ARAŞTIRMA MAKALESİ / *RESEARCH ARTICLE*

The Role of Endosonography in Patients With Moderate and High Probability of Choledocholithiasis

Orta ve Yüksek Olasılıklı Koledokolitiazis Hastalarında Endosonografinin Rolü

Rasim Eren Cankurtaran[1], Zahide Simsek[2], Yusuf Coskun[2]

[1]Department of Gastroenterology, Yıldırım Beyazıt University Faculty of Medicine; [2]Health Sciences University Diskapi Training and Research Hospital, Ankara, Türkiye

ABSTRACT

Aim: *In this study, we aimed to investigate the diagnostic efficiency and place of EUS in clinical practice in patients with moderate to a high probability of choledocholithiasis according to their ASGE score.*

Material and Method: *This study includes patients with moderate to high risk of CBDSs who were admitted to the Department of Gastroenterology between August 2015-August 2016. The results of patients undergoing EUS and ERCP for suspected choledocholithiasis were retrospectively reviewed from the hospital registry.*

Results: *Two hundred and twenty nine patients were included in the present study and 56.3% of the patients (n=129) were female, and the average age of the patients was 62.8±18.3 (20–91). The sensitivity of EUS was found to be 89.2%. The specificity was 94.6%, the positive predictive value was 95.6%, and the negative predictive value was 86.9%. In addition, the choledochal diameter measured in AUS and EUS was found to have diagnostic values in predicting the CBDSs [AUC (95% GA p); respectively, 0.617 (0.409–0.825) p=0.310 and 0.765 (0.619–0.915) 0.020].*

Conclusion: *Endosonography is both a high-diagnostic and a low-invasive diagnostic method, so it is increasingly used in patients with suspected CBDSs. Referral of suspected patients with CBDSs to a center with EUS and an experienced endoscopist will ensure that the patient receives the correct diagnosis and is not subjected to unnecessary invasive procedures.*

Key words: *EUS; ERCP; choledocholitiasis*

ÖZET

Amaç: *Bu çalışmada ASGE skoruna göre orta-yüksek olasılıklı koledokolitiazis hastalarında EUS'nin tanısal etkinliğini ve klinik pratikteki yerini araştırmayı amaçladık.*

Materyal ve Metot: *Bu çalışma Ağustos 2015-Ağustos 2016 tarihleri arasında Gastroenteroloji kliniğine başvuran orta ve yüksek olasılıklı koledokolitiazis hastalarını içermektedir. Koledokolitiazis şüphesiyle EUS ve/veya ERCP yapılan hastaların sonuçları hastane kayıtlarından retrospektif olarak tarandı.*

Bulgular: *Çalışmaya 229 hasta dâhil edildi ve bunların %56,3 (n=129)'ü kadın ve hastaların yaş ortalaması 62,8±18,3 (20–91) idi. "Endosonography"nin duyarlılığı % 89,2, özgüllüğü %94,6, pozitif prediktif değeri %95,6, negative prediktif değeri % 86,9 olarak bulundu. "Abdominal ultrasonography" ve EUS'de ölçülen koledok çapının CBDSs'leri öngörmede tanısal değerlere sahip olduğu bulundu [AUC (% 95 GA p); sırasıyla, 0,617 (0,409–0,825) p=0,310 ve 0,765 (0,619–0,915) 0,020].*

Sonuç: *Endosonography hem yüksek tanısal hem de düşük invaziv bir prosedür tanı yöntemi olduğundan CBDSs şüphesi olan hastalarda giderek daha fazla kullanılmaktadır. "Common bile duct stone" şüphesi olan hastaların EUS ve deneyimli bir endoscopist olan bir merkeze yönlendirilmesi hastanın doğru tanı almasını ve gereksiz invaziv müdahalelere maruz kalmamasını sağlayacaktır.*

Anahtar kelimeler: *EUS; ERCP; koledokolitiazis*

Introduction

Common bile duct stones (CBDSs) are a common clinical condition in daily practice. The migration of gallstones to the main bile duct causes patients with symptoms to apply frequently to the clinic. In addition, CBDSs can cause serious complications such as pancreatitis, cholangitis, obstructive jaundice, and secondary biliary cirrhosis[1]. Therefore, early diagnosis and treatment of gallstonesis vital.

Abdominal ultrasonography (AUS) is recommended for patients with choledocholithiasis based on the clinical and laboratory findings. However, AUS is relatively insufficient in diagnosis, and additional diagnostic methods are needed[2]. Diagnosis of choledocholithiasis includes multiple images such as endosonography (EUS), Endoscopic retrograde cholangiopancreatography

İletişim/Contact: *Rasim Eren Cankurtaran, Üniversiteler Mahallesi 1604. Cadde No: 9 Çankaya / Ankara - Türkiye* • ***Tel:*** *0506 509 13 64* • ***E-mail:*** *drcankurtaran88@gmail.com* • ***Geliş/Received:*** *01.04.2022* • ***Kabul/Accepted:*** *20.06.2022*

ORCID: *Rasim Eren Cankurtaran, 0000-0002-3687-3845* • *Zahide Şimşek, 0000-0003-0212-064X* • *Yusuf Coşkun, 0000-0001-6016-6297*

(ERCP), magnetic resonance cholangiopancreatography (MRCP), Computed Tomography (CT), and intraoperative cholangiography. In previous years, ERCP was preferred as both a diagnostic and therapeutic method. The sensitivity of ERCP in patients with CBDSs was found to vary between 80–93% and the specificity was reported to be 99–100%[3,4]. The ERCP application, which is used as a very important therapeutic method, is an invasive procedure that requires experience and can lead to some complications. In addition, patients are exposed to radiation during this process. Endoscopic retrograde cholangiopancreatography related complications such as pancreatitis, cholangitis, bleeding, and perforation may occur[5].

The aforementioned information shows that AUS is non-invasive but has a low diagnostic value and that ERCP is the gold standard in diagnosis and is a therapeutic method since it is an invasive procedure[6]. However, neither method is considered ideal in the diagnosis of CBDSs. Patients with suspected CBDSs need a diagnostic method that has a high diagnostic specificity and a lower risk of complications.

In 2010, the American Society for Gastrointestinal Endoscopy (ASGE) divided patients with suspected choledocholithiasis into three groups as high, moderate, and low probability. According to the ASGE score, preoperative ERCP is recommended because patients with a high risk of choledochal stones are above 50% clinically. Intraoperative cholangiography is another option for these patients. All other patients in the medium risk group were offered EUS, MRCP, intraoperative cholangiography, or laparoscopic ultrasonography before cholecystectomy, depending on cost effectivity[2].

In recent years, EUS has become widely used due to its less invasiveness and high sensitivity in the diagnosis of choledocholithiasis[7]. In particular, there is a widespread belief that EUS reduces unnecessary ERCP and complications associated with this procedure[8]. In this study, we aimed to investigate the diagnostic efficiency and place of EUS in clinical practice in patients with moderate to high probability of choledocholithiasis according to their ASGE score.

Materials and Methods

Patients and Study Design

This study includes 229 patients with moderate to high risk of CBDSs who were hospitalized to Dişkapi Yildirim Beyazit Education and Research Hospital Department of Gastroenterology in Ankara, Turkey, between August 2015-August 2016. The patients' clinical risk of CBDSs was assessed according to the ASGE 2010 guidelines. Based on these criteria, patients were categorized as having a low (<10%), moderate (10% to 50 %), or high (>50%) probability of CBDSs, using their age, liver function test results, and transabdominal ultrasonography findings. We excluded patients who had a history of malignant disease, had previouly undergone endoscopic procedures for biliary reasons, or who were <18 years old. The results of patients undergoing EUS and/or ERCP for suspected choledocholithiasis were retrospectively reviewed from the hospital registry. Preoperative complaints, abdominal USG data, WBC, hemoglobin, platelet, INR, total bilirubin, direct bilirubin, ALT, GGT, amylase, and lipase values were recorded. Dilated CBD was defined as a CBD when diameter was above 6 mm or 10 mm in cases of cholecystectomy on AUS[9]. The results of the EUS and ERCP procedures, complications related to the procedures, and laboratory values obtained 6 months later were retrospectively reviewed.

EUS/ERCP

A radial ultrasonic echoendoscope (model of CLV-180-Aloka; Olympus, Tokyo, Japan) was used for EUS examinations. Endosonography was performed within 24 hours after admission by an experienced endoscopist. Common bile duct stones were positively defined by the observation of a hyperechoic focus within the common biliary duct with or without an acoustic shadow. The widest diameter of the CBD was measured.

Endoscopic retrograde cholangiopancreatography was performed with a lateral scope (Fujinon EPX-4400) when CBDSs were detected on EUS or for patients with a high probability CBDSs according to the ASGE criteria. The patients were treated after at least 12 hours of fasting. The patients were sedated with Midazolam (mean 5–10 mg, maximum 40 mg) and propofol (mean 10–20 mg) after they were informed about the procedure. After selective biliary cannulation, the biliary tract was visualized by contrast agent administration, and sphincterotomy was performed when indicated. If a filling defect or stones were present in the CBD, the stone extraction was performed using a balloon and/or basket. After the procedure, the patients were observed in the hospital for at least 24 hours, and biochemical tests were recorded 6 hours and 24 hours post procedure. Endoscopic retrograde cholangiopancreatography related complications were

defined and graded according to standardized criteria in a consensus panel[5].

Statistical Analysis

All data were evaluated using SPSS 22.0 (Statistical Package for Social Sciences, SPSS Inc, Chicago, IL) for Windows. The suitability of the variables to normal distribution was examined using visual (histogram and probability graphs) and analytical methods (Kolmogorov-Smirnov Test). Descriptive statistics were expressed as mean, median (minimum-maximum), frequency distribution, and percentage. Pearson chi-square tests were used for the evaluation of categorical variables. The diagnostic predictivity of the CBD diameter measured by USG and EUS in predicting CBDSs were analyzed by Receiver Operating Characteristics (ROC) curve analysis. Sensitivity, specificity, and the positive and negative predictive values of these limits were calculated in the presence of significant limit values. Statistical significance level was accepted as $p<0.05$.

Results

56.3% of the patients (n=129) were female, and the average age of the patients was 62.8±18.3 (20–91). 91.7% of patients (n=210) had symptoms of abdominal pain. 66.4% (n=152) of the patients were in the high probability group according to their ASGE scores. 18.8% (n=43) had a history of cholecystectomy. 66.8% (n=153) of the patients were diagnosed with gallstones in AUS, while 24.9% (n=57) had choledochal stones in AUS and 79.0% (n=181) were found to have choledochal dilatation in AUS (Table 1). The mean values of the laboratory data pertaining to the patients are presented in Table 2.

According to the patients' ASGE scores, ERCP was performed on 84 patients in the high-probability choledocholithiasis group, while EUS was performed on 77 patients with moderate probability. Only 68 patients with high-probability comorbid diseases (e.g., advanced cerebral insufficiency, chronic obstructive pulmonary disease, etc.) or with anticoagulant-antiplatelet use were assessed with EUS. Endoscopic retrograde cholangiopancreatography was performed in the same session on 69 patients with choledochal stone in EUS, and follow up visits were conducted with 61 patients. In seven of these patients, choledochal stones were found in three patients who underwent ERCP due to elevated cholestasis enzymes and suspected CBDS. Of the 54 patients who received clinical follow-up, five patients were discharged; however, a few days after discharge, ERCP was performed on these patients due to recurrent cholestasis enzymes and epigastric pain. The remaining 49 patients did not have any clinical or biochemical pathology in their 6-month follow-up (Fig. 1).

Choledocholithiasis was detected by ERCP in 95.7% (n=66) of patients who were suspected of having choledochal stones with EUS. In 13.1% (n=8) of patients who were detected to have choledochal stones without EUS, choledocholithiasis was diagnosed in clinical follow-up (5 patients) and with ERCP (3 patients). Statistically significant differences were found between choledochal stones detection using EUS and the presence of choledocholithiasis ($p<0.001$) (Table 3).

Table 1. *Clinical and demographic data of patients*

Patients	(n=229)
Gender (Female/male) n (%)	129 (56.3) / 100 (43.7)
Age (years) Mean ± SD	62.8±18.3
After cholecystectomy n (%)	43 (18.8)
High probability CBDSs n (%)	152 (66.4)
Moderate probability CBDSs n (%)	77 (33.6)
Symptom n (%)	
Abdominal pain	210 (91.7)
Jaundice	81 (35.4)
Fever	21 (9.2)
AUS findings n (%)	
Stone / sludge in the gallbladder (yes / no)	153 (66.8) / 76 (33.2)
Choledochal dilatation (yes / no)	181 (79.0) / 48 (21.0)
Choledochal stones/ sludge (yes / no)	57 (24.9) / 172 (75.1)

CBDSs: Common bile duct stones; AUS: Abdominal ultrasonography.

Table 2. *Laboratory data of patients*

Patients (n=229)	$\overline{X}$±SD
WBC	9.6±4.7
HB	13.0±1.8
PLT	234.1±82.0
GGT	366.1±363.8
ALT	230.0±218.2
Amylase	421.2±943.6
Lipase	1173.3±3612.6
T. bilirubin	4.5±3.8
D. bilirubin	2.8±3.9

WBC: White blood cells; HB: Hemoglobin; PLT: Platelet; GGT: Gama glutamyl transferase; ALT: Alanine transferase.

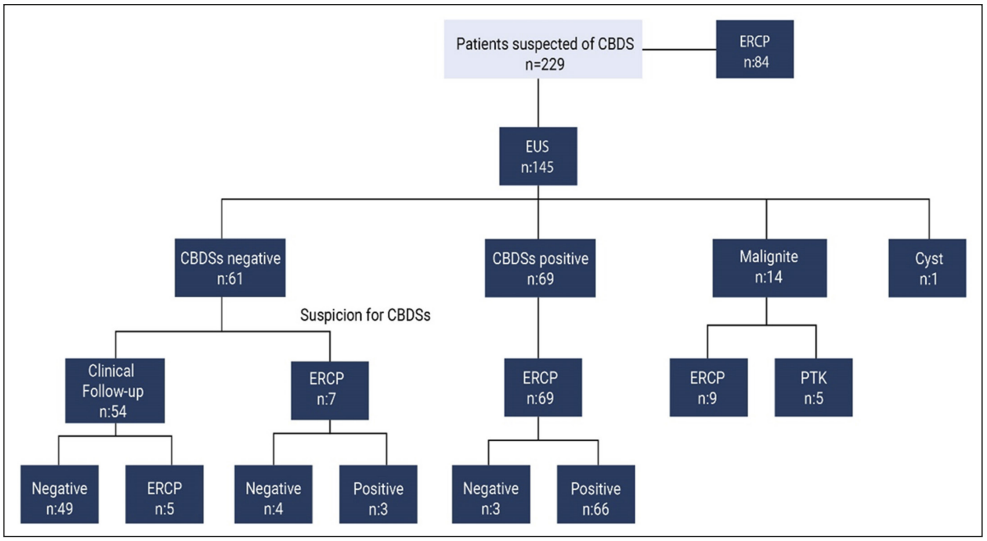

Figure 1. *Flowchart representing patient groups.*

The sensitivity of EUS was found to be 66/74×100=89.2; the specificity was 53/56×100=94.6; positive predictive value was 66/69×100=95.6; and negative predictive value was found as 53/61×100=86.9.

The diagnostic predictivity of the CBD, measured in AUS and EUS, were evaluated by ROC curve analysis in predicting the CBDSs. Accordingly, the choledochal diameter measured in AUS and EUS was found to have diagnostic values in predicting the CBDSs [AUC (% 95 GA p); respectively, 0,617 (0.409–0.825) p=0.310 and 0,765 (0.619–0.915) 0.020] (Fig. 2). Sensitivity, specificity, and the positive and negative predictive values are presented in Table 4 according to different cut-off values of measurement values.

Table 3. *Distribution of choledochal stone presence in EUS according to the presence of choledocholithiasis in participants*

	CBDS		
EUS CBDS	Negative n (%)	Positive n (%)	p
Negative	53 (86,9)	8 (13,1)	**<0.001**
Positive	3 (4,3)	66 (95,7)	

CBDSs: Common bile duct stones; EUS: Endoscopic ultrasonography.

Discussion

This study showed that EUS had high diagnostic efficiency in patients with suspected CBDSs and prevented patients from being exposed to unnecessary ERCP. No pathology was observed in most patients without choledochal stones in the EUS. Furthermore, this study revealed that patients who did not have a choledochal stone in the EUS could be followed up with after they were discharged.

Biliary pain and related complications occur in 10–25% of patients with gallstones[10,11], and major complications in 1–2%[12]. Symptoms often occur due to stones in the main bile duct. This condition can sometimes lead to life-threatening clinical signs. For this reason, the diagnosis and treatment of the main bile duct stones should not be delayed. In a recent guide, stone extraction treatment was recommended for the patients who had main bile duct stones with and without symptoms and who could tolerate the treatment[13].

The first imaging modality to be performed in patients with suspected choledocholithiasis is AUS[2]. Another

Table 4. *The diagnostic value of choledochal diameter measured in AUS and EUS in predicting choledochal stone*

	Choledochal diameter cut-off	Sensitivity	Specificity	PPD	NPD
AUS	8.25	72.8	57.1	94.4	17.3
EUS	7.1	76.8	71.4	96.3	23.8

EUS: Endoscopic ultrasonography; AUS: Abdominal ultrasonography.

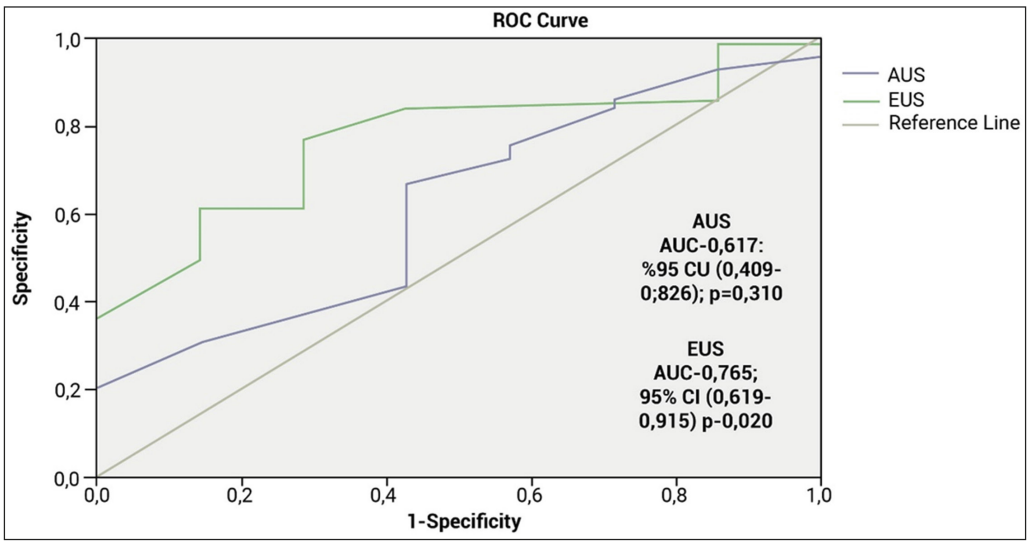

Figure 2. *Diagnostic predictivity of choledochal diameter measured in AUS and EUS in predicting choledochal stones.*

recommended first approach in patients with suspected CBDSs is liver function tests and AUS[9]. While AUS is a successful imaging method in showing gallstones, it is less successful in diagnosing CBDS. Abdominal ultrasonography has a sensitivity of 22–55% in detecting choledochal stones[14,15]. Distal choledochal stones are not often seen in AUS. The experience of a person who performs the ultrasonography, gastric bypass, and obesity are considered as factors restricting the use of AUS[14,16]. The sensitivity of the AUS is only 77–87%[3], even when evaluated in line with another parameter such as choledochal diameter dilatation. In our study, ROC analysis was performed at AUS on the of choledochal diameter to predict choledochal stones. The results showed that when the choledochal diameter is above 8.25 mm, the sensitivity is 72.8% and the PPD is 94.4%. Previous studies revealed that a diameter value above 8 mm strongly predicts biliary obstruction[17]. This study found the sensitivity of the AUS to be consistent with the literature. However, the results suggest that AUS does not have sufficient diagnostic efficacy in patients with choledocholithiasis.

In its 2010 guide, the ASGE recommended the application of ERCP for high-risk CDBS patients, while the application of MRCP or EUS methods were recommended for patients in the medium-risk group[2]. In another study, it was suggested that patients in the high-risk group might be exposed to unnecessary ERCP, and that for this reason, these patients should also first be evaluated with EUS[18].

Several studies were conducted on the diagnostic efficiency of EUS in patients suspected of having CBDSs. In a study that included 93 patients and was conducted to demonstrate the diagnostic efficiency of EUS in CBDSs, EUS was found to have a sensitivity of 100%, a specificity of 80%, a positive predictivity of 96.55%, and a negative predictivity of 100%[19]. In another study involving 62 patients, EUS sensitivity was found to be 96%, specificity was found to be 57%, positive predictivity was 88%, and negative predictivity was 80%[20]. In their study of 78 patients conducted in 2017, Patel et al.[18] found EUS sensitivity to be 93.9%, specificity was 97.3%, positive predictivity was 96.6%, and negative predictivity 94.7%. In a study involving a total of 200 patients at moderate and high risk for choledocholithiasis, Jeon et al.[21] found EUS sensitivity to be 97.5%, specificity to be 79.5%, positive predictivity to be 95.2%, and negative predictivity to be 88.6%.

In our study, the sensitivity of EUS to CBDSs was 89.2%, the specificity was 94.6%, the positive predictivity value was 95.6%, and the negative predictivity value was 86.9%. Subsequent 6-month clinical and biochemical follow-ups of patients who were not detected to have stones using EUS were included in the calculation of these values. In 49 of the 54 patients who received clinical follow-up, no pathology was found in their follow-ups. These findings suggest that EUS can significantly reduce unnecessary ERCP applications. In addition, no EUS-related complications were reported. Patients detected with choledochal stones in EUS were taken to

ERCP in the same session. A recent study has reported that performing EUS and ERCP in the same session is both safer and less expensive[22]. In our study, the predictive feature of the evaluation of the choledochal diameter with EUS in predicting the choledochal stones was detected by ROC analysis. According to this analysis, the sensitivity was found to be 76.8% and the specificity was 71.4% when the choledochal diameter cut off value was at 7.1 mm in EUS.

Since EUS is both a high-diagnostic and a low-invasive diagnostic method, it is increasingly used in patients with suspected CBDSs. One of the most important contributions of the EUS is undoubtedly the prevention of unnecessary ERCPs. In this study, we aimed to investigate the role of EUS in patients with moderate to high probability of CBDSs. Referral of suspected patients with CBDSs to a center with EUS and an experienced endoscopist will ensure that the patient receives the correct diagnosis and is not subjected to unnecessary invasive procedures.

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