ENDOSCOPIC ULTRASONOGRAPHY AS A DIAGNOSTIC TOOL FOR DISTAL BILIARY OBSTRUCTION OF UNKNOWN ETIOLOGY

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ABSTRACT

Background The etiology of distal biliary obstruction cannot be determined by imaging modalities in many patients. The aim of this study was to assess the value
of endoscopic ultrasonography (EUS) in detecting the etiology of distal biliary obstruction in patients in whom ultrasonography and MRCP could not demonstrate the etiology of obstruction.

Methods Prospectively, 55 consecutive patients who were referred for evaluation of distal biliary obstruction of undetermined origin by ultrasonography and MRCP were included in this study. All the patients underwent EUS. Final diagnoses were determined by using endoscopic retrograde cholangiopancreatography (ERCP), EUS-guided fine needle aspiration (FNA), surgical exploration, or follow-up for at least 6 months.

Results 55 patients (60 % male) with distal biliary obstruction were included. Mean (±SD) age of the patients was 54.9 (±10.48) years. Final diagnoses included pancreatic carcinoma in 26 patients (47.3%), chronic pancreatitis 7 (12.73%), choledocholithiasis in 7 (12.73 %), ampullary adenoma 7 (12.73%), ampullary adenocarcinoma 6 (10.9%) and cholangiocarcinoma in 2 patients (3.64%). Sensitivity, specificity and accuracy of EUS for identifying malignant lesions were 93.94 %, 86.36% and 90.91 %, respectively. Sensitivity, specificity and accuracy of EUS FNA for identifying malignant lesions were 90.62%, 100% and 93.62%, respectively.

Conclusion After diagnosis of distal biliary obstruction by transabdominal ultrasonography and MRCP, EUS may be a reasonable choice for determining the etiology of distal biliary obstruction.

KEYWORDS: EUS, Ultrasonography, MRCP, ERCP, Carcinoma

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INTRODUCTION

The diagnostic evaluation of a patient with a bile duct obstruction is designed to differentiate benign lesions such as gallstones from the malignant biliary obstruction and to establish the extent of tumor invasion and spread in cases with malignancy ***(Cohen and Bacon, 2002).*** Endoscopic retrograde cholangiopancreatography (ERCP) was introduced in the world of gastroenterology four decades ago initially as a purely diagnostic procedure, but after the development of endoscopic sphincterotomy and increasingly complex techniques, it moved to the therapeutic area. Furthermore, the emergence and rapid improvement of less invasive modalities, such as Trans abdominal ultrasound (TAU), computed tomography, magnetic resonance cholangiopancreatography, and endoscopic ultrasound (EUS), replaced ERCP in its diagnostic role. In fact, this technique is mainly considered a therapeutic procedure. Despite this "shift" to intervention, the main indications for its performance have not changed, namely cholelithiasis and its complications, biliary and pancreatic ductal abnormalities, and ampullary/periampullary lesions***(Fanelli et al, 2012).*** For this reason, endoscopic ultrasound (EUS) is recommended for evaluation of etiology of obstructive jaundice either gall stones or peri-ampullary or pancreatic lesions ***(Sotoudehmanesh and Nejati, 2016)***.

PATIENTS AND METHODS

This Cross-sectional Study-Descriptive-Diagnostic study was conducted in co-operation between Endemic Medicine Department, Faculty of Medicine, Cairo University and the Gastroenterology and Hepatology Department, Theodor Bilharz Research Institute, Cairo, Egypt.

The work was performed between *March 2019 to May 2021.*

The study was conducted on 55 Patients who presented by jaundice and or abdominal pain with radiological evidence of distal biliary obstruction. Biliary obstruction was diagnosed in the form of dilated CBD(diameter ≥7 mm). The aetiology of

distal biliary obstruction could not be determined by ultrasonography and MRCP.

The study was approved by the ethical committee and an informed consent was obtained from all patients before recruitment in the study.

All Patients were subjected to full medical history with stress on biliary obstructive symptoms as jaundice, dark coloured urine, clay coloured stool, abdominal pain, fever, itching, perception of body masses and weight loss.

All Patients were subjected to full Clinical examination with special stress on signs as jaundice, anemia, abdominal tenderness, abdominal mass, hepatomegaly and cachexia.

All Patients were subjected to l**aboratory investigations included:**Coagulation profile (prothrombin time, partial thromboplastin time, international normalized ratio and bleeding time), Complete blood count, erythrocyte sedimentation rate, liver functions tests (Alkaline phosphatase, Gamma-glutamyltransferase), renal function tests (Urea, Creatinine) and tumor marker (CA19-9).

All patients were subjected to Ultrasonography and MRCP. Patients in whom ultrasonography and MRCP could not detect etiology of distal biliary obstruction were included in this study.

Endoscopic intervention:

Endoscopic ultrasonography:

EUS was done to all patients using an EUS linear array Echoendoscope, Pentax EG-3870UTK attached to Hitachi Avius US machine under propofol deep sedation. During EUS examination, The liver was examined thoroughly to detect hepatic focal lesions with possible EUS-FNA of any detected lesions. The CBD was examined all through its length during gastric, bulbar and postbulbar stations with FNA of any detected lesions. Pancreas (Head, Neck, Body and Tail) was examined for the presence of mass and if any staging and FNA was done. Target lesions were initially identified and their detailed endosonographic features were assessed, then EUS-FNA was carried out using a 22 or 19-gauge needles.

ERCP:

All patients were sent for ERCP for diagnostic and therapeutic management of obstructive jaundice. Management was done according to etiology of obstruction. Patients with calcular biliary obstruction were treated by generous sphincterotomy then balloon sweeping of CBD with removal of stones. In some cases dormia basket was used for removal of stones. Patients with ampullary adenoma underwent endoscopic ampullectomy. Patients with CBD strictures underwent biliary stenting using plastic stents after minor sphincterotomy.

Histopathological Examination:

All patients in this study were examined by EUS. If EUS showed a mass or suspicious lesion FNA was done, and histopathological diagnosis was carried out after an informed consent from the patients. The aspirate was spread over glass slides and fixed by 95% alcohol, also formalin block was provided, then the specimens were subjected to cytological examination, including immunopathological staining if needed.

Final diagnoses were determined by using endoscopic retrograde cholangiopancreatography (ERCP), EUS-guided fine needle aspiration (FNA) or surgical exploration. In patients without evidence of malignancy final diagnoses were determined after follow up for at least 6 months by endoscopic ultrasound and laboratory investigations. Patients with choledocholithiasis were referred for ERCP, sphincterotomy and stone extraction. Patients with operable tumors were referred for surgery. Patients with inoperable tumors underwent biliary stenting and were referred to Oncology Department.

Statistical Methodology:

Descriptive statistics were done for quantitative data as minimum& maximum of the range as well as mea1n±SD (standard deviation) for quantitative parametric data, median and 1^{st}& 3^{rd} inter-quartile range for quantitative non-parametric data, while it was done for qualitative data as number and percentage.

Continuous values were presented as mean ± standard deviation, or in the case of non-normally distributed data as median and inter-quartile range. Continuous data were analyzed using independent samples T-test or Mann-Whitney U test in case of skewed data.

RESULTS

The mean age of our studied patients was 54.9 ±10.48 years with male predominance **(60 %)**.Almost all patients suffered from jaundice (92.73%) and abdominal pain (94.55%) as shown in table 1.

Table 1: Descriptive data for demographic and clinical symptoms of the studied patients.

	Variables	Frequency (%)
Gender	Male	33 (60 %)
	Female	22 (40 %)
Symptoms	Jaundice	51 (92.73%)
	Dark urine	54 (98.18%)
	Clay stool	8 (14.55%)
	Itching	26 (47.27%)
	Fever	8 (14.5%)
	Rigor	3 (5.45%)
	Upper abdominal pain	52 (94.55%)
	Weight loss	32 (58.18%)

The laboratory data of our patients showed hyperbilirubinaemia (median 7.3 mg/dl) which was mainly direct (median 5.3 mg/dl). Alkaline phosphatase was elevated (median 423). GGT was elevated (median 501). CA 19-9 was elevated (median 157) as shown in table 2.

Table (2): Baseline laboratory data .

Variables	Description
CBC	
WBCs / µL Median (IQR)	7600 (5300-11300)
Hemoglobin Mean (SD) (gm/dl)	11.86 (1.73)
Platelets / µL Median (IQR)	247000 (187000-300000)
LFTs	
T Bilirubin (mg/dl) Median (IQR)	7.3 (4.1-11.3)
D Bilirubin (mg/dl)Median (IQR)	5.3 (2.6-7.8)
ALP (U/L)Median (IQR)	423 (280-517)
GGT (U/L)Median (IQR)	501 (267-569)
AST (U/L)Median (IQR)	65 (39-115)
ALT (U/L)Median (IQR)	72 (46-130)
Urea (mg/dl)Median (IQR)	35 (26-45)
Creatinine (mg/dl)Median (IQR)	0.9 (0.75-1.1)
CA-19-9 (U/ml)Median (IQR)	157 (39-712)

All our patients showed dilated intra-hepatic biliary radicles, and showed dilated CBD, with a median diameter 11 mm. Calcular gall bladder was seen in only 23.64 % of patients, and 76.36 % had normal gall bladder, as shown in table 3.

Similar to ultrasound findings, MRCP showed that all patients had dilated intra-hepatic biliary radicles and dilated CBD, with a mean diameter 14 mm. Calcular gall bladder was seen in 23.64% of the patients, as shown in table 3.

EUS diagnoses revealed that pancreatic mass (size of pancreatic mass was less than 2.3 cm in all patients) was the most common finding by EUS 49.09 % of patients. Choledocholithiasis was found in 14.54 % of patients. Ampullary adenoma was found in 12.73% of patients. Ampullary mass was found in 10.91% of patients. Chronic pancreatitis (according to Rosemont criteria) was found in 9.09% of patients .Cholangiocarcinoma was found in 3.64 % of patients, as shown in table 3.

FNA diagnosis revealed that pancreatic adenocarcinoma was the most common finding 42.55% of patients. Chronic pancreatitis was found in 21.28% of patients. Ampullary adenoma was found in 14.89% of patients. Ampullary adenocarcinoma was found in 10.64% of patients. IPMN was found in 4.25% of patients. Cholangiocarcinoma was found in 4.25% of patients. Inflammatory reaction with no malignant cells was found in 2.14% of patients as shown in table 3.

Final diagnosis after follow up revealed that pancreatic adenocarcinoma was the most common diagnosis 43.64% of patients. Chronic pancreatitis was found in 12.73% of patients. Ampullary adenoma was found in 12.73 of patients. Calcular obstructive jaundice was found in 12.73% of patients. Ampullary adenocarcinoma was found in 10.9% of patients. Cholangiocarcinoma was found

in 3.64% of patients. IPMN was found in 3.64% of patients as shown in table 3.

Table 3: Descriptive data findings that was found by different diagnostic modalities in identifying the cause of distal biliary obstruction.

	Variables		Frequency (%)
TUA	Dilated IHBRs		55 (100%)
	Dilated CBD (Median CBD diameter was 11mm)		55 (100%)
	Gall Bladder	Calcular	13 23.64%
		Normal	42 76.36%
MRCP finding	Dilated IHBRs		55 (100%)
	Dilated CBD (Median CBD diameter was 14 mm)		55 (100%)
	Gall Bladder	Calcular	13 23.64%
		Normal	42 76.36 %
	EUS-diagnosis	Pancreatic mass	26 (47.27%)
		Choledocholithiasis	8 (14.54%)
		Ampullary adenoma	7 (12.73%)
		Ampullary mass	6 (10.91%)
		Chronic pancreatitis with benign stricture	6 (10.91%)
		Cholangiocarcinoma	2 (3.64%)
EUS diagnosis	Pancreatic mass		27 (49.09%)
	Choledocholithiasis		8 (14.54%)
	Ampullary adenoma		7 (12.73%)
	Ampullary mass		6 (10.91%)
	Chronic pancreatitis with benign stricture		5 (9.09%)
	Cholangiocarcinoma		2 (3.64%)
EUS FNA diagnosis	Pancreatic adenocarcinoma		20 (42.55%)
	Chronic pancreatitis		10 (21.28%)
	Ampullary adenoma		7 (14.89%)
	Ampullary adenocarcinoma		5 (10.64%)
	IPMN (pancreas)		2 (4.25%)
	cholangiocarcinoma		2 (4.25%)
	Inflammatory reaction with no malignant cells		1 (2.14%)
Final diagnosis	Pancreatic adenocarcinoma		23 (41.82%)
	Chronic pancreatitis		8 (14.55%)
	Calcular obstructive jaundice		7 (12.73%)
	Ampullary adenoma		7 (12.73%)
	Ampullary adenocarcinoma		6 (10.90%)
	Cholangiocarcinoma		2 (3.64%)
	IPMN		2 (3.64%)

Regarding pancreatic lesions: EUS had high sensitivity 92% but low specificity 57.14 % with an accuracy of 80%.

EUS had high sensitivity 100 % and high specificity 100% in diagnosis of ampullary lesions with accuracy of 100 %

EUS had high sensitivity 94 % and specificity of 76 % in diagnosis of CBD stricture with an accuracy of 89%

EUS had high sensitivity 94 % and specificity of 87 % in diagnosis of malignant lesions with an accuracy of 91 % as shown in table 4.

DISCUSSION

Common bile duct (CBD) dilatation caused by biliary obstruction due to gall stones or malignancy as cancer head of pancreas or ampulla of vater or CBD stricture either benign due to chronic pancreatitis or malignant. TUS should be the first imaging study in evaluation the level of biliary obstruction and gallstones ***(Chen and Yang, 2015).*** If etiology of biliary obstructioncan't be detected by U/S and MRCP, more diagnostic modalities such as endoscopic ultrasound (EUS) is recommended for

evaluation of etiology of biliary obstruction ***(Sotoudehmanesh and Nejati, 2016).***

In the current study 55 patients were recruited from outpatient clinic and endoscopy unit at Theodor Bilharz Research Institute and Endemic Medicine Department at Faculty of Medicine, Cairo University. These patients presented by distal biliary obstruction of undetermined etiology by ultrasonography and MRCP.

As regard the clinical presentations of our studied patients, we found that jaundice (92.73 %), abdominal pain (94.55%) and weight loss (58.18%) were the most common clinical presentations. This was similar to **Sotoudehmanesh et al. (2016)**, who noted that abdominal pain, jaundice and weight loss were the most common presentations in their patients. Results were also similar to **Ding et al. (2019)** who found that abdominal pain and jaundice were the most common clinical presentations.

In our work, mainly direct hyperbilirubinaemia was found in all our cases and CA 19.9 (median 157 U/L) was elevated in 40 cases (72.72% of patients), 28 cases of them were malignant 70% . Elevated CA 19.9 in our study is in agreement with the study of **La Greca et al. (2012)** which was conducted on 102 patients 51 patients had malignant obstructive jaundice and CA19-9 was elevated in 42 patients and 51 patients had benign obstructive jaundice and CA 19-9 was elevated in 28 patients so CA19-9 was elevated in 70 patients 68.6% of patients. Elevated CA 19.9 in our study is not in agreement with the study of **Ding et al. (2019)** which was conducted on 115 patients with dilated CBD of unknown etiology by abdominal ultrasonography or MRCP referred for EUS and found that CA 19.9 was elevated only in 31.3% of patients. This difference may be due to the differences in etiology of CBD strictures in the patients included in the 2 studies. In the study of **Ding et al. (2019)** patients with ampullary tumors were 37 patients (32%) in whom CA 19.9 was elevated, patients were choledocholithiasis were 10 patients (8%) and patients with inflammatory CBD stricture were 68 patients (60%).

Regarding the EUS data in our study, we found that almost half of our patients had malignancy, where pancreatic masses 49.09% were the most common finding, then choledocholithiasis 14.54% then ampullary adenoma 12.73% then ampullary mass 10.91% then chronic pancreatitis 9.09% , however the minority of patients were diagnosed with cholangiocarcinoma 3.64%. The results of our study were similar to the results of study of **Sotoudehmanesh et al. (2011)** which was conducted on 107 patientspresented by dilated CBD on abdominal ultrasonography and abnormal liver functions tests with inconclusive magnetic resonance imagingand EUS found that the most common diagnosis was pancreatic adenocarcinoma 29% and the least common diagnosis was cholangiocarcinoma 5.5%.

Unlike the results of our study, **Rana et al. (2013)** study which was conducted on 40 patients presented by dilated CBD on abdominal ultrasonography for evaluation of upper abdominal discomfort and Magnetic resonance imaging didn't find the aetiology of CBD dilatation .EUS showed that the majority of patients were benign, with normal CBD in 50 % of patients and CBD stones in 37.5% of patients and CBD mass in 5 % of patients and benign CBD stricture in 5% of patients and chronic pancreatitis with CBD stricture in 2.5% of cases. This difference due to the difference in inclusion criteria as the study of **Rana et al. (2013)** include patients with only dilated CBD on abdominal U/S with or without jaundice.

Regarding FNA diagnosis, Our study showed that pancreatic adenocarcinoma 42.55% was the most common finding then chronic pancreatitis 21.28 % then ampullary adenoma 14.89% then ampullary adenocarcinoma 10.64% then IPMN and cholangiocarcinoma 4.25% then post pancreatitits inflammatory reaction 2.14 %.

This is in agreement with the study of **Hyun Jo et al. (2018)** which was conducted on 263 patients presented by suspected malignant obstructive jaundice by pre-evaluation CT or MRI who underwent same session EUS FNA and ERCP for confirmation of diagnosis by tissue sampling and showed that 133 patients 50.6% were malignant cases and 48 cases 18.3% were atypical suspected malignant and 24 cases 9.1% were benign and 12 cases 4.6 % were atypical favor benign and 46 cases 17.5% were non diagnostic

Concerning the sensitivity and specificity of different diagnostic modalities in different lesions, regarding pancreatic lesions, Our results showed that EUS had a sensitivity of 92% and specificity of 57.14% in diagnosis of pancreatic lesions with an accuracy of 80%. Our study is in agreement with the study of **Bunganic et al. (2018)** who studied 116 patients presented by pancreatic lesions detected on CT and found that EUS had a sensitivity of 83.1 and specificity of 62.5% in diagnosis of pancreatic lesions with an accuracy of 78.6%

In our study we found that FNA has a sensitivity of 91.67% and specificity of 100% in diagnosis of pancreatic lesions with an accuracy of 93.75 %. This is in agreement with the study of **turner et al. (2010)** which was conducted on 559 patients underwent evaluation of pancreatic masses or diffuse pancreatic parenchymal abnormalities by CT or MRI and found that sensitivity of FNA was 93% and specificity of 100% in diagnosis of pancreatic lesions with an accuracy of 94%. This also is in agreement with the study of with **Bang et al. (2016)** which was done on 576 patients and found that diagnostic accuracy of FNA in pancreatic lesions was 85.6 %.

On the contrary, **senturk et al. (2013)** showed a lower sensitivity of FNA 74.7%, with a specificity

of 100% in diagnosis of pancreatic lesions with an accuracy of 75 %. Also**Kim et al. (2014)** study showed a sensitivity of 78% and specificity of 75 % in diagnosis of pancreatic lesions with an accuracy of 77%. This difference is due to that EUS FNA was done after ERCP and biliary stenting which lower the yield of FNA in pancreatic lesions.

As regard the ampullary lesions in our study, EUS had a sensitivity of 100% and specificity of 100% in diagnosis of ampullary lesions with an accuracy of 100%. This is in agreement with the study of **Manta et al. (2010)**which was conducted on 24 symptomatic patients (referred for increasing liver enzymes, jaundice, abdominal pain or dilation of the biliary tract by abdominal ultrasonography) and found to have ampullary tumors on EUS. The study found that EUS had a sensitivity of 100 % and specificity of 100 % in identifying ampullary lesions. Similar to our results, **Rejeski et al. (2016)** studied 50 patientswho underwent EUS for the purpose of evaluating an ampullary mass or for staging and found that EUS had a sensitivity of 97 % and specificity of 100 % in identifying ampullary lesions.

However, **Menzel et al. (1999),** found lower EUS sensitivity 62.5% and specificity 50% in diagnosis of ampullary tumors with an accuracy of 56.3%. The difference may be related to operator dependent factors or due to very small size of ampullary tumors which was diagnosed later by intraductal U/S.

Regarding CBD strictures, out of the 43 case of CBD stricture, 31 cases proved to be malignant and 12 cases proved to be benign**.** EUS had high sensitivity 94% but relatively low specificity 76% in diagnosis of CBD strictures with an accuracy of 89%. The results of our study is in agreement with the study of **Saifuku et al. (2010)** which was conducted on 34 patients with distal biliary stricture detected by ERCP or MRCP and found that EUS had a sensitivity of 94.1% and specificity of 82.3% in diagnosis of CBD stricture with an accuracy of 88.2%.

On the contrary, **Menzel et al. (2000)** who studied 56 patients with biliary stricture found that EUS had a sensitivity of 75.7% and specificity of 75% in diagnosis of biliary stricture with an accuracy of 75.6%. This difference may be due to operator dependant factors in the early era of endoscopic ultrasonography and the results were compared to intraductal U/S which is more accurate.

EUS FNA in our work showed high sensitivity 90% and excellent specificity 100% in diagnosing the etiology of CBD strictures with an accuracy of 92%. This is in agreement with the study of **Weilert et al. (2014),** who found that sensitivity of FNA was 94% and specificity 100% in diagnosing the etiology of CBD stricture with an accuracy of 94%. Also **Ohshima et al. (2011)** studied 22 patients and found that FNA had a sensitivity of 100% and specificity of 100% in diagnosis of biliary stricture with an accuracy of 100%.

But the results of our study is against the results of study of **Nayar et al. (2011)** which was conducted on 32 patients with proximal CBD stricture and found that FNA had a sensitivity of 52% and specificity of 100% in diagnosing theetiology of CBD stricture with an accuracy of 59%. The difference between results is due to that the study of **Nayar et al. (2011)** was done on small number of patients and they had proximal CBD stricture which is usually difficult for diagnosis than distal CBD stricture.

On studying CBD stones, EUS had excellent sensitivity 100% and high specificity 97.9% in diagnosis of CBD stones with an accuracy of 98.18%. This is in agreement with study of **Jeon et al. (2017)** which was conducted on 200 patients with suspected CBD stones and negative CT findings and found that EUS had a sensitivity of 97.5% and specificity of 79 % in diagnosis of CBD stones with an accuracy of 94%.

In our study we found that EUS has a sensitivity of 94% and specificity of 87 % in identifying malignant lesions with accuracy of 91% which is in agreement with the study of **Sotoudehmanesh et al. (2011)** who found that EUS had a sensitivity of 100% and specificity of 98.4 % in identifying malignant lesions with an accuracy of 99.1%.

CONCLUSION

Patients with inconclusive MRCP diagnosis of the cause of distal biliary obstruction can benefit from EUS. EUS is of great value in cases of inconclusive MRCP indicating other pancreatobiliary disorders .

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