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REVIEW ARTICLE

Assessment of dyspepsia in the era of endoscopic ultrasonography

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ABSTRACT

Dyspepsia is one of the commonest indications for referral to gastroenterology and endoscopy assessment. It includes a wide range of differential diagnosis and variety of pathologies that needs further assessment in depth. Initial evaluation should focus on the identification and treatment of potential causes of symptoms such as peptic ulcer disease and medication side effects but also on recognizing those at risk for more serious conditions such as cancer or premalignant lesions. Dyspepsia is common in clinical practice with frequent relapses that often requires multiple investigations to assess intraluminal and extraluminal aetiologies. The basic gastroscopy represents a widely used tool for dyspepsia assessment for specific indications. Endoscopic ultrasonography (EUS), introduced into gastroenterological diagnostics more than 20 years ago, has undergone extensive evaluation of its diagnostic capability, probably to a larger extent than most other endoscopic and other imaging techniques in gastroenterology. The introduction of EUS in the recent era added the benefit of better visualization, assessment of layers and lesions and sampling for histological and pathological guidance. In this article, we aim to review the diagnostic yield in different causes of dyspepsia. We will also shed some light on role of EUS in staging of specific causes of dyspepsia including gastric, pancreatic, biliary and subepithelial lesions.

Key words: endoscopic ultrasonography, dyspepsia, pancreatic, biliary, ampullary neoplasms, subepithelial lesions

INTRODUCTION

Dyspepsia is one of the most common gastrointestinal conditions seen in both primary and specialist care with an extensive differential diagnosis and a heterogeneous pathophysiology. It is defined as one or more of the following symptoms: postprandial fullness, early satiation, epigastric pain, or burning. The initial diagnostic challenge is to identify those patients who may have a structural disorder requiring expedited and targeted investigation.[1]

Endoscopic ultrasonography (EUS) is a combination of endoscopy and ultrasonography. It was initially developed to improve imaging of the pancreas. EUS can be used to visualize and sample lesions of the gastrointestinal tract, pancreas, posterior mediastinum, and retroperitoneum. Also, it is often used for staging gastrointestinal malignancies such as esophageal, gastric, pancreatic, and rectal cancers. the role of endoscopic ultrasonography has progressed from a diagnostic to a therapeutic modality over the last 15 years.[2]

Recently, the diagnostic role of EUS in assessment of non-explained symptoms of dyspepsia has been expanded. In this article, we will highlight the diagnostic role of EUS in gastrointestinal diseases presents with dyspeptic symptoms.

EPIDEMIOLOGY

A meta-analysis of population-based studies evaluating

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the prevalence of un-investigated dyspepsia found a pooled prevalence of 20.8% (95% CI 17.8% to 23.9%).[3] The prevalence varied according to country (1.8% to 57.0%) and the criteria used to define dyspepsia. The prevalence was higher in women (OR 1.24; 95% CI 1.13 to 1.36), smokers (OR 1.25; 95% CI 1.12 to 1.40), people taking non-steroidal anti-inflammatory drugs (OR 1.59; 95% CI 1.27 to 1.99), and people positive for Helicobacter pylori (OR 1.18; 95% CI 1.04 to 1.33). The sub-type distribution was 61% post-prandial distress syndrome, 18% epigastric pain syndrome, and 21% overlapping variant with both syndromes; this pattern was similar across countries. There is evidence of special issues relating to functional dyspepsia in women.[4] Dyspepsia has been shown to have a significant negative impact on quality of life. The impact relates to changes in sleep, diet, and interference with work and leisure activities. Women who have experienced emotional or physical abuse appear to be particularly vulnerable to developing functional dyspepsia and irritable bowel syndrome (IBS). There is much overlap between functional dyspepsia and IBS. Patients who have both disorders have a substantially greater symptom burden and are more likely to consult a physician.[5]

AETIOLOGY

Approximately 25% of patients with dyspepsia are found to have an underlying organic disease on diagnostic evaluation (Table 1). However, approximately 75% of patients have functional (idiopathic or non-ulcer) dyspepsia.[6]

Table 1: Differential diagnosis of dyspepsia

Gastroesophageal reflux disease
Chronic peptic ulcer
Drug-induced dyspepsia
Infectious disorders (*Giardia*, *Helicobacter*)
Symptomatic cholelithiasis
Chronic pancreatitis
Biliary dyskinesia
Malignant disease (gastric, pancreatic, colonic)
Mesenteric vascular insufficiency
Metabolic disorders (*e.g.*, renal failure, hypercalcemia, hyperthyroidism)
Abdominal wall pain
Ischemic heart disease (referred pain)
Others

APPROACH

The approach to, and extent of, diagnostic evaluation of a patient with dyspepsia is based on the clinical presentation, the patient's age, and the presence of alarm features. The most agreed approach is to perform an upper endoscopy to evaluate dyspepsia in patients age $\geqslant$ 60 years and patients < 60 years with any one of the following: clinically significant weight loss, overt gastrointestinal bleeding, > 1 other alarm feature (Table 2) and rapidly progressive alarm features.[7]

Table 2: Alarm features in dyspepsia

Unintentional weight loss
Dysphagia
Odynophagia
Unexplained iron deficiency anemia
Persistent vomiting
Palpable mass or lymphadenopathy
Family history of upper gastrointestinal cancer

ENDOSCOPY

Upper gastrointestinal (UGI) endoscopic examination is recommended when the presentation suggests complicated UGI disease (obstruction, perforation, and hemorrhage) or a serious underlying cause for the symptoms explained by alarm features (Table 2). Endoscopic examination should be considered for older patients (> 60 years old) with new onset (within a few months) of progressively worsening symptoms. The age recommendation reflects American College of Gastroenterology and Canadian Association of Gastroenterology guidance on the management of dyspepsia. In the UK, NICE recommends urgent gastrointestinal endoscopy for those aged 55 years or over with weight loss and dyspepsia. Other patients who might benefit from endoscopy include those with dyspepsia that fails to respond to treatment; NICE recommends consideration of endoscopy in patients aged 55 years or over with treatment-resistant dyspepsia. In some populations and regions, for example Asia and parts of eastern Europe, UGI malignancies are an important consideration in younger people; therefore, the threshold for investigation should be tailored to local protocols.[8] Other patients who might benefit from endoscopy include those with ongoing symptoms after 1 to 2 months of treatment using proton pump inhibitors (PPIs) or *H. pylori* eradication treatment. Endoscopy may also benefit patients with unusual case presentations or significant comorbid conditions, as well as those who are unable to be reassured in the absence of an endoscopic examination.[9]

FUNCTIONAL DYSPEPSIA

Functional dyspepsia refers to a case where UGI endoscopy did not reveal a potential cause for the dyspepsia. Functional dyspepsia may be due to gut

hypersensitivity, motility disturbances, *H. pylori* infection, non-erosive reflux disease with epigastric symptoms only, post-infectious irritability, and psychosocial factors These changes may be caused by the post-infectious state, may be idiopathic, or may have their origin in complex brain-to-gut interactions. Psychosocial factors (including a history of violence and abuse) have been implicated in the generation of symptoms; psychological therapies, such as cognitive behavioral therapy and psychotherapy, may reduce dyspeptic symptoms in the short term in individual people.[10] A clinical diagnosis of functional dyspepsia requires the fulfillment of symptom-based diagnostic criteria and an evaluation to exclude other causes of dyspepsia (Table 3).

Table 3: The Rome IV criteria for functional dyspepsia

One or more of the following:
Bothersome epigastric pain
Bothersome epigastric burning
Bothersome postprandial fullness
Bothersome early satiation
Symptom onset at least 6 months prior to diagnosis
Symptoms should be active within the past 3 months
No evidence of structural disease (including at upper endoscopy) likely to explain the symptoms

The agreed approach for treatment of FD includes 4–8 weeks trial of a once daily PPI in patients with functional dyspepsia and no evidence of *H. pylori* and patients with persistent symptoms after eradication of *H. pylori* as a first line therapy. Tricyclic antidepressant drugs can be used as second line for patients with persistent symptoms after an eight-week trial of a PPI. the use of prokinetics is suggested in patients in whom eradication of *H. pylori* and a trial of PPIs and tricyclic antidepressant has failed. motivated patients who fail medical therapy and patients who associate symptoms with stressors for psychotherapy.[11]

DIAGNOSTIC ENDOSCOPIC ULTRASONOGRAPHY INDICATIONS IN DYSPEPSIA

Stomach
GASTRIC CANCER

A major clinical challenge is to diagnose early gastric cancer which increases the possibility of curable treatment. Endoscopic ultrasonography is an accurate method for local staging of gastric cancer as it can visualize infiltrating malignancies, appear as diffuse thickening of the normal layers of the gastric wall. It can also assess tumor invasion based on disruption of wall layers. The overall accuracy of EUS for T-stage ranges from 70% to 93%. EUS T-staging is lowest for T2 lesions (accuracy 60%–70%), as the differentiation between subserosa (T2) from serosal (T3) involvement is difficult. This related to the fact that the entire stomach is not covered by a serosa. The depth of invasion may be overestimated if there is an ulcer scar or inflammatory reaction below the cancer or a protruding lesion.[12] On the other hand, it may underestimate the depth of invasion if there is microinvasion. The accuracy of EUS nodal staging in gastric cancer ranges from 50% to 87% and is highest for T3 and T4 lesions, for lymph nodes located within 3 cm of the tumor, and along the lesser curvature. EUS is better than CT at assessing tumor depth (T stage) and perhaps lymph node involvement (N stage), particularly if fine-needle aspiration (FNA) is also performed.[13]

GASTRIC WALL LAYER ABNORMALITIES

The normal thickness of the gastric wall ranges from 0.8 mm to 3.6 mm and is considered to be thickened when the diameter of the five—layer EUS image of the gastric wall is greater than 4mm. Thick gastric folds should be suspected if failed to flatten with endoscopic insufflation or if an upper gastrointestinal series or CT revealed a thickness greater than 1.5 cm. The differential diagnosis of thickened gastric wall is mentioned in Table 4.[14] The role of EUS in assessment of gastric wall layer abnormalities is to narrow the differential diagnosis. Thickened 3rd and 4th layer of gastric wall should raise a suspicion of malignancy while thickened 2nd and 3rd layer may be benign or malignant. EUS has a diagnostic yield in early infiltrative diseases *e.g.*, Non-Hodgkin lymphoma. Also, EUS is diagnostic for gastric varices.[15]

SUBEPITHELIAL LESIONS

Subepithelial lesion (SEL) is defined as endoscopically visible bump or elevation encountered during examination with normal overlying mucosa. The differential diagnosis of SEL is described in Table 5.[16] EUS is an excellent tool for evaluating submucosal lesions because of its ability to visualize gut wall layers and abdominal structures as well as being able to sample the lesion safely. SEL can be divided into 2 main categories: intramural and extramural lesion with characteristic features that guide appropriate approach.[16]

Ampullary and pancreatic neoplasms
AMPULLARY NEOPLASMS

The role of EUS in assessment of ampullary lesion including benign and malignant lesions has merged from just identifying the lesion to assessment, staging and also tissue acquisition for confirmation of diagnosis. Ampullary adenomas are the most common ampullary

Table 4: Thickened gastric folds differential diagnosis

Gastritis
Menetrier disease
Zollinger–Ellison syndrome
Gastritis cystica profunda
Hyperrugosity
Gastric varices
Portal hypertensive gastropathy
Secondary syphilis
Tuberculosis
Cytomegalovirus
Helicobacter pylori
Herpes simplex virus
Histoplasmosis
Aspergillosis
Anisakiasis
Sarcoidosis
Amyloidosis
Crohn's disease
Adenocarcinoma
Linitis plastica
Lymphoma
Gastritis

Table 5: Subepithelial lesions differential diagnosis

Extrinsic compression
Heterotopic pancreas
Lymphoma
Metastatic deposits
Glomus tumor
Inflammatory polyp
Cysts
Varices
Granular cell tumor
Carcinoid
Lipoma
Stromal cell tumor

tumors. EUS is sensitive for diagnosing small ampullary neoplasms. Specific features for malignancy include malignant invasion (at least infiltration of the duodenal muscularis propria) or growth into the biliary or pancreatic ductal system. However, In the absence of these invasive features, EUS cannot differentiate between malignant and benign conditions (*e.g.*, inflammation, normal ampulla). EUS is the most reliable modality for T-staging of ampullary tumors. If malignancy is suspected in a patient undergoing EUS, fine-needle aspiration (FNA) of the ampulla, papilla, and surrounding deeper structures, including the local lymph nodes, can be obtained during the procedure. However, a negative result does not exclude the presence of a malignant focus within an adenoma.[17]

PANCREATIC NEOPLASMS

EUS remains the most sensitive test for identifying small pancreatic cancers. In addition, in patients with indeterminate findings on CT. Also, normal EUS of the pancreas in the setting of subtle radiological findings, nonspecific symptoms, or laboratory values effectively rules out a pancreatic neoplasm. A common indication for EUS is to obtain tissue diagnosis of a pancreatic mass. EUS-guided FNA of a pancreatic mass is the preferred method for tissue acquisition. Another important aspect is the role of EUS in the preoperative staging of pancreatic cancer. For locoregional staging of pancreatic cancer, multidetector CT and MRI are superior to EUS for detection of metastatic disease, but EUS can provide information suggesting metastatic disease by detecting previously unknown hepatic metastases, small pockets of ascites, and malignant mediastinal lymphadenopathy which will preclude surgical resection.[18] The accuracy of EUS in assessing for vascular invasion ranges from 62% to 100%. Practically, optimal assessment of tumor invasion continues to be accomplished with multidetector CT or MRI.[19]

SCREENING FOR PANCREATIC CANCER IN HIGH-RISK POPULATIONS

Guidance from the International Cancer of the Pancreas Screening (CAPS) Consortium recommends that individuals with a familial risk of pancreatic cancer or who have an inherited germline mutation should commence surveillance at 50 years of age or 10 years earlier than the youngest relative with pancreatic cancer. EUS and MRI were agreed as the optimal surveillance methods in this situation and that surveillance should be performed annually in the absence of concerning lesions and should be continued as long as patients are fit to undergo pancreatic surgery.[20]

PANCREATIC NEUROENDOCRINE TUMORS

EUS examination of pancreases detects about 77%–94% of neuroendocrine neoplasms not detected by CT or MRI especially with lesions less than 5 mm. Careful examination of the pancreas with EUS detects about Islet cell neoplasms are usually round, well-circumscribed, homogeneous, and hypoechoic compared with the surrounding parenchyma. The use of contrast enhanced EUS increasing the yield of EUS in detection of pancreatic neuroendocrine neoplasms.[21]

CHRONIC PANCREATITIS

Abdominal pain is the most common clinical symptom in chronic pancreatitis. EUS allows a highly detailed examination of the pancreatic parenchyma and duct. However, EUS features of chronic pancreatitis are not specific. Similar changes in the pancreas can be also be seen in patients who do not appear to have chronic pancreatitis, including older individuals, chronic alcoholics, social drinkers, smokers, diabetics, and those with chronic renal insufficiency. EUS diagnosis of chronic pancreatitis based on Rosemont criteria is described in Table 6.[22]

Table 6: Rosemont endoscopic ultrasonography diagnosis criteria of chronic pancreatitis

Parenchyma	Duct
Hyperechoic foci with acoustic shadows (Major A): body and tail	Stones in the duct (Major A)
Honeycomb-like lobulation (Major B): body/tail	Irregular duct (minor): body/tail
Lobulation without honeycombing(minor): body /tail	Dilated side ducts (minor): body/tail
Hyperechoic foci without acoustic shadows (minor): body/tail	Dilated main duct (minor): body/tail
Cysts (minor)	Hyperechoic contours on the main duct (minor): body/tail
Echo-dense septa(minor): body/tail	

PANCREATIC CYSTS

Pancreatic cysts are diagnosed with increasing frequency because of the widespread use of cross-sectional imaging. Many patients with pancreatic cysts are asymptomatic. However, when symptoms are present, abdominal pain and dyspeptic symptoms are of the most frequent symptoms.[23] The EUS examination of a cystic lesion should note the following cyst characteristics: size, location, wall thickness, presence of focal wall irregularity, associated mass or mural nodule, septae, echogenic debris or mucus and dilation of the main pancreatic duct. The presence of a solid component or dilated pancreatic duct is concerning and associated with a higher risk of high-grade dysplasia or adenocarcinoma. The absence of these features does not exclude the presence of malignancy. For patients who do not have an indication for resection based on cross-sectional imaging alone, additional evaluation with EUS with fine-needle aspiration in cysts > 1.5 cm in size and for lesions with worrisome features (solid component within the cyst, main pancreatic duct > 0.5 cm in size, symptoms related to the cyst, family history of pancreatic cancer). Different types of pancreatic cysts that can be found in pancreatic EUS examination are summarized in Table 7.[24]

Table 7: Different types of pancreatic cysts

NON-NEOPLASTIC PANCREATIC CYSTS
True cysts
Retention cysts
Mucinous non-neoplastic cysts
Lymphoepithelial cysts
PANCREATIC CYSTIC NEOPLASMS
Serous cystadenoma
Serous cystadenocarcinoma
Mucinous cystic neoplasms
Intraductal papillary mucinous neoplasms
Solid pseudopapillary neoplasms
CYSTIC DEGENERATION IN SOLID PANCREATIC TUMORS

Biliary tract indications and cholangiocarcinoma

CHOLEDOCHOLITHIASIS

Choledocholithiasis is one of the documented causes of dyspepsia. Endoscopic ultrasonography is superior to other imaging modalities for evaluation of the extrahepatic biliary tree for suspected choledocholithiasis. Patients at intermediate risk of choledocholithiasis (abnormal liver biochemical tests/age > 55 years /dilated CBD on ultrasound or cross-sectional imaging) may be considered for cholecystectomy with intraoperative cholangiography or additional imaging to confirm the presence of a CBD stone prior to an ERCP. MRCP is often the preferred imaging modality for CBD stones in patients at intermediate risk. If the MRCP is negative for a CBD stone, but the suspicion for a CBD stone remains moderate to high (*e.g.*, in a patient whose laboratory tests are not improving), EUS is an appropriate next step. In many centers, the endoscopist performing the EUS can perform an ERCP during the same session if a stone is found. If the MRCP or EUS is positive for a CBD stone, patients should undergo either preoperative ERCP and elective cholecystectomy or laparoscopic cholecystectomy with intraoperative ERCP, CBD exploration, or postoperative ERCP.[25]

INDETERMINATE BILIARY STRICTURES AND CHOLANGIOCARCINOMA

Biliary malignancies is one of the causes of dyspepsia that is difficult to diagnose. EUS can visualize the extrahepatic biliary tree and extrinsic masses with characterization of an indeterminate bile duct stricture whether the stricture is malignant or not. Also, intraductal US (IDUS) has been reported to be useful for lesions located in the porta hepatis region, with findings concerning for malignancy including disruption of the bile duct wall, sessile lesions, and tumor size

greater than 10 mm. When cholangiocarcinoma is diagnosed, EUS can assist in staging and assessment of surgical resectability.[26]

PRACTICAL APPLICATION OF EUS IN DYSPEPSIA ASSESSMENT

A number of studies discussed the diagnostic yield of EUS in diagnosis of uninvestigated dyspepsia. One study in a Colombian population found that the diagnostic yield of EUS exceeds that of upper endoscopy by 30% in patients with uninvestigated dyspepsia. EUS identified pathologies in 58.3% of the patients whereas upper endoscopy alone could only identify them in 28.3% of the patients these findings indicate the potential for using EUS as the initial evaluation examination as well as the potential for using it as a follow-up examination instead of a CT scan or MRI when symptoms persist.[27] Investigators in Hong Kong examined the role of EUS in the evaluation of dyspepsia compared with EGD as the gold standard for identifying endoluminal causes of dyspepsia, EUS had a sensitivity of 80% and a specificity of 92%. Inaccurate diagnoses with EUS occurred most often in the duodenum and esophagus, areas that are more difficult to visualize with the EUS scope. EUS was more sensitive and specific than US for the diagnosis of extraluminal abnormalities; EUS detected extraluminal abnormalities in 11.5% patients (who had normal US studies), and US detected only 23 of 48 pancreaticobiliary disorders identified by EUS. EUS also identified lymphadenopathy, liver masses, and a lung cancer not seen on US. EUS findings altered management in 50 patients. The authors concluded that EUS is a useful one-step method for investigating dyspepsia, with the ability to identify both luminal and extraluminal causes. EUS adds the ability to stage cancer, when present, and to identify lesions not otherwise visible with US. The real advantage of EUS in assessment of uninvestigated dyspepsia is the ability for extended assessment of luminal causes and the ability for detection of extraluminal causes of dyspepsia.

CONCLUSION

EUS has an immerging role in assessment of non-common causes of dyspepsia as discussed above. EUS should be considered as a tool for assessment +/- tissue acquisition in patients with radiologically or endoscopically suggestive lesions attributed to dyspepsia symptoms in which EUS has an approved role. Also, should be considered in assessment of resistant dyspepsia patients at high risk of pancreaticobiliary malignancy for GI infiltration. The role of EUS has extended to the pre-operative and stagging tool which is considered final of dyspepsia management. The priority of using EUS *vs.* other imaging modalities need to be further studied with consideration of risk and benefits related to the patient, physician and health care system. The limitation of endoscopy units resources for EUS as a diagnostic tool for dyspepsia should be considered.

DECLARATIONS

Author contributions

Talkhan MG wrote the paper; Omar Khalifa Elsayed M revised the paper and wrote the abstract.

Informed Consent

Not applicable.

Ethical Approval

Not applicable.

Conflict of interest

Authors declare no conflict of interests for this article.

Data sharing statement

No additional data is available.

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