Update 2008: The Esophagus

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Abstract: The entire field of gastroenterology is primed to take an enormous step forward, with scientific and endoscopic advances which will be to this decade what the treatments of peptic ulcer disease and viral hepatitis conditions were for the 80's and 90's. So also in the area of esophagology there are numerous emerging techniques and scientific advances in our understanding of the motor and sensory function of the esophagus. These contribute to our better understanding of common conditions such as gastroesophageal reflux disease (GERD) including erosive esophagitis (EE), normal endoscopy reflux disease (NERD), Barrett's epithelium (BE), and esophageal adenocarcinoma (ECA), as well as the less common esophageal motility disorders, oro-pharyngeal dysphagia and eosinophilic esophagitis.

Keywords: barrett's, eosinophilic esophagitis, esophageal physiology and pathophysiology, motor disorders, new techniques, oropharyngeal dysphagia

Emerging Techniques

We may all have made use of esophageal manometry to investigate patients with suspected non-structural causes of symptoms, but it may be difficult to determine whether these motility disorders are necessarily related to symptoms. Which gastrointestinal (GI) function test provides the most relevant information on the motility of the esophagus?

- Esophageal manometry—Standard esophageal manometry only provides information on motility pattern at the sensors, and not between the sensors. It also measures esophageal distensibility of the lower esophageal sphincter (LES). There is also low inter-observer reliability in the interpretation of esophageal manometry. Standard manometry is an intraluminal pressure recording technique that measures circular muscle (CM) contraction. Using simultaneous recordings from manometry and real time ultrasound imaging demonstrate perfect temporal synchrony between the circular and the longitudinal muscle (LM) layers. During a swallow, LM contraction increases muscle wall thickness at the very site and time that the CM contracts to increase pressure (Pal and Brausseur, 2002). There is asynchrony in the contraction of those two muscle layers in nutcracker esophagus (NUT), with high amplitude contractions (Jung et al. 2005). Video manometry is useful for modeling of esophageal events.
- High resolution manometry (HRM)—HRM is useful to evaluate lower esophageal sphincter (LES) pressure, and prolonged recordings to capture less common events, such as segmented aperistalsis. HRM involves closely spaced side holes in the manometry tube, with topographic pressure plots developed for visualization of both esophageal pressures and peristalsis. This technique gives detailed space-time structure of pressure events, detailed information providing a topographic plot of pressure vs. time (Fox et al. 2004).
- Intraluminal esophageal electrical impedance (IEEI)—IEEI is useful to detect weakly-acid and non-acid reflux., as well as reflux of liquid and air; it also measures the extent of proximal reflux, and clearance of a bolus (Zeribib et al. 2005). There is good reproducibility for the number, acidity and gas-liquid composition of the refluxate when testing is repeated. This method uses no radiation, and it compliments fluoroscopy. Even in persons with normal standard manometry about 1/3 of persons will experience abnormal liquid or viscous boluses. These numbers increase to 2/3 of persons with diffuse esophageal spasm (DES), and 100% in achalasia. Ambulatory IEEI monitoring is reproducible.

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In healthy volunteers 58% of reflux episodes are acidic, 28% are weakly acidic, and 10% are weakly alkaline ("non-acid")(Conchillo et al. 2005; Zeribib et al. 2005).

- High frequency intra-luminal ultrasound (HFUS) imaging may be combined with manometry. The HFUS component measures muscle thickness, coordination between contraction of CM and LM, and distention of the esophagus during reflux episodes (Mittal et al. 2005). Using this technique, it has been possible to show hypertrophy of the muscle of the body of the esophagus as well as the LES in patients with spastic disorders of the esophagus (achalasia, diffuse esophageal spasm [DES], and nutcracker esophagus [NUT]) (Mittal et al. 2003).
- Barium swallowing study—This standard radiological investigation is useful for the detection and evaluation of esophageal narrowing, diverticulae, hiatus hernia, esophageal emptying. Note that there may be considerable day-to-day variability in the barium swallowing study.
- Modified barium swallow (MBS)—MBS assesses esophageal bolus transit. There is good correlation between MBS and IEEI in the measurement of esophageal transit (Imam et al. 2005). Liquids clear faster than do viscous swallows (chewed food mixed with saliva). If there is a non-peristaltic wave, liquids are more likely to clear than is a viscous bolus.
- Capsule endoscopy (ESOCAM)—As compared to esophagogastroduodenoscopy (EGD), ESOCAM is 89% sensitive and 99% specific for the detection of esophageal mucosa suspicious for Barrett's epithelium (BE). The sensitivity and specificity of ESOCAM to identify esophageal abnormalities is 92% and 95%, respectively (Eliakim et al. 2005).
- Video fluoroscopy—This is perhaps the best test to evaluate esophageal function and contour of the esophageal wall in patients with dysphagia.
- Endoscopic ultrasound (EUS) and fine needle aspiration (FNA)—EUS/FNA are more sensitive than CT for staging BE, but understandably do not detect distant metastases.
- Narrow band imaging (NBI) with zoom—NBI demonstrates mucosal and capillary patterns, examines a wide area, with magnification; the colour reflects the depth of lesions (red, deep; blue, superficial). NBI is compatible with high definition technology, and has high sensitivity and specificity for the demonstration of esophageal mucosa suspicious for BE (Kara et al. 2005; Kara et al. 2006).
- Chromoendoscopy—Chromoendoscopy with crystal violet staining has a sensitivity of 89% and a specificity of 86% for histologically proven BE (Amano et al. 2005).
- Optical coherence tomography (OCT)—OCT has an accuracy of 78% to distinguish BE with and without dysplasia (Isenberg et al. 2005).
- New diagnostic tests of the cortical sensing and motor control of the foregut are discussed in Section 2 below.

Basics of Esophageal Peristalsis: Motor and Sensory Function and Dysfunction

Motor

The brain-foregut connections from the afferent and efferent pathways are connected in the brain stem. Afferent input from peripheral nociceptors to the medullary central pattern generator is important. The protective reflexes (LES, esophageal-laryngeal, pharyngeal-upper esophageal sphincter [UES] for example) are brainstem mediated. The relationship between the brainstem circuits and the foregut can be shown neuroanatomically, electrophysiologically, and neuropharmacologically.

The passage of food from the mouth to the stomach involves a complex process of coordinated peristaltic activity of the upper third skeletal, lower third smooth muscle, and middle third mixed muscle, with afferent and efferent sensory pathways to and from the modular swallowing center. Peristalsis is associated with the contraction of a portion of the esophagus, and the length of the contracted segment may exceed as much as 15 cm (Clouse and Staiano, 1991; Clouse and Staiano, 1996). An understanding of the basic physiology will improve our understanding of the pathophysiology and will therefore also possibly improve our understanding of the management of patients with esophageal motility disorders. These include hypocontractility disorders such as gastroesophageal reflux disease (GERD), scleroderma, as well as ineffective esophageal motility (IEM), as well as hypercontractility disorders such as achalasia, DES and NUT.

High frequency ultrasound examination of the esophagus during swallowing has shown a

coordination of the contraction of the inner CM and outer LM (Mittal et al. 2006). CM shortens more than LM, and it is the contraction of LM that may result in non-cardiac chest pain (NCCP). Contraction of the LM moves the LES in an axial direction, contributing to the relaxation of the LES. Relaxation and opening of the LES may be separate processes. Upper esophageal contraction of the muscle stops with the upper contraction wave, a second contraction wave appears distally, and a trough appears in the mid esophagus from an indentation wave (Ghosh et al. 2006). Stretch receptors in the proximal stomach act through a vago-vagal reflex to trigger transient lower esophageal relaxation (TLESR). Metabotropic receptors in the vagal pathways are present in the nodose ganglia of humans (Asunuma et al. 2005), and antagonists to those receptors inhibit TLESR in a dose-dependent manner (Frisby et al. 2005).

Sensory

Visceral sensory afferents also pass along sympathetic neuron paths, and increased sympathetic tone may contribute to esophageal pain. Acid sensitive ion channels may exist in the esophagus (Holzer, 2003), and acid activates the vanilloid TRPVI receptor (Matthews et al. 2004). Anxiety, depression and stress distort central afferent processing, and influence the psychophysiological aspects of esophageal pain, including the patient's interpretation of his or her symptoms.

Both the motor and the sensory components of esophageal peristalsis are important to consider as part of the stimulus-response function of this organ. The nociceptors in the wall of the esophagus may sense thermal, chemical or mechanical stimuli, transmitted through the superior laryngeal nerve. Persons with non-cardiac chest pain (NCCP) and normal endoscopy reflux disease (NERD) are hypersensitive to stimulae (Sarkar et al. 2000). The vagal receptors also sense painful stimuli, and may involve the transmitters TRPVI, calcitonin gene related peptide (CGRP) and colretinin (Matthews et al. 2004; Cheng et al. 2005). Acid in the esophageal lumen may release TRPVI from the epithelium, as well as platelet activating factor (PAF) and substance P (SP) from the neurons. Spinal afferent (sensory) fibers run from the esophagus to the brainstem in the myenteric connective bundles or within the myenteric ganglia. About a quarter of the sensory fibers for esophageal distention pass to the cervical and thoracic dorsal horn neurons. These also receive convergent input from the heart, explaining the clinical difficulty sometimes in distinguishing angina from esophageal pain, including NCCP. The brainstem in turn may stimulate or inhibit the spinal neuronal activity (Dunckley et al. 2005). The esophagus is represented in the anterior insular and anterior cingulate cortex (Aziz et al. 2000). The biochemical basis for esophageal pain may be from increased cross-sectional area from muscle thickening during contraction (Nicosia et al. 2001), or possibly from ischemia.

Cortical sensing and motor control of the foregut can be demonstrated non-invasively in man, using the following techniques:

- Position emission tomography (PET)—Using a radioactive sugar, PET is useful in demonstrating changes in blood flow to an area of the esophagus during swallowing, or in disease processes.
- Functional magnetic resonance imaging (fMRI)—fMRI has the same use as PET to show changes in esophageal blood flow, but without the use of radiation.
- Magnetoencephalography (MEG)—MEG shows real time activation of the cortex, and provides high density, dynamic, whole cortex mapping.
- Transcranial magnetic stimulation (TMS)—Magnetic stimulation may be provided over the skull bone in order to stimulate the cortex and assess alterations in esophageal function.
- Electrical stimulation may be used to directly activate esophageal afferents, with measurement of cerebral evoked potentials.
- High frequency ultrasound examination of the esophagus during swallowing has been discussed above (Section 1), and the flexible endoscopic evaluation swallowing and sensation test (FEE SST) is discussed below.

Motor Disorders

The motor disorders of the esophagus may be broadly classified as those with motor hyperactivity (achalasia, DES, corkscrew esophagus or NUT), and those with hypomotility (GERD, scleroderma, and ineffective esophageal motility [IEM]). IEM has been defined as 3 or more ineffective esophageal manometric contractions (Leite et al. 1997). With high amplitude esophageal contractions, there is thickening of the esophageal muscle from increased muscle cross sectional area.

- Lower Esophageal Sphincter (LES)—The LES and transient lower esophageal relaxation (TLESR) are involved in the pathogenesis of GERD. The smooth muscle of the LES are comprised of a semicircular portion in the upper part, and slings in the lower part. The sling fibers carry on from the lower esophagus and into the upper portion of the stomach. The upper clasp fibers of the LES produce a high resting tone. The sling fibers are more responsive to cholinergic stimulation (Muinuddin et al. 2001; Preiksaitis and Diamant, 1997). In response to a swallow (primary peristalsis) or to esophageal distention (secondary peristalsis), the myenteric nerves release nitric oxide (NO) (Mashimo et al. 1996). The inhibitory neurotransmission may be influenced as well by the interstitial cells of Cajal (Sivarao et al. 2001; Ward et al. 1998). When the esophageal LM contracts, the skeletal muscle diaphragmatic sphincter relaxes (Liu et al. 2005). The gamma amino butyric acid (GABA) agonist baclofen inhibits both the LM contraction and esophageal distention induced diaphragmatic sphincter relaxation (Liu et al. 2005). Baclofen may have a limited role in the treatment of selected persons with GERD.

The LES needs both to relax, and to open at the appropriate time of the passage of the food bolus along the length of the esophagus from the mouth to the stomach. Neurotransmitters and neural circuits cause relaxation, but the opening is due to "….visco-elastic properties of the LES, the diaphragmatic sphincter, possibly the phenol-esophageal ligament, and the surrounding abdominal viscera" (Dogan and Mittal, 2006, page 418). About 10% of achalasia patients have normal complete relaxation of LES, but LES does not open. From the patient's GERD symptoms, it is not possible to predict whether the patient will have erosive esophagitis (EE) on endoscopy (EGD), or normal endoscopy reflux disease (NERD). These persons are treated the same as persons with achalasia showing failure of relaxation of the LES. There are several recent advances in NERD. Dilated intercellular spaces of the esophageal mucosa have been reported in NERD (Vieth et al. 2004; Caviglia et al. 2005). Biopsies taken at the Z-line may show subtle changes in GERD, such as eosinophilic intraepithelial cells, basal cell hyperplasia, elongation of the papillae, and DIS (Zentilin et al. 2005) 76% of NERD patients having some of the abnormalities. In patients with NERD, early mucosal abnormalities shown on chromendoscopy include vascular spots above the Z-line, a villous mucosal surface, and islands of squamous cell epithelium below the Z-line (Kiesslich et al. 2004).

- Diffuse esophageal spasm (DES)—In DES there are no pathological neural abnormalities, but the neural function is abnormal with increased sensitivity to methacholine. Nitroglycerine prolongs the neuronal latency in DES, but there may also be a functional defect in NO (Murray et al. 1995). DES may be associated with a hypertensive LES. The absolute criterion for the diagnosis of DES is the manometric finding of >20% simultaneous waves. The esophageal peristaltic pressure in these waves may be high or low. Rarely, DES may progress to achalasia, and DES and vigorous achalasia are thought to be part of the same spectrum of disease pathophysiology. The clinical presentation of DES and vigorous achalasia is the same, but a myotomy through the thoracic approach is used in DES, whereas an abdominal approach is used for the myotomy in achalasia. DES has been variably treated with nitrates, anticholinergics, calcium channel blockers, xylocaine/antacid/benadryl, tricyclics (but not selective serotonin reuptake inhibitors [SSRIs]), biofeedback, bougie dilation, botoxin injection, or myotomy.
- Achalasia—In achalasia, the absence of NO-containing nerves leads to a loss of the inhibitory innervations of the esophageal body and LES (Hirano et al. 2001). This results in the typical failure of relaxation of the LES on swallowing. Interestingly, as many as a third of achalasia patients will have normal LES relaxation (Amaravadi et al. 2005), possibly due to continued LM contraction and associated esophageal shortening (Tutian et al. 2006). The characteristic defect in GERD is reduced LES pressure and inappropriate TLESR. There is an afferent pathway from the stomach to the vagus, and from there to the brain stem, with efferent fibers to the LES (Martin et al. 1986). Adrenergic activity keeps the LES closed, but vagal fibers relax the LES during a swallow. The most distal muscle of the LES acts as a sphincter, which is an intrinsic property of the muscle. When the intrinsic nerves in this lower portion of the LES muscle are stimulated, an inhibitory reflex

causes the muscle to relax (without the need for hormones or extrinsic nerves). The vagal fibers impinge on those intermediate inhibitory nerves in the lower LES muscle, causing the LES to relax in swallowing.

Only half of patients are satisfied at one year with botulism injection for their achalasia. Pneumatic dilation gives a 76% success rate at 11 years, but unfortunately at the cost of a 5%–10% perforation risk (Karamanolis et al. 2005). The success rate at 17 years is about 50%. Most studies suggest the Heller myotomy is highly successful in the short and long term for the treatment of achalasia, but more than half the patients will have heartburn, even before the procedures (Gupta et al. 2005). Because of the possible association/complication of GERD, the laparoscopic Heller myotomy may be combined with a partial fundoplication (Bonatti et al. 2005; Rosetti et al. 2005).

Pseudoachalasia may occur secondarily or in association with a number of conditions such as GERD, post fundoplication, cancer, Chagas' disease, and paraneoplastic syndromes. Secondary achalasia accounts for less than 5% of all cases of achalasia, but clearly it is important to recognize serious causes of secondary achalasia, such as cancer of the gastric cardia. In young persons, secondary achalasia may be associated with lymphoma, peripheral neuropathy, or occur post encephalitis.

- Nutcracker esophagus (NUT)—About 8% of NUT is associated GERD. Some 30%–50% of NUT may be associated with NCCP, or with irritable bowel syndrome (IBS) (Clouse and Lustman, 1983; Mujica et al. 2001; Sayuk and Clouse, 2005), DES (15%). In NUT, about 10% of peristaltic waves with wet swallows may be abnormal. The pressure of the contraction waves is high in NUT (>180 mm Hg), and the interval between the pressure waves is greater than 6 seconds. Treatment of NUT is with a proton pump inhibitor (PPI), with a surprising 90% of patients enjoying symptom control. Calcium channel blockers have little benefit. Antidepressants given in low doses may help NUT, even if there is no associated anxiety, depression or IBS. If myotomy is performed, fundoplication may be added because of the common association of GERD. In NUT, dysphagia disappears in about 70% of subjects after a fundoplication.

Oro-Pharyngeal Dysphagia (OPD)

In order to understand the pathophysiology of OPD, a consideration of sensory and motor pathways in the upper esophagus, as well as the UES, is required. There is no gold standard to quantify the severity of OPD, and clinical measurement of the UES pressure is notoriously unreliable. The optimal methods to assess OPD include videoesophagogram, or a modified barium swallow (MBS) study. OPD may also be assessed by flexible endoscopic evaluation of swallowing and sensation test (FEESST). This helps to identify the patient with OPD who is at risk of aspiration. FEESST may be superior to MBS to assess OPD in the patient with a cerebral vascular accident (CVA), to determine the optimal dietary and bilinear management, where outcome is measured as pneumonia free days.

Laryngoscopic examination may be helpful in the patient with OPD, particularly if the patient has pain on or pain with swallowing and the cause is not obvious. If there is abnormal closure of the glottis, the OPD may be from an upper rather than a lower motor neuron lesion. Pharyngeal electrical stimulation may improve the OPD after a CVA (Freed et al. 2001).

Barrett's Epithelium (BE) and Esophageal Adenocarcinoma (ECA)

A recent population-based study has shown a prevalence of BE of 2.3% in those with, and 1.4% in those without GERD symptoms (Ronkainen et al. 2005). BE is also increased in patients with celiac disease and possibly systemic sclerosis (Maieron et al. 2005; Wipiff et al. 2005).

The incidence of squamous cell carcinoma is holding steady at about $1/10^5$, and is associated with smoking and alcohol use. The incidence of esophageal adenocarcinoma (ECA) is rising rapidly, but thankfully the rate of $3/10^5$ is low. It is not clear why ECA is increasing. BE is thought to be a precursor of at least some persons with ECA, but not esophageal squamous cancer. Over the interval when BE and ECA have become more prevalent, there has been an increasing prevalence of GERD in North America or Europe. *H. pylori* may be protective for GERD (Ye et al. 2004). The use of certain medications which contribute to GERD (such as B-agonists, calcium channel blockers, nitrates, anticholenergics) may thereby contribute

to BE. Another increasingly common risk factor for GERD, BE and ECA, is obesity (Hampel et al. 2005). An increased body mass index (BMI) due to visceral adiposity contributes to an increased risk of BE (El-Serag et al. 2005). There is also greater awareness on the part of physicians about the possible role of screening in the person with a long history of frequent and severe GERD symptoms. There is a need for the endoscopist's astuteness to carefully look for and find BE, the use of targeted biopsies to identify the presence of BE, and the skill of the pathologist in making the diagnosis of BE, as well as low grade (LGD) or high grade dysplasia (HGD). We will not consider the debate of the cost-effectiveness or ethics of screening for BE, or the interval of follow-up.

GERD is associated with the development of ECA, particularly when GERD symptoms have been present for many years, occur more than 3 times a week, and are severe in nature. BE is thought to be the intermediate step between GERD and cancer, although not all persons with ECA will have BE, and not everyone with BE will have had symptoms of GERD (possibly "silent" or asymptomatic refluxers). The reflux of bile acids and pancreatic juice into the stomach, and then into the esophagus, may add to the damaging effect of acid or may be pathophysiologically important in their own right. Depending upon the pKa of the bile acid or its conjugate, the bile acid may be soluble and ionized or non-ionized, or insoluble. Thus, the pH of the refluxed acid will determine if the bile acid is hydrophobic (lipophilic) and readily soluble in diffusing through the esophageal epithelial barrier. Bile acids have many potential mechanisms of damage to the esophagus which could lead to BE, such as increased cell proliferation and apoptosis, increased reactive oxygen species and DNA damage, and increased COX2 activity. Stem cell differentiation, or transdifferentiation, may lead to metaplasia, dysplasia genomic instability and cancer (Kazumori et al. 2006).

As yet, there are no biological markers that clearly distinguish between metaplasia and dysplasia, or between the spectrum of LGD and HGD. Interleukin (IL)-8 and IL-IB are elevated in esophagitis, BE, dysplasia and ECA, but an elevated NF-kB is seen only in BE and ECA (O'Riordan et al. 2005). Unfortunately this is not yet ready for "prime time" as a marker that can be used clinically. Instillation of acid into the esophagus of humans increases ERK1/2 activity and phosphorylation in GERD subjects but not in BE or contral subjects (Souza et al. 2005). Survivin is an inhibitor of apoptosis, and is higher in dysplastic as compared to non-dysplastic BE (Vallbohmer et al. 2005). Future studies will be needed to determine if survivin may be used to identify the patient with BE in whom the metaplasia is likely to progress to dysplasia. Such early detection would allow for the early treatment of the BE and possible prevention of ECA.

Pathologists will generally agree on what is a normal esophageal biopsy, what is BE or ECA, but the kappa value between LGD and HGD is large. This variability is not surprising when there are no firm criteria for diagnosing HGD; where does the highest severity of LGD end and the lowest grade of HGD begin? Nuclear cytosolic and architectural changes are present. To the clinician, HGD has important therapeutic implications, ranging from increasingly frequent endoscopic surveillance, photodynamic therapy (PDT), endoscopic mucosal resection (EMR), or esophagectomy.

Why is ECA so feared? Up to 85% of ECA sufferers present with dysphagia or weight loss, 80% have a T3/T4 lesions at diagnosis, and of those with a T3/T4 lesion, 80% have lymph node involvement, and 50% have distant metastatic disease (Watt and Whytem, 2003). The methods for diagnosis and staging of ECA include histological assessment of biopsy tissue, EUS and FNA, PET or PET-CT, and CT. EUS is more accurate than CT to detect T3 (Lightdale and Kulkarni, 2005), but there remains an important role to perform both EUS and CT (Zuccaro et al. 2005). PET scanning may detect 15% of metastases not seen by other methods, and thereby avoid what will turn out to be unnecessary surgery (van Westreenen, 2005). The number of PET-positive metastases has prognostic value. There is a correlation between changes in the tumor metabolic activity assessed by PET and the pathologic response after induction chemotherapy (Wieder et al. 2005), so that PET may be a useful tool for response assessment.

EMR is being increasingly performed for HGD in BE. The depth of the dysplastic lesion dictates the prognosis, but it has not been possible to correlate resection margin data with recurrence. Synchronous or recurrent dysplasia/ECA occurs in almost half of patients, possibly because dysplasia/cancer may be multifactorial, or may be present in remaining and undetected BE (Mino-Kenudson et al. 2005). This leads to the concept of removing all the BE by EMR, not just the targeted HGD. The risk of adenocarcinoma

increases with the depth of the lesion (M1, 0%; M2, <1%; M3, 6%; SM, 36%). EUS provides accurate staging of BE-HGD or ECA in 85% of patients (Larghi et al. 2005), so that EUS may be combined with pathological examination of tissues removed by EMR to assess the adequacy of the resection. The aim of EMR is to remove the abnormal mucosa (mucosectomy) and 2/3 of the submucosa. If there is more than mucosal involvement, then surgery rather than EMR is to be utilized. PPIs in twice daily dosing are used to encourage the squamous re-epithelization after EMR.

A randomized Phase III trial of PDT with porfimer sodium plus PPI bid in HGD gave higher 24 month ablation rates than PPI therapy alone (77% vs. 39%, $p < 0.001$, and many fewer developed EAC (Overholt et al. 2005). PDT with 5-aminolevulinic acid (ALD) gave local remission in 99% or more of HGD or early ECA, with calculated 5-year survival rates of 97% and 80%, respectively (Pech et al. 2005). Common adverse effects of PDT included dysphagia, pain, vomiting, and skin photosensitivity. The serious complications with PDT with porfimer sodium includes skin sensitivity to light (69%), esophageal strictures (36%), nausea and vomiting, 32%, dysphagia, 20%, fever, 20%, and pain, 20% (Overholt et al. 2005). The rate of occurrence of lymph node metastasis treated with EMR for superficial BE (T1, ml-5 ml) is lower than the mortality rate for esophagectomy (Westerterp et al. 2005; Stein et al. 2005). Early squamous cell cancer of the esophagus can also be treated with EMR, with a 3-year recurrence rate of 39% in persons with multifocal lesions, and 14% in those with unifocal early squamous cell cancer of the esophagus (Katada et al. 2005). With these relatively high recurrence rates, surveillance endoscopy and biopsy needs to be continued after EMR. If necessary, EMR can be followed with PDT or Argon plasma coagulation to destroy any remaining BE after EMR (Peters et al. 2005).

For T1-2 disease with limited or no lymph node involvement, esophagectomy gives a 5-year survival rate of over 90% for T1NO and over 60% for TxNO tumors (Enzinger and Mayer, 2003). The transthoracic *en bloc* esophagectomy and extended two-field lymphadenectomy is superior in most patients to transhiatal esophagectomy, with a 17% survival benefit (Hulsher and Van Lanschot, 2005). The benefit of neo-adjuvant chemotherapy is seen only after 5 years (Malthaner and Fenlon, 2003). In contrast, induction chemoradiotherapy plus surgery gives a lower 3-year mortality than surgery alone (Fiorica et al. 2004; Urschel and Vasan, 2003). Some authorities argue the surgery-alone approach, because of the higher postoperative mortality and morbidity when chemotherapy has been used (Fiorica et al. 2004).

The Merendins procedure (esophagectomy, jejunal interposition, vagal preservation) may be used for incomplete mucosectomy, and although there is a 50% morbidity, the mortality rate is 2%–10%, with good emptying of the jejunal interponate. Vagal sparing procedures reduce the pathophysiological complications of vagotomy, such as decreased receptive relaxation, decreased antral and gall bladder motility, and increased pyloric contraction, all of which contribute to the morbidity of delayed gastric emptying and the associated nutritional problems of vagotomy.

Eosinophilic Esophagitis (EE)

Biopsies from patients with EE show increased mast cells, T-cells, and enhanced levels of IL-4, IL-5, IL-13 and tumor necrosis factor (TNF)-2 (Mishra et al. 2002). Interestingly, peripheral eosinophils also have increased IL-5 and IL-13. Animal studies have suggested the sequence of cutaneous allergic response, activation of bone marrow eosinophils; with these homing to the esophagus (Akei et al. 2005). Patients with EE usually present with dysphagia, including food impaction (Desai et al. 2005). Rings and strictures ("feline esophagus") may be seen radiologically on barium studies, or on endoscopy (Zimmerman et al. 2005). Of importance to the endoscopist, the esophagus may easily tear (Straumann et al. 2003a). At least in children, half of persons with EE will have a history of allergic disorders such as asthma, allergic rhinitis and eczema (Liacouras et al. 2005).

The studies showing a beneficial role of inhaled steroids such as fluticasone have been short-term, and there have been reports of one year follow-up showing progression of the disease (Straumann et al. 2003b). Identification of possibly offending foods may be undertaken by comprehensive skin prick and patch testing, with strict avoidance of those foods testing positive. Even without positive testing, some patients do better when avoiding milk (Spergel et al. 2005).

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Abbreviations

BE: Barrett's epithelium; BMI: body mass index; CM: circular muscle; CVA: cerebral vascular accident; DES: diffuse esophageal spasm; ECA: esophageal adenocarcinoma; EE: erosive esophagitis; EGD: esophagogastroduodenoscopy; EMR: endoscopic mucosal resection; EUS: endoscopic ultrasound; FEESST: flexible endoscopic evaluation of swallowing and sensation test; fMRI: functional magnetic resonance imaging; FNA: fine needle aspiration; GABA: gamma amino butryic acid; GERD: gastroesophageal reflux disease; GI: gastrointestinal; HGD: high grade dysplasia; HFUS: high frequency intra-luminal ultrasound; HRM: high resolution manometry; IBS: irritable bowel syndrome; IEEI: intraluminal esophageal electrical impedence; IEM: ineffective esophageal motility; IL: interleukin; LES: lower esophageal sphincter; LGD: low grade dysplasia; LM: longitudinal muscle; MBS: modified barium swallow; MEG: magnetoencephalography; NBI: narrow band imaging; NCCP: non-cardiac chest pain; NERD: normal endoscopy reflux disease; NO: nitric oxide; NUT: nutcracker esophagus; OCT: optical coherence tomography; OPD: oro-pharyngeal dysphagia; PAF: platelet activating factor; PDT: photodynamic therapy; PET: position emission tomography; PPI: proton pump inhibitor; SP: substance P; SSRIs: selective serotonin reuptake inhibitors; TMS: transcranial magnetic stimulation; TNF: tumor necrosis factor; TLESR: transient lower esophageal relaxation; UES: upper esophageal sphincter.

References

Akei, H.S., Mishra, A., Blanchard, C. et al. 2005. Epicutaneous antigen exposure primes for experimental eosinophilic esophagitis in mice. *Gastroenterology*, 129:985–94.

Amano, Y., Kushiyama, Y., Ishihara, S. et al. 2005. Crystal violet chromoendoscopy with mucosal pit pattern diagnosis is useful for surveillance of short-segment Barrett's esophagus. *Am. J. Gastroenterol.*, 100:21–6.

Amaravadi, R., Levine, M.S., Rebesin, S.E. et al. 2005. Achalasia with complete relaxation of lower esophageal sphincter: radiographic-manometric correlation. *Radiology*, 235:886–91.

Asunuma, K., Iijima, K., Sugata, H. et al. 2005. Diffusion of cytotoxic concentrations of nitric oxide generated luminally at the gastro-oesophageal junction of rats. *Gut.*, 54:1072–7.

Aziz, Q., Thompson, D.G., Ng, V.K. et al. 2000. Cortical Processing of Human Somatic and Visceral Sensation. *J. Neurosci.*, 20:2657–63.

Bonatti, H., Hinder, R.A., Klocker, J. et al. 2005. Long-term results of laparoscopic Heller myotomy with partial fundoplication for the treatment of achalasia. *Am. J. Surg.*, 190:874–8.

Caviglia, R., Ribolsi, M., Maggiano, N. et al. 2005. Dilated intercellular spaces of esophageal epithelium in nonerosive reflux disease patients with physiological esophageal acid exposure. *Am. J. Gastroenterol.*, 100:543–8.

Cheng, L., Cao, W., Fiocchi, C., Behar, J., Biancani, P. and Harnett, K.M. 2005. In vitro model of acute esophagitis in the cat. *Am. J. Physiol. Gastrointest Liver Physiol.*, 289:G860–G9.

Clouse, R.E. and Lustman, P.J. 1983. Psychiatric illness and contraction abnormalities of the esophagus. *N. Engl. J. Med.*, 309:1337–42.

Clouse, R.E. and Staiano, A. 1991. Topography of the esophageal peristaltic pressure wave. *Am. J. Physiol. Gastrointest Liver Physiol.*, 261: G677–G684.

Clouse, R.E., Staiano, A., Bickston, S.J. and Cohn, S.M. 1996. Characteristics of the propagating pressure wave in the esophagus. *Dig Dis. Sci.*, 41:2369–76.

Conchillo, J.M., Nguyen, N.Q., Samson, M. et al. 2005. Multichannel intraluminal impedance monitoring in the evaluation of patients with non-obstructive dysphagia. *Am. J. Gastroenterol.*, 100:2624–32.

Desai, T.K., Stecevic, V., Chang, C-H. et al. 2005. Association of eosinophilic inflammation with esophageal food impaction in adults. *Gastrointest. Endosc.*, 61:795–801.

Dogan, I. and Mittal, R.K. 2006. Esophageal motor disorders: recent advances. *Current Opinion in Gastroenterology*, 22:417.

Dunckley, P., Wise, R.G., Fairhurst, M. et al. 2005. A Comparison of Visceral and Somatic Pain Processing in the Human Brainstem Using Functional Magnetic Resonance Imaging. *J. Neurosci*, 25:7333–41.

Eliakim, R., Sharma, V.K., Yassin, K. et al. 2005. A prospective study of the diagnostic accuracy of PillCam ESO esophageal capsule endoscopy versus conventional upper endoscopy in patients with chronic gastroesophageal reflux diseases. *J. Clin. Gastroenterol.*, 39:572–8.

El-Serag, H.B., Kvapil, P., Hacken-Bitar, J. and Kramer, J.R. 2005. Abdominal obesity and the risk of Barrett's esophagus. *Am. J. Gastroenterol.*, 100:2151–6.

Enzinger, P. and Mayer, R. 2003. Esophageal cancer. *N. Engl. J. Med.*, 23:2241–52.

Fiorica, F., Di Bona, D., Schepis, F. et al. 2004. Preoperative chemoradiotherapy for oesophageal cancer: a systematic review and metaanalysis. *Gut.*, 53:925–30.

Fox, M., Hebbard, G., Janiak, P. et al. 2004. High-resolution manometry predicts the success of oesophageal bolus transport and identifies clinically important abnormalities not detected by conventional manometry. *Neurogastroenterol. Motil.*, 16:533–42.

Freed, M.L., Freed, L., Chatburn, R.L. and Christian, M. 2001. Electrical stimulation for swallowing disorders caused by stroke. *Respir. Car*, 46:466–74.

Frisby, C.L., Mattsson, J.P., Jensen, J.M. et al. 2005. Inhibition of transient lower esophageal sphincter relaxation and gastroesophageal reflux by metabotropic glutamate receptor ligands. *Gastroenterology*, 129:995–1004.

Ghosh, S.K., Janiak, P., Schwizer, W., Hebbard, G.S. and Brasseur, J.G. 2006. Physiology of the esophageal pressure transition zone: separate contraction waves above and below. *Am. J. Physiol. Gastrointest. Liver Physiol.*, 290:G568–G76.

Gupta, R., Sample, C., Bamehriz, F. et al. 2005. Long-term outcomes of laparoscopic heller cardiomyotomy without an anti-reflux procedure. *Surg. Laparosc. Endosc. Percutan. Tech.*, 15:129–32.

Hampel, H., Abraham, N.S. and El-Serag, H.B. 2005. Met-analysis: obesity and the risk for gastroesophageal reflux disease and its complications. *Ann. Intern. Med.*, 143:199–211.

Hirano, I., Tatum, R.P., Shi, G. et al. 2001. Manometric heterogeneity in patients with idiopathic achalasia. *Gastroenterology*, 120:789–798.

Holzer, P. 2003. Acid-sensitive ion channels in gastrointestinal function. *Curr. Opin. Pharmacol.*, 3:618–25.

Hulscher, J.B. and Van Lanschot, J.J. 2005. Individualized surgical treatment of patients with adenocarcinoma of the distal esophagus and gastro-esophageal junction. *Dig. Surg.*, 22:130–34.

Imam, H., Shay, S., Ali, A. and Baker, M. 2005. Bolus transit patterns in healthy subjects: a study using simultaneous impedance monitoring, videoesophagram, and esophageal manometry. *Am. J. Physiol. Gastrointest Liver Physiol.*, 288:G1000–G6.

Isenberg, G., Sivak, M.V., Chak, A. et al. 2005. Accuracy of endoscopic optical coherence tomography in the detection of dysplasia in Barrett's esophagus: a prospective, double-blinded study. *Gastrointest. Endosc.*, 62:825–31.

Jung, H.Y., Puckett, J.L., Bhalla, V. et al. 2005. Asynchrony between the circular and the longitudinal muscle contraction in patients with nutcracker esophagus. *Gastroenterology*, 128:1179–86.

Kara , M.A., Peters , F.P., Rosmolen , W.D. et al. 2005. High-Resolution Endoscopy plus Chromoendoscopy or Narrow-Band Imaging in Barrett's Esophagus: a Prospective Randomized Crossover Study. *Endo.*, 37:929–36.

Kara, M.A., Ennahachi, M., Fockens, P. et al. 2006. Detection and classification of the mucosal and vascular patterns (mucosal morphology) in Barrett's esophagus by using narrow band imaging. *GI Endo.*, 64:155–85.

Karamanolis, G., Sgouros, S., Karatzias, G. et al. 2005. Long-term outcome of pheumatic dilation in the treatment of achalasia. *Am. J. Gastroenterol.*, 100:270–4.

Katada, C., Muto, M., Manabe, T. et al. 2005. Local recurrence of squamous-cell carcinoma of the esophagus. *Gastrointest. Endosc.*, 61:219–25.

Kazumori, H., Ishihara, S., Rumi, MAK., Kadowaki, Y. and Kinoshita, Y. 2006. Bile acids directly augment caudal related homeobox gene Cdx2 expression in oesophageal keratinocytes in Barrett's epithelium. *Gut.*, 55:16–25.

Kiesslich, R., Kanzler, S., Vieth, M. et al. 2004. Minimal change esophagitis: prospective comparison of endoscopic and histological markers between patients with non-erosive reflux disease and normal controls using magnifying endoscopy. *Dig. Dis.*, 22:221–7.

Larghi, A., Lightdale, C.J., Memeo, L. et al. 2005. EUS followed by EMR. for staging of a high-grade dysplasia and early cancer in Barrett's esophagus. *Gastrointest. Endosc.*, 62:16–23.

Leite, L.P., Johnston, B.T., Barrett, J., Castell, J.A. and Castell, D.O. 1997. Ineffective esophageal motility (IEM): the primary finding in patients with nonspecific esophageal motility disorder. *Dig. Dis. Sci.*, 42:1859–65.

Liacouras, C.A., Spergel, J.M., Ruchelli, E. et al. 2005. Eosinophilic esophagitis: a 10-year experience in 381 children. *Clin. Gastroenterol. Hepatol.*, 3:1198–1206.

Lightdale, C.J. and Kulkarni, K.G. 2005. Role of endoscopic ultrasonography in the staging and follow-up of esophageal cancer. *J. Clin. Oncol.*, 23:4483–9.

Liu, J., Puckett, J.L., Takeda, T. et al. 2005. Crural diaphragm inhibition during esophageal distension correlates with contraction of the esophageal longitudinal muscle in cats. *Am. J. Physiol. Gastrointest Liver Physiol.*, 288:G927–G32.

Maieron, R., Elli, L., Marino, M. et al. 2005. Celiac disease and intestinal metaplasia of the esophagus (Barrett's esophagus). *Dig Dis. Sci.*, 50:126–9.

Malthaner, R. and Fenlon, D. 2003. Preoperative chemotherapy for respectable esophageal cancer. *Cochrane Database Syst. Rev.*, 4: CD001556.

Martin, C.J., Patrikios, J. and Dent, J. 1986. Abolition of gas reflux and transient lower esophageal sphincter relaxation by vagal blockade in the dog. *Gastroenterology*, 91:890–6.

Mashimo, H., He, X.D., Huang, P.L. et al. 1996. Neuronal constitutive nitric oxide synthase is involved in murine enteric inhibitory neurotransmission. *J. Clin. Invest.*, 98:8–13.

Matthews, P.J., Aziz, Q.A., Facer, P.B., Davis, J.B.C., Thompson, D.G. and Anand, P.B. 2004. Increased capsaicin receptor TRPV1 nerve fibres in the inflamed human oesophagus. Eur. J. Gastroenterol. Hepatol, 16:897–902.

Mino-Kenudson, M., Brugge, W., Puricelli, W.P. et al. 2005. Management of Superficial Barrett's Epithelium-Related Neoplasms by Endoscopic Mucosal Resection: Clinicopathologic Analysis of 27 Cases. *Am. J. Surg. Path*, 29:680–6.

Mishra, A., Hogan, S.P., Brandt, E.B. et al. 2002. IL-5 promotes eosinophil trafficking to the esophagus. *J. Immunol.*, 168:2464–9.

Mittal, R.K., Kassab, G., Puckett, J.L. and Liu, J. 2003. Hypertrophy of the muscularis propria of the lower esophageal sphincter and the body of the esophagus in patients with primary motility disorders of the esophagus. *Am. J. Gastroenterol.*, 98:1705–12.

Mittal, R.K., Liu, J., Puckett, J.L. et al. 2005. Sensory and motor function of the esophagus: lessons from ultrasound imaging. *Gastroenterology*, 128:487–97.

Mittal, R.K., Padda, B., Bhalla, V. et al. 2006. Synchrony between circular and longitudinal muscle contractions during peristalsis in normal subjects. *Am. J. Physiol. Gastrointest. Liver Physiol.*, 290:431–8.

Mujica, V.R., Mudpalli, R.M. and Rao, S.S. 2001. Pathophysiology of chest pain in patients with nutcracker esophagus. *Am. J. Gastroenterol.*, 96:1371–7.

Muinuddin, A., Xue, S. and Diamant, N.E. 2001. Regional differences in the response of feline esophageal smooth muscle to stretch and cholinergic stimulation. *Am. J. Physiol. Gastrointest. Liver Physiol.*, 281:G1460–G7.

Murray, J.A., Ledlow, A., Launspach, J., Evans, D., Loveday, M. and Conklin, J.L. 1995. The effects of recombinant human hemoglobin on esophageal motor function in humans. *Gastroenterology*, 109:1241–8.

Nicosia, M.A., Brasseur, J.G., Liu, J.B. and Miller, L.S. 2001. Local longitudinal muscle shortening of the human esophagus from high-frequency ultrasonography. *Am. J. Physiol. Gastrointest. Liver Physiol.*, 281:G1022–33.

O'Riordan, J.M., Abdel-latif, M.M., Ravi, N. et al. 2005. Proinflammatory cytokine and nuclear factor kappa-B. expression along the inflammation-metaplasia-dysplasia-adenocarcinoma sequence in the esophagus. *Am. J. Gastroenterol.*, 100:1257–1264.

Overholt, B.F., Lightdale, C.J., Wang, K.K. et al. 2005. Photodynamic therapy with porfimer sodium for ablation of high-grade dysplasia in Barrett's esophagus: international partially blinded, randomized phase iii trial. *Gastrointest. Endosc.*, 62:488–98.

Pal, A. and Brasseur, J.G. 2002. The mechanical advantage of local longitudinal shortening on peristaltic transport. *J. Biomech. Eng.*, 124:94–100.

Pech, O., Gossner, L., May, A. et al. 2005. Long-term results of photodynamic therapy with 5-aminolevulinic acid for superficial Barrett's cancer and high-grade intraepithelial neoplasia. *Gastrointest. Endosc.*, 62:24–30.

Peters, F.P., Kara, M.A., Rosmolen, W.D. et al. 2005. Endoscopic treatment of high-grade dysplasia and early stage cancer in Barrett's esophagus. *Gastrointest. Endosc.*, 61:506–14.

Preiksaitis, H.G. and Diamant, N.E. 1997. Regional differences in cholinergic activity of muscle fibers from the human gastroesophageal junction. *Am. J. Physliol. Gastrointest. Liver Physiol.*, 272:G1321–G7.

Ronkainen, J., Aro, P., Storskrubb, T. et al. 2005. Prevalence of Barrett's esophagus in the general population: an endoscopic study. *Gastroenterology*, 129:1825–31.

Rosetti, G., Brusciano, L., Amato, G. et al. 2005. A total fundoplication is not an obstacle to esophageal emptying after Heller myotomy for achalasia: results of a long-term follow up. *Ann. Surg.*, 241:614–21.

Sarkar, S., Aziz, Q., Woolf, C.J., Hobson, Ar. and Thompson, D.G. 2000. Contribution of central sensitisation to the development of non-cardiac chest pain. *Lancet*, 356:1154–9.

Sayuk, G.S. and Clouse, R.E. 2005. Management of esophageal symptoms following fundoplication. *Curr. Treat Options Gastroenterol.*, 8:293–303.

Sivarao, D.V., Mashimo, H.L., Thatte, H.S. and Goyal, R.K. 2001. Lower esophageal sphincter is achalasic in nNos (-/-) and hypotensive in W/W (v) mutant mice. *Gastroenterology*, 121:34–42.

Souza, R.F., Shewmake, K.L., Shen, Y. et al. 2005. Differences in ERK activation in squamous mucosa in patients who have gastroesophageal reflux disease with and without Barrett's esophagus. *Am. J. Gastroenterol.*, 100:551–9.

Spergel, J.M., Andrews, T., Brown-Whitehorn, T.F. et al. 2005. Treatment of eosinophilic esophagitis with specific food elimination diet directed by a combination of skin prick and patch tests. *Ann. Allergy Asthma Immunol.*, 95:336–43.

Stein, H.J., Reith, M., Bruecher, B.L. et al. 2005. Early esophageal cancer: pattern of lymphatic spread and prognostic factors for long-term survival after surgical resection. *Ann. Surg.*, 242:566–73.

Straumann, A., Spichtin, h-P., Grize, L. et al. 2003(a). Natural history of primary eosinophilic esophagitis: a follow-up of 30 adult patients for up to 11.5 years. *Gastroenterology*, 125:1660–9.

Straumann, A., Rossi, L., Simon, H.U. et al. 2003(b). Fragility of the esophageal mucosa: a pathognomonic endoscopic sign of primary eosinophilic esophagitis? *Gastrointest Endosc.*, 57:407–12.

Tutian, R., Pohl, D., Castell, D.O. and Fried, M. 2006. Clearance mechanisms of the aperistaltic oesophagus: the "pump-gun" hypothesis. *Gut.*, 55:584–5.

Urschel, J.D. and Vasan, H. 2003. A metal analysis of randomized controlled trials that compared neoadjuvant chemoradiation and surgery to surgery alone for resectable esophageal cancer. *Am. J. Surg.*, 185:538–43.

Vallbohmer, D., Peters, J.H., Oh, D. et al. 2005. Survinin, a potential biomarker in the development of Barrett's adenocarcinoma. *Surgery*, 100:701–7.

van Westreenen, H. 2005. Positron emission tomography in staging of esophageal cancer (thesis) Groningen: University of Groningen. *Enschede: Print Partner Ipskamp*.

Vieth, M., Fiocca, R., Haningsma, J. et al. 2004. Radial distribution of dilated intercellular spaces of the esophageal squamous epithelium in patients with reflux disease exhibiting discrete endoscopic lesions. *Dig Dis.*, 22:208–12.

Ward, S.M., Morris, G., Reese, L. et al. 1998. Interstitial cells of Cajal mediate enteric inhibitory neurotransmission in the lower esophageal and pyloric sphincters. *Gastroenterology*, 115:314–29.

Watt, E. and Whyte, F. 2003. The experience of dysphagia and its effect on the quality of life patients with esophageal cancer. *Eur. J. Cancer Care*, 12:183–93.

Westerterp, M., Koppert, L.B., Buskens, C.J. et al. 2005. Outcome of surgical treatment for early adenocarcinoma of the esophagus or gastroesophageal junction. *Virchows. Arch.*, 446:497–504.

Wieder, H.A., Beer, A.J., Lordick, F. et al. 2005. Comparison of changes in tumor metabolic activity and tumor size during chemotherapy of adenocarcinomas of the esophagogastric junction. *J. Nucl. Med.*, 46:2029–34.

Wipff, J., Allanore, Y., Soussi, F. et al. 2005. Prevalence of Barrett's esophagus in systematic sclerosis. *Arthritis Rheum.*, 52:2882–8.

Ye, W., Held, M., Lagergren, J. et al. 2004 Mar. Helicobacter pylori infection and gastric atrophy: risk of adenocarcinoma and squamous-cell carcinoma of the esophagus and adenocarcinoma of the gastric cardia. *J. Natl. Cancer Inst.*, 96:388–96.

Zeribib, F., des Varannes, S.B., Roman, S. et al. 2005. Normal values and day-to-day variability of 24-h ambulatory oesophageal impedance-pH monitoring in a Belgian-French cohort of healthy subjects. *Aliment Pharmacol. Ther.*, 22:1011–21.

Zentilin, P., Savarino, V., Mastracci, L. et al. 2005. Reassessment of the diagnostic value of histology in patients with GERD, using multiple biopsy sites and an appropriate control group. *Am. J. Gastroenterol.*, 100:2299–306.

Zimmerman, S.L., Levine, M.S., Rubesin, S.E. et al. 2005. Idiopathic eosinophilic esophagitis in adults; the ringed esophagus. *Radiology*, 236:159–65.

Zuccaro, G. Jr., Rice, T.W., Vargo, J.J. et al. 2005. Endoscopic ultrasound errors in esophageal cancer. *Am. J. Gastroenterol.*, 100:1216.