significant.

RESULTS

Demographic findings: This study involved 80 patients, at inclusion the mean age was (57.96 ± 9.84 years), Most of the enrolled patients were males, urban, and non-smokers (Table 1).

Table (1): Demographic findings of the studied group

Age	**Range**	**29-80**	
	Mean ±SD	**57.963±9.846**	
		N	**%**
Sex	**Male**	**50**	**62.50**
	Female	**30**	**37.50**
Residence	**Urban**	**51**	**63.75**
	Rural	**29**	**36.25**
Special habits of medical importance	**No**	**32**	**40.00**
	Smoker	**8**	**10.00**
	Canal water contact	**40**	**50.00**

Physical examination findings:

The main complaints in most patients were abdominal pain and jaundice, while fatigue, itching, fever, and weight loss were less common. The most common comorbidities were DM, HTN, and ischemic heart diseases respectively (Table 2).

Table (2): Physical examination findings of the studied group

		N	%
Complaint	**Abdominal pain**	**66**	**82.5**
	Weight loss	**19**	**23.75**
	Jaundice	**60**	**75**
	Fever	**35**	**43.75**
	Fatigue	**45**	**56.25**
	Itching	**37**	**46.25**
Comorbidities	**DM**	**53**	**66.25**
	HTN	**27**	**33.75**
	IHD	**15**	**18.75**
	Chronic liver disease	**12**	**15**
	Decompensated liver cirrhosis	**6**	**7.5**

Imaging findings: Ultrasound of the studied patients before performing ERCP for biliary drainage showed dilated CBD, and intrahepatic biliary radicle dilatation (IHBRD) was **minimal** in 60%, **mild** in 13%, **moderate** in 20% and **marked** 5% of the studied patients, while only one patient (1%) had NO IHBRD. Ultrasound detected enlarged abdominal lymph nodes in only seven patients (8%) (Table 3).

Table (3): Ultrasound findings of the studied group

Total			
		N	**%**
Ultrasound (IHBR)	**Not dilated**	**1**	**1.25**
	Minimal dilatation	**48**	**60**
	Mild dilatation	**11**	**13.75**
	Moderate dilatation	**16**	**20**
	Marked dilatation	**4**	**5**
Ultrasound (Abdominal LNs)	**Positive**	**7**	**8.75**
	Negative	**73**	**91.25**

Endoscopic findings (ERCP and EUS):

Regarding ERCP findings, 85% of patients had intrahepatic biliary radicles dilatation, while it was not dilated in 10 patients, and only 2 patients had stenotic segments with dilated IHBR. CBD was dilated at proximal segment with distal end stricture in 90% of patients, while there was distal smooth tapering in five patients, and abrupt distal narrowing in only 2 patients. CBD was normal in only one patient. A cholangiogram revealed that most patients had a normal main pancreatic duct. Number of patients had difficult papillary cannulation during ERCP and needed to apply different interventions e.g. Papillotomy and Precut or Sphincterotomy. Most patients completed one trial of ERCP, while some needed two trials for drainage, and a few patients required three trials**.** Only one patient had failed 2 trials of ERCP (Table 4).

Table (4): ERCP findings of the studied group

Total			
		N	**%**
ERCP (IHBR)	**Not dilated**	**10**	**12.50**
	Dilated (without stenotic segments)	**68**	**85.00**
	Dilated (with stenotic segments)	**2**	**2.50**
ERCP (CBD)	**Normal**	**1**	**1.25**
	Dilated proximal e distal stricture	**72**	**90**
	Dilated proximal e distal smooth tapering	**5**	**6.25**
	Dilated e abrupt distal narrowing	**2**	**2.50**
ERCP (papillae)	**Normal**	**56**	**70.00**
	Maneuver done to papillae (Precut, papillotomy, sphincterotomy)	**24**	**30.00**
ERCP (pancreatic duct)	**Normal**	**79**	**98.75**
	Dilated	**1**	**1.25**
ERCP (no. of ERCP trials)	**Once**	**61**	**76.25**
	Twice	**16**	**20.00**
	3times	**2**	**2.50**
	Failed 2 trial	**1**	**1.25**

With regard to EUS findings, the patients were classified as having **malignant** strictures (n=51) diagnosed as distal cholangiocarcinoma, pancreatic head lesions, ampullary masses, and main branch IPMN intraductal papillary mucinous neoplasm or **benign** strictures (n=29) diagnosed as inflammatory strictures, primary sclerosing cholangitis in only 2 patients, and hydatidosis in also 2 patients. Mean distal CBD wall thickness was 3.9 ± 1.43 mm, it was regular in more than 62%. The main pancreatic duct was dilated in 28 patients. With regard to lymph nodes detected on EUS, malignant looking lymph nodes (LN) were found in 35% of patients, and likely reactive LN in only nine, while no LN were detected in the remaining patients (Table 5).

Table (5): Endoscopic ultrasound findings of the studied group

		N	**%**
Diagnosis	**Distal cholangiocarcinoma**	21	26.25
	Inflammatory stricture	25	31.25
	Pancreatic head mass	17	21.25
	Ampullary mass lesion	11	13.75
	Main branch IPMN (intraductal papillary mucinous neoplasm	2	2.50
	Primary sclerosing cholangitis	2	2.50
	Hydatidosis	2	2.50
Benign or malignant	**Benign**	29	36.25
	Malignant	51	63.75
Distal CBD wall thickness (mm)	**Range**	2-7.5	
	Mean ±SD	3.906±1.437	
Regular or irregular wall thickness of distal CBD	**Regular**	50	62.50
	Irregular	30	37.50
Pancreatic duct dilatation	**Not dilated**	52	65.00
	Dilated	28	35.00
Pancreatic duct dilatation (mm)	**Range**	2-18	
	Mean ±SD	8.004±4.370	
Lymph nodes	**No LN**	43	53.75
	Malignant looking	28	35.00
	Likely reactive	9	11.25

Comparison of EUS finding between benign and malignant strictures:

The mean distal CBD wall thickness in patients with benign strictures was 2.87 ± 0.76 mm while it was higher in patients with malignant strictures (4.49 ± 1.4 mm, P-value <0.001). Regarding the preservation of normal CBD layers, only one out of 29 patients with benign strictures had irregular wall thickness, while most patients with malignant strictures had irregular wall thickness (29 out of 51) with a statistically significant difference (P-value <0.001). Main pancreatic duct was found dilated in 24% of patients with benign strictures, while 41% of patients with malignant strictures had dilated main pancreatic duct with mean pancreatic duct dilatation of statistical significant difference between patients with benign and malignant strictures (Table 6).

Table (6): Comparison of EUS findings between patients diagnosed with benign and malignant strictures.

		Benign or malignant				Chi-Square	
		Benign		Malignant			
		N	%	N	%	X^2	P-value
Diagnosis	Distal cholangiocarcinoma	0	0.00	21	41.17	80.000	<0.001*
	Inflammatory stricture	25	86.20	0	0.00		
	Pancreatic head mass	0	0.00	17	33.33		
	Ampullary mass lesion	0	0.00	11	21.56		
	Main branch IPMN (intraductal papillary mucinous neoplasm	0	0.00	2	3.92		
	Primary sclerosing cholangitis	2	6.89	0	0.00		
	Hydatidosis	2	6.89	0	0.00		
T-Test						t	P-value
Distal CBD wall thickness (mm)	Range	2.1-5.4		2-7.5		-5.730	<0.001*
	Mean ±SD	2.876±0.767		4.492±1.402			
Chi-Square		N	%	N	%	X^2	P-value
Regular or irregular Wall thickness of distal CBD	Regular	28	96.55	22	43.14	22.505	<0.001*
	Irregular	1	3.45	29	56.86		
Pancreatic duct dilatation	Not dilated	22	75.86	30	58.82	2.359	0.125
	Dilated	7	24.14	21	41.18		
T-Test						t	P-value
Pancreatic duct dilatation (mm)	Range	3.3-8		2-18		-2.189	0.038*
	Mean ±SD	5.071±2.050		8.981±4.528			

ROC analysis between malignant and benign strictures for distal CBD wall thickness showed a cut-off value of > 3.2 (sensitivity of 80.39%, specificity of 89.66%, positive predictive value (PPV) of 93.2%, negative predictive value (NPV) of 72.2% and accuracy of 85.7%) (Table 7 and Figure 1).

Table (7): ROC analysis between benign and malignant strictures regarding distal CBD wall thickness

ROC curve between Malignant and Benign						
	Cutoff	Sens.	Spec.	PPV	NPV	Accuracy
Distal CBD wall thickness (mm)	>3.2	80.39%	89.66%	93.2	72.2	85.7%

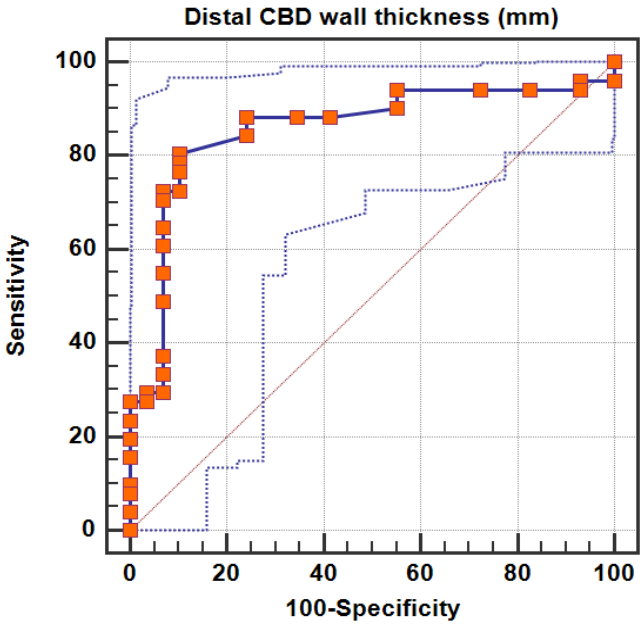

Figure (1): ROC analysis between benign and malignant strictures regarding distal CBD wall thickness

The diagnosis established by EUS features was compared with the results obtained from EUS-FNA. All patients diagnosed with malignant strictures had done fine needle aspiration during EUS. Histopathological diagnoses obtained and confirmed the diagnosis of malignant strictures were pancreatic head adenocarcinoma, mucinous cystadenocarcinoma and neuroendocrine tumors, ampullary carcinomas, and distal cholangiocarcinoma. Benign strictures histopathological diagnoses were established as inflammatory strictures, primary sclerosing cholangitis, and papillary adenoma in only one patient. Eleven patients diagnosed with benign strictures had not done EUS-FNA (Table 8).

Table (8): Results of EUS-FNA in patients diagnosed with benign and malignant strictures

Result of EUS-FNA	Benign or malignant						Chi-Square	
	Benign		Malignant		Total			
	N	%	N	%	N	%	X^2	P-value
No FNA	11	37.93	0	0.00	11	13.75	80.000	<0.001*
Distal cholangiocarcinoma	0	0.00	23	45.10	23	28.75		
Inflammatory stricture	15	51.72	0	0.00	15	18.75		
Pancreatic head mass (Adenocarcinoma)	0	0.00	8	15.69	8	10.00		
Pancreatic head mass (Mucinous cystadenocarcinoma)	0	0.00	5	9.80	5	6.25		
Pancreatic head mass (Neuroendocrine tumor)	0	0.00	3	5.88	3	3.75		
Papillary adenoma (benign)	1	3.45	0	0.00	1	1.25		
Main branch IPMN(intraductal papillary mucinous neoplasm	0	0.00	2	3.92	2	2.50		
Ampullary mass lesion (Ampullary carcinoma)	0	0.00	10	19.61	10	12.50		
Primary sclerosing cholangitis (Onion skin apperance)	2	6.90	0	0.00	2	2.50		
Total	29	100.00	51	100.00	80	100.00		

(*) symbol signifies that the P-value is statistically significant

DISCUSSION

Determining whether intrahepatic and/or extrahepatic biliary strictures are benign or malignant can sometimes be a diagnostic issue for those with cholestatic medical conditions. A proper diagnosis is critical to prevent surgically exploring benign illness that mimics malignancy or failing to detect cancer in strictures that seem benign [11].

In our study, most patients complained of abdominal pain (n=66: 82.5%), jaundice (n=60: 75%), fatigue (n=45: 56.25%), itching (n=37: 46.25%), fever (n=35: 43.75%), or weight loss (n=19: 23.75%). A study by **Sousa *et al.*** [12] was conducted on 56 individuals who had EUS between 2010 and 2017 due to an inexplicable dilated CBD seen by ultrasound or (CT). Most patients were asymptomatic (n=28: 50%). Abdominal pain was the most common presenting symptom in symptomatic patients (n=20: 36%), followed by jaundice (n=5: 9%), weight loss (n=2: 4%), and itching (n=1: 2%). A study by **Saifuku *et al.*** [7] was conducted on 34 patients who had unexplained biliary strictures identified by ERCP or MRCP and were assessed using EUS. Thirteen individuals had jaundice at the time of presentation. Of the twenty-one individuals who did not have jaundice, eight had abnormal liver blood tests. 34 patients had their tumor markers measured of them 17 showed malignant strictures, 13 were accurately recognized as malignant, and 12 of the remaining 17 strictures were correctly classified as benign. Patients with benign and malignant lesions did not significantly vary in the proportion of accurate diagnosis (76.5% vs. 70.6%, $P > 0.05$) [7].

In our study, the diagnoses were Distal cholangicarcinoma (n=21: 26%), pancreatic head mass (n=17: 21%), ampullary mass lesions (n=11: 13%), main branch IPMN intraductal papillary mucinous neoplasm (n=2: 2%), inflammatory strictures (n=25: 31%), primary sclerosing cholangitis (n=2: 2%) and hydatidosis (n=2: 2%). The patients were classified as having malignant strictures (n=51: 63%) or benign strictures (n=29: 36%). In the study by **Sousa *et al.*** [12] pancreatico-biliary EUS operations were carried out on 56 patients for a dilated CBD. 39 patients had normal EUS results. In 30% of cases, abnormal EUS results were noted. These included six cases of choledocholithiasis, three cases of ampuloma, two cases of choledochal cyst, two cases of benign CBD stenosis, one case of pancreatic head cyst, one case of cholangiocarcinoma, one case of chronic pancreatitis, and one case of CBD compression by adenomegaly**.**

LIMITATION OF THE STUDY:

Due to the small sample size of the study, more data are needed to confirm the diagnosis of unexplained distal CBD strictures, and not all patients underwent EUS-FNA.

CONCLUSION

EUS is a promising investigational procedure for patients with challenging distal CBD strictures, and can predict the nature of the strictures whether benign or malignant.

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Conflict of Interest disclosure: The authors declared that there were no conflicts of interest.

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