The Possible Diagnostic Role of Endoscopic Ultrasound in Patients with Dyspepsia

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Background: *Dyspepsia is common in clinical practice with frequent relapses and often requires multiple investigations to assess intraluminal and extraluminal etiologies. Endoscopic ultrasound (EUS) has the potential of serving both purposes in a single setting.*
Material and Method: *Patients with dyspepsia who underwent EUS in four-year period were retrospectively reviewed. Diagnostic findings of EUS, final diagnoses were noted and compared with the reference standards.*
Results: *131 patients with a mean age ± SD of 50 ± 12.7 years were included. The common diagnoses were non-ulcer dyspepsia in 56%, symptomatic gallstone (GS) in 22.9%. EUS detected two GS missed by transabdominal ultrasound (TUS). EUS missed one GS documented by surgery. EUS detected seven cases of ERCP-proven CBD stones undetected by TUS and had a sensitivity, specificity, positive predictive value and negative predictive value for CBD stones of 87.5%, 91.7%, 87.5%, and 91.7% respectively.*
Conclusion: *EUS is a potential investigation for the management of dyspepsia.*

Keywords: *Dyspepsia, Endoscopic ultrasound, EUS*

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Dyspepsia, defined as pain or discomfort centered in the upper abdomen[1,2], is a common clinical syndrome affecting up to 25% of the population[3]. The etiologies of dyspepsia include peptic ulcer disease (PUD), atypical gastroesophageal reflux disease (GERD), functional and drug-induced dyspepsia, symptomatic biliary stones, chronic pancreatitis and gastrointestinal malignancies such as gastric cancer, liver cancer and pancreatic cancer[2,4-7]. Unfortunately, most clinical symptoms of this condition are usually unhelpful and poorly correlated to the underlying causes[8-10]. In some clinical circumstances, further investigations may be required to search for the etiologies.

Esophagogastroduodenoscopy (EGD) is the main standard investigation for dyspepsia[1,11]. However, EGD provides information on the intraluminal pathology only, and other imaging investigations are required in up to 64% of patients with persistent symptoms after the non-diagnostic EGD[12]. Endoscopic ultrasound (EUS), first introduced to clinical practice 20 years ago[13], can provide not only information on the intraluminal pathology, but also ultrasonographic images of the biliary tree, submucosal lesions, parts of the liver, pancreas, and other organs adjacent to the gut wall[14-17]. Therefore, EUS adds the advantage of providing additional information unavailable by EGD in the evaluation of dyspepsia in a single setting. In one study in patients with persistent dyspepsia, EUS was found to reduce the overall costs of investigation in a tertiary care setting[12]. EUS has also been demonstrated to be comparable in terms of accuracy and adequacy to EGD for luminal lesions, and superior to transabdominal ultrasound (TUS) for extraluminal lesions[18]. In addition, diagnostic EUS has also been shown to be as safe as EGD[19].

The current study was carried out to review the authors' experience of EUS in patients with dyspepsia in our tertiary care center.

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Material and Method

This was a retrospective review of patients aged over 17 years who underwent EUS to evaluate dyspepsia at Songklanagarind Hospital from January 2001 to December 2004.

All the patients were investigated in accordance with the dyspepsia management guideline of the Gastroenterological Association of Thailand[20]. There were 160 dyspeptic patients identified, but 29 were excluded from the present study due to incomplete medical records in 23 and cystic lesions of the pancreas or gastric submucosal masses detected by Computed Tomography (CT) prior to EUS in 6. The remaining 131 patients were included for analysis of demographic data, EUS diagnosis, operative findings where relevant, prior investigations before EUS and final outcome or diagnosis.

The EUS was performed by one of the investigators (BO) using an Olympus mechanical radial scan GF-UM 130 echoendoscope with the patients under conscious sedation. The endoscopic examination was done first, followed by a standard ultrasonographic examination starting from below the ampulla.

Diagnosis of "non-ulcer dyspepsia" (NUD) was made when neither significant mucosal nor extraluminal lesions responsible for the symptoms were detected. Symptomatic gallstone was diagnosed when biliary colic, defined as episodic pain in the epigastrium or right upper quadrant with or without radiation to the back and lasting not more than 24 hours, was present. Gallstone (GS) was defined as definite when documented by surgery or by at least two imaging methods. Common bile duct (CBD) stone was defined as definite when endoscopic retrograde cholangiopancreatography (ERCP) confirmed the presence of stone by balloon or Dormia basket retrieval. Diagnosis of definite malignancy needed pathological verification.

Statistical analysis

All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS 12.0 for windows: SPSS Inc., Chicago, IL, USA). The sensitivity, specificity, positive predictive value, and negative predictive value of EUS were calculated as compared with the reference standard.

The study was approved by the Institutional Ethics Committee of the Faculty of Medicine, Prince of Songkla University.

Results

There were 131 patients included in the present study, 85 females and 46 males, mean age $\pm$ SD of 50.1 $\pm$ 12.7 (Table 1). The duration of dyspepsia was available in 87 patients and the mean $\pm$ SD of dyspeptic duration was 16.6 $\pm$ 31.7 months. All patients had EUS successfully done and no major EUS-related complications were noted.

NUD was the most common diagnosis, made in 73 patients (55.7%), including six patients with positive EUS findings (two with "silent GS" and four with a small GB polyp) irrelevant to the dyspeptic symptoms. Definite symptomatic biliary stones were diagnosed in 30 of the 131 patients (22.9%). Malignant diseases were found in 6 (4.7%) (GB cancer 1, duodenal cancer 1, colorectal cancer 1, pancreatic cancer 1, gastric lymphoma 1, and gastrointestinal stromal tumor, GIST, of stomach 1). Five patients were initially diagnosed as NUD but subsequent diagnoses were IBS in 2 and GERD in 3. Twelve patients were classified as "inconclusive". Four of these had GS detected by EUS (but inflamed GB without GS was found during a subsequent operation in three, and no mention of GS in one), four GS detected solely by EUS refused surgery, one with CBD stone diagnosed by EUS without ERCP confirmation, one with suspected pancreatic nodules by EUS but normal CT and no tissue diagnosis, one with unexplained persistent pain despite extensive investi-

Table 1. Demographic data in 131 patients with dyspepsia

Age, mean $\pm$ SD, years	50.1 $\pm$ 12.7
Sex, Male: Female	46:85
Onset of dyspepsia, N = 87	
Mean $\pm$ SD, months	16.6 $\pm$ 31.7
Other Investigations done, N (%)	
TUS	37 (28.2)
EGD	11 (8.4)
CT Abdomen	7 (5.3)
ERCP	20 (15.3)
Final diagnosis, N (%)	
Non-ulcer dyspepsia*	73 (55.7)
GS & sludge	22 (16.8)
CBD stones	2 (1.5)
Both GS and CBD stones	6 (4.7)
PUD	3 (2.3)
Malignancies	6 (4.7)
GERD	3 (2.3)
IBS	2 (1.5)
Chronic pancreatitis	1 (0.8)
CBD stricturewith uncertain caused	1 (0.8)
Inconclusive	12 (9.2)

* including two patients with silent GS detected by one imaging method and four with small GB polyps

gation including biliary manometry, and one with isolated dilated CBD detected by EUS and ERCP but was lost to follow up.

TUS was performed in 37 patients (38.2%). Thirty-three were performed prior to EUS study. GS (17 of 37, 45.9%) and normal (10 of 37, 27.0%) were the most common findings. EGD was performed in 11 patients (8.4%), a median time 17 months (range 0.3-48 months) prior to EUS. Seven patients (5.3%) also had an additional CT abdomen, six after having EUS done as a part of disease staging or in cases of clinical incompatibility with the EUS finding. An ERCP was performed when clinically indicated after the EUS in 20 patients.

EUS Findings

EUS yielded normal findings in 51 patients (38.9%) and abnormal findings in 80 patients (61.1%) (Table 2). Of non-biliary related findings, there were three peptic ulcers (2 gastric and 1 duodenal), two gastric neoplasms (1 lymphoma and 1 GIST), one duodenal cancer, one pancreatic cancer, 18 erosive gastritis and two erosive duodenitis. In the patient with GIST, liver metastasis was not detected by EUS but was detected by TUS. EUS demonstrated a pancreatic nodule of uncertain nature not detected by CT in one patient since there was no facility to perform EUS-guided fine needle aspiration at that time. In another patient, the EUS findings were interpreted to be hydronephrosis of the left kidney but CT showed a pancreatic cyst at the tail and subsequent surgery showed only chronicpancreatitis. One patient with dyspepsia had a negative EUS who subsequently had a colonic cancer at the transverse colon detected by CT scan.

Table 2. Summary of abnormal EUS findings in 80 patients

EUS findings	N (% of 131 patients)
Intraluminal lesions	
Erosive gastritis	18 (13.7)
Erosive duodenitis	2 (1.5)
Gastric ulcer	2 (1.5)
Duodenal ulcer	1 (0.8)
Gastric tumors	2 (1.5)
Total	25 (19.1)
Extraluminal lesions	
Gallstones*	30 (22.9)
CBD stones	4 (3.1)
CBD stone &GS	5 (3.8)
Poor visualized GB	2 (1.5)
Small GB	1 (0.8)
Dilated CBD	5 (3.8)
GB polyp	4 (3.1)
Duodenal tumor	1 (0.8)
Pancreatic cancer	1 (0.8)
Pancreatic nodule	1 (0.8)
Hydronephrosis of Lt. kidney	1 (0.8)
Total	55 (42.0)

* including one GB sludge, five with concomitant minute mucosal lesions: 4 erosive gastroduodenitis, 1 gastric ulcers. All had clinical symptoms compatible with GS

Thirty-five patients had GS detected by EUS and five of these had concomitant CBD stones. GS was definite in 27 patients, 21 confirmed by surgery and 6 through correspondent TUS findings. Four patients were diagnosed as having GS by EUS but no stones were found at surgery in three and surgically proven T3 stage of GB cancer was undetected by EUS in one. In four patients with GS diagnosed solely by EUS, the operative report did not state the presence or absence of the GS in one and three refused to have surgery (two with normal prior TUS and one without TUS done). Of the 27 definite GS cases diagnosed by EUS, two had been missed by prior TUS, one of which had a TUS finding of thick wall GB and the other a GB polyp.

One patient with EUS findings of a small GB without stone had a surgically proven GS. EUS did not detect a TUS-detected GS in three patients, two had poor visualization of GB by EUS and one had no detectable GS by EUS in a well-distended GB even after a careful retrospective review of the video-record. However, no surgery was done in these patients to clarify the discrepancy.

In nine patients diagnosed as having CBD stones by EUS, seven were confirmed by ERCP, one had normal ERCP and one refused to proceed ERCP. Of those with an ERCP-proven CBD stone, four had prior TUS done but neither CBD stone nor dilated CBD was detected. One patient whose EUS study revealed a small GB with normal CBD finally had an ERCP-proven CBD stone. Thus, by comparison with ERCP set as a reference standard for diagnosis of CBD stone, EUS produced an accurate diagnosis in seven patients, a false positive in one, a false negative in one and a true negative in eleven. The false negative one, an isolated GS detected by EUS with abnormal liver tests, was later found to have two tiny CBD stones by ERCP. The sensitivity, specificity, positive predictive value (PPV), and negative predictive values (NPV) of EUS for CBD stones were 87.5%, 91.7%, 87.5%, and 91.7% respectively.

In five patients, EUS showed dilated CBD but only one had a positive ERCP finding of distal CBD stricture of uncertain nature.

Discussion

The etiologies of dyspepsia in the current study were somewhat different from the findings from other studies using EGD as the investigative tool. In the literature review by Talley et al[2], peptic ulcer was found in 15-25%, cancer in 1-5%, and 27-83% were normal. In a survey by the Stomach Research Club of Thailand in 1999 based on endoscopic reports from 13 hospitals located in different parts of Thailand including over 4000 patients, the findings were peptic ulcer in 19%, gastric cancer in 2%, gastritis 53%, normal 25% and other 1% (unpublished data). In the current study, the prevalence of 2.3% for peptic ulcer is quite low. This may be due to selection bias as a referral tertiary center where most patients in the current study were empirically treated with acid suppression and/or *H. pylori* eradication therapy.

In other studies, symptomatic GS has been reported in 2.2-3.9% of patients with dyspepsia[6,7]. It was found in 20% of the present study. Since GS is a common entity, it is not surprising when it is detected in some patients with dyspepsia. The diagnosis of symptomatic GS is based primarily on medical history. However, the symptom of 'biliary colic' is found to have low discriminative capability between patients with and without GS[21,22]. Furthermore, in some individuals, biliary colic superimposed on the background dyspepsia can be a challenging problem. A thorough history and appropriate investigations are needed to elucidate the actual etiology of the symptoms in this special clinical circumstance. The high prevalence of symptomatic GS in the present study may be due to selection bias of dyspepsia management in a referral tertiary center.

In the evaluation of patients with dyspepsia, endoscopy by itself may be not adequate since only intraluminal lesions can be detected by this method. Additional imaging is usually required, particularly in those patients with normal endoscopy and persistent symptoms[12,23]. EUS may serve the purpose of combined endoscopy and TUS for the primary investigation of dyspepsia. EUS can provide comparable accuracy and adequacy to EGD for luminal lesions and is superior to TUS for pancreato-biliary lesions[14,15,18], although it has a limited depth of penetration and so it is not adequate to evaluate the whole liver. In patients with pancreatic lesions, EUS evaluation was difficult without prior CT image to guide the EUS examination even for the most experienced endosonographer. In the present study, EUS provided additional information regarding staging in patients with duodenal cancer, pancreatic cancer and gastric lymphoma. The EUS was misinterpreted in one patient with chronic pancreatitis who had an EUS done before CT, although this may have been due to the fact that the endoscopist was still in the early stages of the EUS learning curve. EUS failed to identify the lesion in one patient with cancer of the transverse colon presenting with epigastric discomfort. Evaluation of the adjacent colon by EUS may be difficult due to limited depth penetration of EUS and bowel gas interference.

EUS was also reported to be more sensitive than TUS in diagnosing GB stone[24], but as accurate as ERCP for diagnosis of CBD stone[25-26]. In the current study, EUS detected GB stones in 3 patients with negative TUS. Nevertheless, four false positive GS readings with the EUS were found. Possible explanations for these false positives include gas trapped between the bowel walls, the EUS balloon or transducer producing artifacts, or the stone had spontaneously passed out since two of the false positive stones were small stones detected by EUS (1.8 and 2 mm) and the operation was done at some later time, or the surgeon lost them during the manipulation of the gallbladder. In the present study, the sensitivity of EUS for CBD stones was, however, a little bit lower than in other reports, but the specificity and negative predictive value of EUS for CBD stones were high. The authors believe that in patients with a low risk of CBD stone, EUS evaluation before laparoscopic surgery is adequate in the authors' center.

One GB cancer was missed by EUS and this was due to the lack of experience in using EUS to evaluate GB cancer by the endoscopist in the present study. According to the classification of EUS imaging of GB cancers proposed by Fujita[27], EUS finding of type B GB cancer was a sessile mass with intact of outer hyperechoic layer of adjacent wall. This may cause misinterpreted EUS findings as a GS, particularly in cases with a low index of suspicion.

A suspected submucosal gastric mass detected by endoscopy was disproved in one patient by EUS examination. EUS is highly accurate for the diagnosis of and differentiation between submucosal tumors originating in the gut wall and extrinsic compressive lesions of the gastrointestinal tract[28] and has an impact on the management[29]. EUS readily diagnosed one gastric GIST but failed to detect con-

comitant multiple metastatic liver masses detected by TUS. The limited depth of penetration of EUS poses a limit for EUS in detecting lesions in the right lobe of the liver, so additional imaging is still required to completely evaluate the liver.

The main limitation of the current study was that it was a retrospective study, with some missing data, particularly some clinical outcomes during the follow-up period. Also, the endoscopist performing the EUS was still perfecting his technical skill. However, this is the first study from Thailand of EUS examinations being used to evaluate patients with dyspepsia, and it confirms that EUS used together with good clinical judgment can provide some useful information for the management of dyspepsia. It is particularly helpful in a clinical setting where GS is under consideration in patients with background dyspepsia and in patients suspected of having a pancreatic problem. A prospective study with EUS in dyspeptic patients to validate these points is warranted.

Unfortunately, EUS is not yet widely available, as the instrument is expensive and the operator needs considerable skill and experience to perform a reliable EUS evaluation.

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บทบาทของ endoscopic ultrasound ในการตรวจวินิจฉัยผู้ป่วย dyspepsia

ศิริบูรณ์ อัตศรัณย์, บัญชา โอวาทราพพร

***ที่มา**: Dyspepsia เป็นกลุ่มอาการที่พบบ่อย และเรื้อรัง ผู้ป่วยมักได้รับการส่งตรวจการสืบค้นหลายวิธี เพื่อค้นหาพยาธิสภาพ ทั้งภายในและภายนอก lumen endoscopic ultrasound (EUS) สามารถตรวจหาพยาธิสภาพดังกล่าวได้ในเวลาเดียวกัน*

***วัสดุและวิธีการ**: เป็นการศึกษาย้อนหลังเป็นเวลา 4 ปี ในผู้ป่วย dyspepsia ที่ได้รับการตรวจด้วย EUS โดยรวบรวมผลการตรวจด้วย EUS ผลการตรวจรักษาด้วยวิธีอื่น ๆ และ การวินิจฉัยโรค พร้อมทั้งเปรียบเทียบ ผลการตรวจ EUS กับ วิธีมาตรฐาน*

***ผลการศึกษา**: ผู้ป่วยจำนวน 131 ราย อายุเฉลี่ย $\pm$ ค่าเบี่ยงเบน เท่ากับ 50 $\pm$ 12.7 ปี โรคที่พบบ่อยได้แก่ non-ulcer dyspepsia ร้อยละ 56, นิ่วในระบบทางเดินน้ำดีที่มีอาการ ร้อยละ 22.9, EUS สามารถตรวจวินิจฉัยนิ่วในถุงน้ำดีเพิ่มเติมจากการตรวจด้วย transabdominal ultrasound (TUS) 2 ราย โดยวินิจฉัยนิ่วในถุงน้ำดีผิดพลาด 1 ราย และตรวจพบนิ่วในท่อน้ำดีจำนวน 7 ราย ที่ตรวจไม่พบโดย TUS โดยรวมแล้ว EUS มีsensitivity, specificity, positive predictive value, และ negative predictive value สำหรับการตรวจวินิจฉัยนิ่วในท่อน้ำดีร้อยละ 87.5, 91.7, 87.5 และ 91.7 ตามลำดับ*

***สรุป**: EUS เป็นวิธีการตรวจที่อาจนำมาใช้ได้ในผู้ป่วย dyspepsia*