

Update on endoscopic diagnosis, management and surveillance strategies of esophageal diseases

Fernando Fornari, Rafaela Wagner

Fernando Fornari, Rafaela Wagner, Department of Gastroenterology, School of Medicine, Universidade de Passo Fundo, CEP 99010080, Centro, Passo Fundo-RS, Brazil

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Correspondence to: Fernando Fornari, PhD, Department of Gastroenterology, School of Medicine, Universidade de Passo Fundo, Rua Teixeira Soares 817, CEP 99010080, Centro, Passo Fundo-RS, Brazil. fernandofofornari@gmail.com

Telephone: +55-54-33168553 Fax: +55-54-33168553

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Abstract

In the last few decades, upper gastrointestinal endoscopy has become the most complementary test for investigation of esophageal diseases. Its accessibility and safety guarantee wide clinical utilization in patients with suspected benign and malignant diseases of the esophagus. Recent technological advances in endoscopic imaging and tissue analysis obtained from the esophagus have been useful to better understand and manage highly relevant diseases such as gastro-esophageal reflux disease, eosinophilic esophagitis and esophageal cancer. Using endoscopy to elucidate esophageal disorders in children has been another field of intensive and challenging research. This editorial highlights the latest advances in the endoscopic management of esophageal diseases, and focuses on Barrett's esophagus, esophageal cancer, eosinophilic esophagitis, as well as esophageal disorders in the pediatric population.

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INTRODUCTION

Upper gastrointestinal endoscopy is a technique widely employed for diagnostic and therapeutic purposes. Diseases affecting the esophagus, stomach and/or duodenum have been described and eventually treated by endoscopy in routine clinical practice. This technique also allows biopsy collection, which helps with the characterization of conditions such as inflammation, infection and neoplasia. Recent technological advances have increased the capability of endoscopy in recognizing and treating GI diseases, including those affecting the esophagus. This editorial provides an update on the role of endoscopy in the management of esophageal diseases. Our discussion is limited to relevant conditions commonly seen in adults, such as Barrett's metaplasia and esophageal cancer, as well as diseases affecting the pediatric population, including eosinophilic esophagitis and gastroesophageal reflux disease (GERD). We also point to recent evidence regarding the utility of magnifying endoscopy in the management of esophageal disorders.

BARRETT'S ESOPHAGUS AND ADENOCARCINOMA

Barrett's esophagus (BE) is the replacement of normal esophageal mucosa (stratified squamous epithelium) by metaplastic columnar epithelium that predisposes to cancer development^[1]. Metaplastic columnar epithelium can

be of three types: gastric fundic-type, cardia-type, and intestinal-type. This latter type is known to be associated with an increased risk of adenocarcinoma, and most authorities agree that its presence is needed to define BE. However, recent evidence has suggested that cardia-type metaplasia can also predispose to cancer development in the esophagus^[2-4], which leads us to infer that the concept of BE remains far from a consensus, as highlighted by Segal and colleagues in this issue of *World Journal of Gastrointestinal Endoscopy (WJGE)*.

GERD is considered the main risk factor for BE, and the association of obesity, alcohol and tobacco consumption, male sex, White race and hiatal hernia increases the risk of adenocarcinoma development. Therefore, the management of patients with BE involves adequate reflux control with medical or surgical approaches, measures to prevent cancer such as tobacco cessation, endoscopic surveillance to detect premalignant conditions or early stage cancer, and treatment of advanced adenocarcinoma.

Endoscopic surveillance continues to be a matter of intense debate. Regular surveillance can detect curable early neoplasia, but questions remain unanswered: who, when and how to perform surveillance in an evidence-based way with cost-utility? At present, accepted surveillance includes endoscopy every 3-5 years for Barrett's metaplasia without dysplasia, intervals of 6-12 mo for low grade dysplasia, and every 3 mo for high grade dysplasia when no invasive therapy is offered^[1,5]. The diagnosis of BE is suspected when, during endoscopic examination, columnar epithelium is observed to extend above the gastroesophageal junction (GEJ) into the esophagus. Although still controversial, most studies addressing BE have used the proximal extent of the gastric folds as the landmark for the GEJ. Biopsies of the columnar epithelium can reveal three different histological types, including gastric fundic-type, cardia-type and intestinal-type epithelium. This latter type has been adopted to define the presence of BE, since intestinal metaplasia is the only one of the 3 types that clearly predisposes to malignancy. Different biopsy protocols have been proposed, with controversial results in the comparison of random and targeted sampling^[6]. New endoscopy technologies combining chromoendoscopy and magnification have been tested to improve patient selection and an earlier recognition of premalignant and malignant lesions in patients with BE^[7]. However, given the relatively low incidence of adenocarcinoma from the pool of patients with BE, further studies are needed to support the employment of these costly technologies in BE management.

Therapeutic endoscopy has evolved tremendously in the last decade. Barrett's metaplasia can be removed by endoscopic mucosal resection (EMR), and residual epithelium may be destroyed with endoscopic ablative techniques, such as photodynamic therapy, radiofrequency ablation and cryotherapy^[8-10]. There is also an ongoing debate on the potential use of endoscopic submucosal

dissection (ESD) for treating early esophageal neoplasia related to BE and its risks and potential advantages over EMR^[11]. Again, additional studies are mandatory to establish the exact role of these tools in the management of BE.

SQUAMOUS CELL CARCINOMA OF THE ESOPHAGUS

Squamous cell carcinoma of the esophagus (SCCE) is a common cause of morbidity and mortality in developing countries^[12]. High mortality rates are secondary to late diagnosis, since most patients seek medical assistance after the appearance of symptoms such as dysphagia and weight loss. This delay has a negative impact on the 5-year survival of patients with SCCE treated with multimodality therapy, reaching between 5% and 15% even in developed countries^[13,14]. Therefore, early diagnosis is the best way to achieve higher rates of cure and longer survival. In this issue of *WJGE*, Fagundes *et al* highlight the effort to enhance early diagnosis of SCCE and its precursor lesions.

Early diagnosis is based on the identification of lesions such as high-grade dysplasia or carcinoma *in situ*, which are restricted to esophageal mucosa^[15]. Tumors limited to the upper two thirds of esophageal mucosa are also characterized as early SCCE. Treatment of these lesions results in a 5-year survival of more than 90% after endoscopic or surgical approaches^[16]. The diagnosis of early SCCE must not be based on symptoms, since they are usually limited to advanced stages of the disease. Consequently, screening techniques must be used in asymptomatic individuals exposed to risk factors. As highlighted by Fagundes *et al* in this issue of *WJGE*, potential etiologic factors for SCCE in high risk areas include poor nutritional and socioeconomic status, exposure to polycyclic aromatic hydrocarbons, low intake of vegetables and fruits, drinking hot beverages, and genetic factors. Screening of SCCE in high risk areas must include the largest number of people living in these places, using widely available techniques. In moderate and lower risk areas, the main risk factors include tobacco smoking, excessive alcohol consumption, previous diagnosis of head and neck squamous cell carcinoma, and consumption of hot beverages. These risk factors characterize the population that should be screened for SCCE.

Several techniques have been developed and tested for SCCE screening. Esophageal balloon cytology is a patient-acceptable sampling technique, although the current methods are insufficient for primary screening due to sampling errors^[17]. Molecular markers combined with esophageal cytology are promising, but the use of biomarkers still lacks validation and availability. Conventional white light endoscopy with biopsy remains the standard procedure for the identification of pre-malignant and early malignant changes in esophageal mucosa. Endoscopic detection may be enhanced by several techniques such as dye and optical chromoendoscopy, mag-

nifying endoscopy, and optical-based spectroscopic and imaging modalities. The most efficient and cost-effective tool for targeting biopsies may be Lugol dye chromoendoscopy, since it is an easy, accurate, inexpensive and worldwide available endoscopic technique^[18-20]. In areas of medium and low risk, individual cases should be considered for screening if the risk and costs to the individual warrant aggressive screening and follow-up evaluation, such as in certain groups of subjects at especially high risk, like alcoholics and smokers. Further studies are needed to establish the best approach for SCCE screening in populations with different risks.

NEW TECHNOLOGIES AND MAGNIFYING IMAGING IN ESOPHAGOSCOPY

The advent of imaging magnification has opened new horizons in the diagnostic process of gastrointestinal diseases, as highlighted by Torresini and colleagues in this issue of *WJGE*. New technologies have been developed, including high-resolution endoscopy, magnification endoscopy, chromoendoscopy, light spectral analysis, confocal laser microscopy and optical coherence tomography. The use of these techniques has provided diagnostic advances not only for benign lesions such as GERD, but also for pre-malignant and malignant diseases of the esophagus. However, the widespread use of these technologies is still limited due to the lack of evidence-based data centered in study outcomes and cost-effective analysis.

Magnifying endoscopy is particularly used in the evaluation of patients with non-erosive reflux disease (NERD). This category of GERD includes patients in whom the genesis of symptoms may be related to subtle mucosal changes not detected by conventional endoscopy. Features such as vascular dilation, villous mucosal surface, microerosions, and dilated intercellular spaces have been described as peculiar characteristics of NERD^[21,22]. Some of these changes, detected by magnifying endoscopy, may represent remission after acid-suppressive therapy, suggesting that this new imaging modality can be used not only for diagnostic purpose but also for therapeutic control^[23]. Although promising, the lack of consensus on subtle mucosal changes, the diversion of imaging techniques, as well as their high cost are still important shortcomings. Further studies are needed to support the widespread use of these technologies in the clinical approach of GERD patients.

Magnifying endoscopy can also be applied in the management of esophageal cancer, including adenocarcinoma and squamous cell carcinoma. The identification of precursor lesions and early stage cancer in the esophagus can be achieved more easily with magnifying endoscopy and related technologies. Esophageal changes associated with the evolving process of Barrett's metaplasia to dysplasia, and finally to adenocarcinoma, may be detected earlier and more precisely using the techniques of imaging magnification and chromoendos-

copy^[24-26]. Moreover, a recent medical position statement of the American Gastroenterology Association on the matter of BE management recommended the use of light endoscopy in standard care of patients who participate in the surveillance program^[1].

Esophageal capsule endoscopy (ECE) has been tested as an alternative technique to evaluate the esophagus. In a recent study, Nakos *et al*^[27] assessed the positive general attitude concerning the comparison among ECE, sedated conventional endoscopy and unsedated ultrathin endoscopy. Although the three methods carried comparable diagnostic accuracy, ECE caused less pain and discomfort, and more patients referred that they would repeat ECE in the future. Despite the increased patient acceptance, major limitations of the technique such as partial and inadequate exploration of the stomach and duodenum and inability to obtain biopsies, may limit its applicability. Among new technologies, endocytoscopy deserves a mention. It is based on the principle of light contact microscopy, allowing real-time visualization of the cellular structures of the superficial epithelial layer previously prepared with absorptive contrast agents^[28].

EOSINOPHILIC ESOPHAGITIS

Eosinophilic esophagitis (EoE) is a chronic clinical entity with increasing prevalence, which affects children and adults^[29,30]. It is characterized by eosinophilic infiltration of the esophageal epithelium potentially related to an antigen-driven immunologic process^[31]. Patients with this condition may complain of dysphagia and reflux-like symptoms, compatible with esophageal dysfunction. The differentiation with GERD may be difficult, since clinical, endoscopic and histological findings of EoE and reflux disease may overlap.

The diagnosis of EoE in suspected cases is based on endoscopic findings and histological examination of the esophageal mucosa. For optimal pathologic evaluation, multiple biopsy specimens from the proximal and distal esophagus should be obtained^[31]. Endoscopic findings include mucosal friability, erythema and loss of vascularity, linear furrowing, white plaques or exudates, concentric rings, delicate mucosa prone to tearing and diffuse luminal narrowing or strictures^[32]. However, endoscopy can often be normal or show misleading features. According to recent guidelines, histological criteria for EoE requires the demonstration of 15 or more eosinophils per high-power field (hpf) of esophageal tissue, after proper treatment for GERD^[31,33,34]. Endoscopy can also be used to verify the therapeutic response, assess disease remission, and evaluate symptom recurrence of EoE^[35]. Some patients may benefit from endoscopic dilations in the case of eosinophilic strictures.

As highlighted by Ferreira and Goldani in this issue of *WJGE*, the treatment of EoE in the majority of children relies on elemental diets or elimination of food allergens. In older children and adults, treatment usually involves a topical corticosteroid or short courses of

systemic steroids. A multidisciplinary approach to EoE is recommended because of its frequent association with atypical manifestations. Therefore, it is essential to coordinate the work between gastroenterologists and allergologists, and it is also very important to involve nutrition experts in cases of significant food restriction.

GASTROESOPHAGEAL REFLUX DISEASE IN THE PEDIATRIC POPULATION

In the pediatric population, GERD is present when reflux of gastric contents causes troublesome symptoms and/or complications^[36]. However, this definition is complicated by unreliable reporting of symptoms in children younger than 8 years. In this scenario, upper gastrointestinal endoscopy with biopsies of the esophageal mucosa may be useful to assess the type and severity of tissue damage. However, the lack of a standardized protocol for biopsy sampling limits the utilization of esophageal histology as a diagnostic tool^[36]. Endoscopic findings observed in GERD patients include normal mucosa, esophageal erosions and columnar lined epithelium. Although the presence of endoscopically normal mucosa does not exclude the diagnosis of non-erosive reflux disease, it helps to rule out alarming conditions such as BE. Although observed in a minority of the pediatric population, the finding of esophageal erosions in the distal esophagus has been considered a good indicator of the presence of GERD. The Los Angeles Classification is preferred to describe erosive esophagitis in both children and adults^[37]. This practice has provided a trustful interpretation of endoscopic findings, as well as an assessment of the impact of acid suppressive therapy in treating reflux esophagitis.

More recently, endoscopy has been used to detect other potential causes of esophagitis, in particular eosinophilic esophagitis^[31]. Regardless of macroscopic findings, the performance of biopsies may be helpful to identify a specific entity affecting the esophagus, and to rule out differential diagnoses such as BE and infections. Although there is insufficient evidence to support the use of histology to diagnose GERD, the diagnostic potential of biopsies is increased if multiple samples of good size and orientation are obtained from sites that are related to major esophageal landmarks. Nevertheless, the macroscopic findings, especially visible breaks in the distal esophageal mucosa are the most reliable interobserver findings in reflux esophagitis^[37].

In patients with severe esophagitis, the risk of overcalling a diagnosis of BE should induce a 12-week course of acid suppressive treatment, in order to recover the main landmarks, as well as mucosa integrity, therefore enabling an adequate evaluation. Endoscopic monitoring of therapeutic efficacy is only indicated in patients presenting atypical findings and symptoms, cases in which the symptoms persist despite adequate treatment, or in patients with severe esophagitis at onset. Thus, in the majority of cases, symptom assessment after acid sup-

pressive therapy is sufficient for an adequate follow up. Endoscopy is also important in the evaluation of specific situations that may be linked to GERD, such as children aged more than 18 mo with chronic regurgitation or vomiting, infants with unexplained crying/distressed behavior, dysphagia and food refusal, apnea or apparent life threatening events, reactive airway disease, recurrent pneumonia, upper airway symptoms, dental erosions, and Sandifer syndrome.

Empiric treatment of GERD symptoms may be more cost-effective in comparison to endoscopy followed by treatment based on mucosal findings. Nevertheless, a study showed that the use of gastric acid inhibitors was associated with an increased risk of acute gastroenteritis and community-acquired pneumonia in GERD-affected children^[38]. Therefore, the unrestricted use of acid-suppressive therapy in children should be avoided^[39], and therapeutic measures should warrant the individual risks associated with its intake.

Although many techniques have been used to diagnose GERD, the lack of a gold standard exam impairs the accurate assessment of the various approaches used to evaluate this condition. The role of newer endoscopic technologies and endoluminal therapy for GERD are still uncertain. Further studies are needed to establish its reliability.

CONCLUSION

The advent of endoscopy has been revolutionary in the diagnosis of benign and malignant esophageal diseases. This technique allows adequate examination of the entire esophageal mucosa, as well as acquisition of biopsies and resection of focal lesions. In clinical practice, endoscopy has been useful in diagnosing esophagitis, including GERD-related and other causes, monitor persistent lesions such as metaplasia and dysplasia, and in assessing the effect of acid suppressive therapy in healing GERD-related lesions. The incorporation of biopsies and histological analyses to macroscopic visualization increases the list of differential diagnoses and allows the detection of premalignant lesions in the early stage of development. The current use of imaging magnification, especially in the detection of non-erosive reflux disease as well as the use of Lugol dye chromoendoscopy to detect precursor lesions of squamous cell carcinoma, constitute important alternatives that can help in the preventive or therapeutic approach. Endoscopic screening of populations exposed to malignancy risk factors such as tobacco and obesity should be a priority, since the majority of cancerous lesions in the initial stage do not provide a large symptom spectrum. In children, due to the unreliability of symptoms assessment, especially in those under 8 years of age, a careful evaluation of global development, feeding routine, repetitive airway infections, amongst other factors, is crucial to rule out the potential diagnosis of GERD, and to indicate endoscopic screening. Despite the wide use of endoscopy in evaluating and

treating esophageal diseases, further studies are needed to improve current protocols and consensus in use to guide the screening of esophageal lesions and support the employment of newer technologies in the clinical approach to patients with esophageal diseases.

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