Clinical advances in the evaluation of oesophageal disease

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The rising incidence of gastro-oesophageal reflux disease and its sequelae means the evaluation of oesophageal disease is set to expand beyond routine endoscopic assessment. The techniques used in the evaluation of both benign and malignant oesophageal disease are outlined in this article.

The rising incidence in gastro-oesophageal reflux disease (GORD) and its recognized sequelae, Barrett's columnar lined oesophagus (CLO) and junctional gastro-oesophageal adenocarcinoma has resulted in a huge expansion in the diagnostic evaluation of the oesophagus. The increase in GORD may be attributable to the wholesale eradication of *Helicobacter pylori*, in particular the cag A substrain, which has been suggested to be protective against GORD and its sequelae (Chow et al, 1998). In order to exclude malignant disease, a large number of symptomatic benign disorders would have been identified, which require further evaluation.

OESOPHAGEAL ANATOMY

The oesophagus is 25.0 cm in length and commences 15.0 cm from the upper incisors, the site of the upper oesophageal sphincter (UOS), which is composed primarily of the cricopharyngeus. This corresponds to the inferior border of the cricoid cartilage at the sixth cervical vertebra (C6). As it descends through the superior mediastinum, at the level of the sternum angle, it is crossed anteriorly by the aortic arch at 22.5 cm and by the left main bronchus at 25.0 cm. It enters the gastro-oesophageal junction at 40.0 cm, at the 11th thoracic vertebre (T11), passing through the diaphragmatic hiatus at T10.

All anatomical landmarks are described as a standard distance from the upper incisors. Histologically the oesophagus is composed of four layers. The mucosa is composed of non-keratinized stratified squamous epithelium, an underlying submucosa containing a vast collection of blood vessels and mucous glands which are intimately associated with the muscularis externa. This layer consists of an inner circular and outer longitudinal muscle coats which are closely approximated to the outermost serosa.

OESOPHAGEAL PHYSIOLOGY AND THE SWALLOWING MECHANISM

The main function of the oesophagus is to ensure the efficient propagation of a bolus from the pharynx towards the gastro-oesophageal junction. Swallowing occurs on relaxation of the UOS, which on closure initiates oesophageal peristalsis. This is further mediated by the distension of the smooth muscle component of the distal oesophagus. This permits the passage of a bolus across the existing pressure gradient between the negative pressure of the intrathoracic oesophagus and the positive pressure intra-abdominal oesophagus, on relaxation of the lower oesophageal sphincter (LOS) (Watson, 1993).

The UOS and LOS represent physiological sphincters which are readily identified as high pressure zones on oesophageal manometry. They actively resist the retrograde passage of contents into the pharynx and distal oesophagus respectively, thus maintaining the integrity of the epithelium.

SYMPTOMS

The main symptoms compatible with oesophageal disease include heartburn, dysphagia, odynophagia, chest pain and atypical symptoms, such as abdominal bloating.

RADIOLOGY

Contrast studies are now rarely used in oesophageal assessment, because of the expansion of endoscopic facilities. They have a role in

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the assessment of dysphagia, disorders of the UOS and in the secondary investigation of motility disorders such as achalasia (*Figure 1*). A contemporary role has emerged in the evaluation of symptomatic reflux, following antireflux surgery, in assessing the competence of the procedure.

ENDOSCOPY

Endoscopic evaluation (with confirmatory histology) of the oesophagus is an obligatory first-line investigation to exclude malignancy. In addition, it enables regular surveillance of a premalignant lesion and endoscopic grading of conditions such as oesophagitis (*Table 1*) as per the Savary Miller classification (Miller, 1978) (*Figure 2*). The 13C urea breath test and *H. pylori* serology should be used in close combination with endoscopy in the dyspeptic patient.

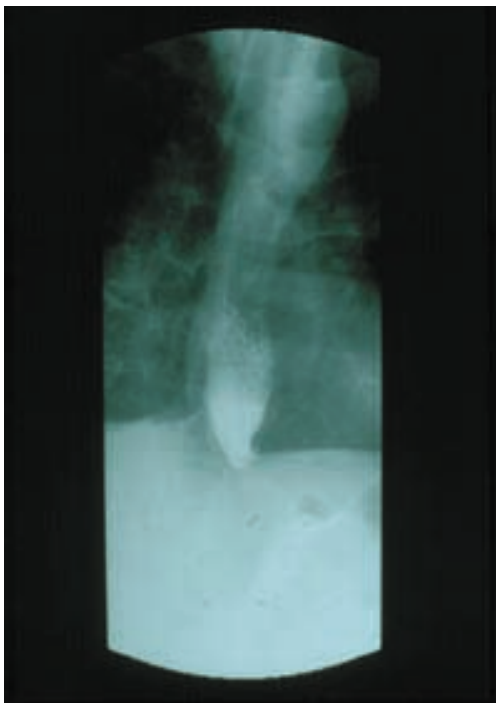

Figure 1. Barium swallow of achalasia, demonstrating characteristic distal oesophageal 'birds beak' appearance and proximal distension.

TABLE 1.
Endoscopic grading of gastro-oesophageal reflux disease

Grade I	Mucosal erythema or superficial erosion in the absence of confluent mucosal lesions
Grade II	Confluent erosive and exudated mucosal lesions, in the absence of circumferential lesions
Grade III	Circumferential erosive and exudated lesions, in the absence of stricture
Grade IV	Chronic mucosal lesions, e.g. ulcer, stricture or fibrosis

Diagnostic endoscopy and endoscopic surveillance have a significant role to play in the management of Barrett's CLO (*Figure 3*), the condition whereby the stratified squamous epithelium of the distal 3 cm of the oesophagus is replaced by metaplastic columnar epithelium. Endoscopic surveillance is important in order to identify specialized intestinal metaplasia (SIM), one of the three histological variants of Barrett's CLO originally described in view of its premalignant nature. SIM is found in 18% of patients with GORD (Spechler et al, 1994). In addition, the presence or absence of dysplastic changes should be noted. In the absence of dysplasia, endoscopic surveillance should be undertaken every 18–24 months. The presence of high grade dysplastic changes (HGD) is associated with a diagnosis of invasive carcinoma in 50% of cases (Wright, 1997). Management of confirmed HGD, by two independent pathologists, invariably involves oesophagectomy, in view of the strong association with invasive malignancy. Previous reports have suggested a role for the use of photodynamic therapy in HGD (Barr et al, 1996), however, this should now be reserved for those patients who are deemed unsuitable for oesophagectomy.

The endoscopic similarity between dysplastic and non-dysplastic epithelium (Spechler et al,

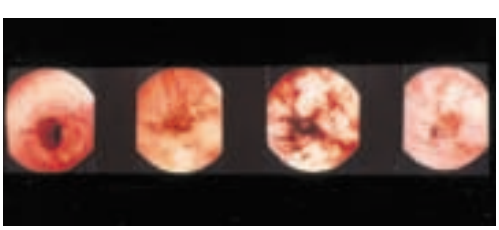

Figure 2. Increasing endoscopic severity of oesophagitis.

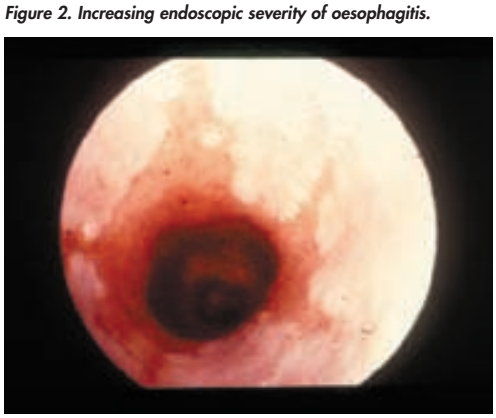

Figure 3. Barrett's CLO, with characteristic 'finger like' projection of metaplastic tissue.

1994) produces a diagnostic dilemma. Light-induced fluorescence endoscopy, however, may be used to differentiate between normal, dysplastic epithelium and early malignant change in the presence of similar endoscopic features. Abnormal epithelium has different fluorescence spectra and intensities when activated by light of a specific wavelength in comparison to normal epithelium. This can facilitate screening and enables biopsies to be targeted to abnormal areas (von Holstein et al, 1996).

ENDOSCOPIC ULTRASOUND

Endoscopic ultrasound (EUS) has been acknowledged as the most accurate means of staging oesophageal malignancy (Caletti et al, 1994), with values for tumour thickness (T stage) quoted as 75–95% and regional lymphadenopathy (N stage) as 70–90% (Tio et al, 1990; Zieglar et al, 1993). It is based on the combination of high frequency ultrasound scanning (frequencies of 7.5/12 Mhz) and endoscopy, producing accurate high resolution images of the upper and lower gastrointestinal tracts and hepatobiliary systems.

The demonstration of locoregional spread from a primary malignancy may result in a patient being offered neoadjuvant radiochemotherapy as an alternative form of management to a trial dissection. This is supported by the evidence that the incidence of nodal (N1) involvement for T1 lesions is 11%, T2 lesions 50%, T3 lesions 74% and T4 lesions 80% respectively (*Table 2*) (Maruyama, 1986).

EUS is not as accurate as T staging in the assessment of regional lymphadenopathy (N stage). Mediastinal lymph nodes tend to be overstaged, especially large nodes, although this may be overcome with the development of EUS-guided fine needle aspiration cytology. Intra-abdominal nodes are difficult to visualize because of the increased technical difficulties associated with gastric EUS in comparison to oesophageal EUS. The clinical relevance of this remains significant, as the demonstration of seven or more involved nodes is associated with a reduced long-term prognosis (Abe et al, 1990).

A stenotic oesophageal malignancy, producing luminal obstruction, represents a technical challenge. The majority of these lesions, however, are T3 in nature and are frequently associated with mediastinal lymphadenopathy, which may be detected by a limited EUS examination (Vickers and Alderson, 1998).

The use of EUS as a diagnostic tool in Barrett's oesophagus, to aid in the differentiation between non-dysplastic and HGD tissue, has not proven to be as successful as hoped (Yoshikane et al, 1994).

The place of magnetic resonance imaging (MRI) and computed tomography (CT) scanning in evaluating serosal disease in gastro-oesophageal malignancy have not been ascertained. The use of water as an intragastric contrast agent in CT scanning, and positioning the patient prone in order to improve the examination of the lesser sac as the stomach falls away from the pancreas, has produced some improvement (Allum, 1998).

Diagnostic laparoscopy combined with laparoscopic ultrasonography may also be used for the purpose of tumour staging and can accurately identify evidence of serosal spread or occult hepatic metastases which are not readily evident on EUS, CT or MRI examination.

TABLE 2.
Tumour node metastasis (TNM) staging of oesophageal cancer

Stage	Description
T0	No evidence of malignancy
Tis	Carcinoma in situ
T1	Tumour invades mucosa/submucosa
T2	Tumour invades muscularis propria
T3	Tumour invades subserosa
T4	Tumour invades regional organs
N0	No lymph node involvement
N1	1–3 lymph nodes involved
N2	> 3 lymph nodes involved
Mx	Metastases unknown
M1	No evidence of metastases
M2	Confirmed metastases (histologically)

From Hermanek and Sobin (1987)

OESOPHAGEAL MANOMETRY

Oesophageal manometry remains the investigation of choice for LOS identification and in the evaluation of oesophageal motility disorders. Alternative methods of LOS identification by either endoscopic means or the pH withdrawal technique are inaccurate.

TABLE 3.
Normal lower oesophageal sphincter (LOS) parameters

LOS pressure	15 mmHg (6–30 mmHg)
LOS total length	20–60 mm
LOS abdominal length	10–45 mm

TABLE 4.
Conditions identified by oesophageal manometry

Condition	Findings on manometry
GORD	LOS pressure < 6 mmHg
	LOS total length < 20 mmHg
	LOS abdominal length < 10 mmHg
	Low amplitude contractions
Achalasia	High resting LOS pressure >30 mmHg
	Inability of LOS to relax on swallowing
	Low amplitude simultaneous contractions
	Aperistalsis of distal oesophagus (severe disease)
Diffuse oesophageal spasm	Simultaneous disordered contractions
	Prolonged and repetitive contractions
	Occasional high amplitude contractions
Scleroderma oesophagus	Low resting LOS pressure
	Absent peristalsis

GORD = gastro-oesophageal reflux disease;
LOS = lower oesophageal sphincter

Physiological parameters reliably identified by oesophageal manometry include the LOS resting pressure, total and intra-abdominal length and oesophageal peristalsis (*Table 3*).

They are of particular importance in the evaluation of LOS competence in GORD. A resting LOS pressure <6 mmHg, a total length <20 mm and an intra-abdominal length <10 mm (*Table 4*) have resulted in the probability of a patient experiencing symptoms compatible with GORD of 92%, 65–88% and 69–76% respectively, dependent on the number of abnormal variables present (Zaninotto et al, 1988).

Manometry has proven to be a more sensitive diagnostic tool in the investigation of motility disorders in comparison to scintigraphy.

24-HOUR AMBULATORY PH MONITORING

Twenty-four-hour pH monitoring preceded by oesophageal manometry remains the gold standard investigation of GORD. LOS identification by oesophageal manometry facilitates accurate transnasal placement of the pH catheter, 5.0 cm proximal to the LOS. The DeMeester scoring system has been created using the following parameters (*Table 5*) and its sensitivity is approximately 90% with a specificity approaching 90% (Johnson and DeMeester, 1986). The following variables are evaluated:

The symptom index (value >50% is clinically significant) =

$$\frac{\text{no. of symptoms when pH <4}}{\text{total no. of symptoms}} \times 100$$

A computer-generated DeMeester score of 14 or greater is considered significant in terms of symptomatic acid reflux.

VECTOR VOLUME ANALYSIS

Vector volume analysis remains an experimental tool used in the assessment of LOS competence. The LOS has been described as being composed of a number of individual contractile units, which are asymmetrical in nature.

Assessment of sphincter pressure vector volume (SPVV) establishes the sphincter pressure at individual points along a reproduced three-dimensional image of the LOS. The volume is calculated using a standardized formula and is equivalent to the sum of all the cross-sectional sphincter pressure areas over the entire length of the LOS.

Estimation of total SPVV and intra-abdominal SPVV have been noted to be reduced in patients with GORD in comparison to normal subjects (Scott and Kadirkamanathan, 1997). The procedure is performed in a manner similar to oesophageal manometry, using a transnasal manometry catheter which is withdrawn in a stepwise manner. Normal SPVV values have been recorded in patients with increased distal oesophageal acid exposure (Stein et al, 1995). In view of this shortcoming and the variable reproducibility of the results obtained with vector volume analysis, oesophageal manometry and 24-hour pH analysis remains the investigation of choice in the assessment of GORD.

THE BILITEC

The Bilitec 2000 (Synetics, Stockholm) is used in the spectrophotometric evaluation of alkaline bile reflux in the distal oesophagus. A fibreoptic probe, emitting light of 453 nm, is placed 5 cm above the manometrically determined LOS, in a position similar to that used in 24-hour ambulatory pH monitoring. Bilirubin has a characteristic absorption peak of 453 nm.

TABLE 5.
Assessment of DeMeester score

1. Percentage total time oesophageal acidity <pH 4 (value > 4% is significant)
2. Percentage upright time oesophageal acidity <pH 4
3. Percentage supine time oesophageal acidity <pH 4
4. No of episodes where acidity falls <pH 4 in 24 hours
5. No of reflux episodes longer than 5 minutes in 24 hours
6. Duration of the longest reflux episode recorded

The instrument works on the principle that an absorption peak at approximately 450 nm is indicative of bilirubin being present within the refluxate (Vaezi et al, 1994). However, in an acidic environment (pH <3.5) bilirubin dimerization occurs, which results in a change in the absorption wavelength to 400 nm, which can affect bilirubin estimation by 30%. The primary indication for the procedure is a patient with GORD who remains refractory to a management regimen based on acid suppression, or 24-hour pH analysis compatible with alkaline reflux.

ELECTROGASTROGRAPHY

Electrogastrography (EGG), although still a research tool, is used in the assessment of gastric and oesophageal motility disorders. Its use is based on the premise of a pacemaker situated in the gastric body, along the greater curve, from which slow waves are generated towards the pylorus at a dominant frequency of three cycles per minute (Hinder and Kelly, 1997).

Three abnormal variants (tachygastria, bradygastria and a non-specific gastric arrhythmia) have been detected and are found as normal physiological variants (Stoddard et al, 1981) and in the disease states gastroparesis (both idiopathic and diabetic), anorexia nervosa (Abell et al, 1985) and non-ulcer dyspepsia (NUD). The gastric arrhythmias identified in NUD may ensure that NUD is no longer a diagnosis of exclusion, which is important as it is quoted as the most common cause of dyspepsia in adults (Heikkinen et al, 1995).

In addition, the identification of gastric arrhythmias has been strongly implicated in duodenogastro-oesophageal reflux, the presumed mechanism of alkaline/bile reflux.

A preprandial EGG recording for 60 minutes is undertaken, during which time the dominant frequency (cycles per minute) is noted. A test meal is given and a postprandial EGG recording is then performed. The ratio of change in the dominant frequency and the presence of any gastric arrhythmia is noted (*Figure 4*).

ANTRAL ULTRASOUND

Antral ultrasound can identify antral hypomotility (King et al, 1987), which can complement EGG analysis in the assessment of NUD and duodenogastro-oesophageal reflux. The pyloric antrum is readily visible by placing the ultrasound probe midway between the xiphisternum and the umbilicus. The antrum is initially empty following an overnight fast, however, the luminal contents become visible after a test meal. Pre- and postprandial scans are recorded, measuring antral diameter. The time taken to allow gastric emptying is measured and can be compared to standardized observations.

ELECTRICAL INTRALUMINAL IMPEDANCE

Electrical intraluminal impedance (EII) remains an experimental tool used in the evaluation of GORD and also in the investigation of atypical chest infections in children. Impedance studies are based on the measurement of change in EII, during the passage of an oesophageal fluid bolus and the height reached by the refluxate in the oesophagus, which may be used to predict aspiration in children.

A combined impedance, 24-hour pH catheter is inserted transnasally and positioned 5.0 cm proximal to the LOS. The presence of a combined catheter enables the simultaneous analysis of impedance and acid reflux episodes. Symptomatic reflux episodes occurring within a neutral pH range would theoretically be missed by conventional 24-hour pH monitoring, in the absence of a comparative method, as pH analysis is dependent on hydrogen ion detection at the analysing electrode. Impedance is independent of pH measurement and thus has the potential to increase diagnostic yield (Skopnik et al, 1996).

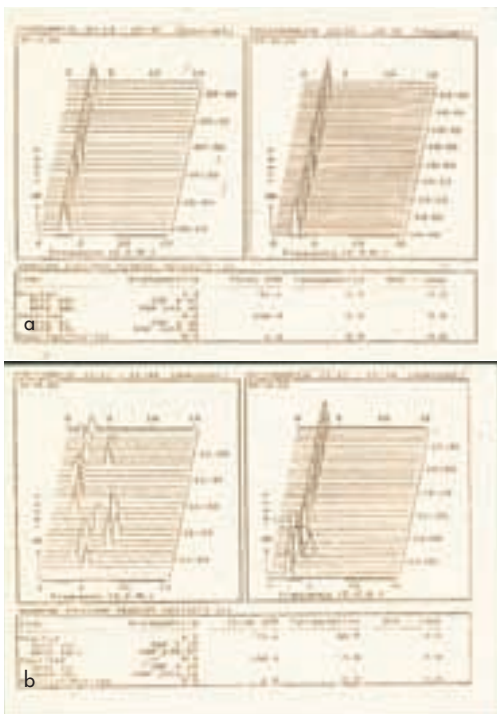

Figure 4. Electrogastrography (EGG) (a) in the normal situation (top). b. EGG demonstrating a preprandial bradygastria.

CONCLUSIONS

The role of the Bilitec, EGG and antral ultrasound in the assessment of alkaline reflux and NUD (probably the leading cause of adult dyspeptic symptoms) represents the most exciting advance made in the evaluation of non-malignant oesophageal disease.

EUS remains the most significant advance made in the assessment of oesophageal malignancy. The accurate demonstration of locoregional involvement has the potential to revolutionize the management of oesophageal malignancy. HM

Conflict of interest: none

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KEY POINTS

- Bilitec analysis should be considered in symptomatic gastro-oesophageal reflux disease refractory to acid suppression in patients with equivocal oesophageal manometry and 24-hour pH monitoring. *Helicobacter pylori* analysis should also be undertaken.
- Electrogastrography should be considered in non-ulcer dyspepsia, which remains the commonest cause of dyspepsia in adults.
- Endoscopic surveillance should be undertaken in Barrett's columnar lined oesophagus patients, in the absence of dysplastic changes every 18–24 months.
- In the presence of high grade dysplasia, confirmed by two independent pathologists, consider oesophagectomy (in view of 50% incidence of invasive carcinoma).
- Pesophageal manometry should be considered in the evaluation of dysphagia to exclude a motility disorder once a malignant cause has been excluded.
- Endoscopic ultrasonography is at present the most accurate means of staging oesophageal malignancy.