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TOPIC HIGHLIGHT

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Esophageal squamous cell carcinoma - precursor lesions and early diagnosis

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Abstract

Squamous cell carcinoma of the esophagus (SCCE) carries a poor prognosis due to late diagnosis. Early detection is highly desirable, since surgical and endoscopic resection offers the only possible cure for esophageal cancer. Population screening should be undertaken in high risk areas, and in low or moderate risk areas for people with risk factors (alcoholics, smokers, mate drinkers, history of head and neck cancer, achalasia and lye stricture of the esophagus). Esophageal balloon cytology is an easy and inexpensive sampling technique, but the current methods are insufficient for primary screening due to sampling errors. Conventional endoscopy with biopsy remains the standard procedure for the identification of pre-malignant and early malignant changes in esophageal mucosa and endoscopic detection. It may be enhanced by several techniques such as dye and optic chromoendoscopy, magnifying endoscopy, and optical-based spectroscopic and imaging modalities. Since more than 80% of SCCE deaths occur in developing countries, where expensive techniques such as narrow band imaging (NBI) and autofluorescence imaging are unavailable, the most cost-effective tool for targeting biopsies may be Lugol dye chromoendoscopy, since it is easy, accurate, inexpensive and available worldwide. In ideal conditions, or in developed countries, is it reasonable to think that optimal detection will require a combination of techniques, such as the combination of Lugol' s chromoendoscopy and NBI to identify esophageal areas that require further characterization by a high resolution technique. The efficacy and cost-effectiveness will determine whether these modalities will become part of standard endoscopy practice.

Key words: Autofluorescence endoscopy; Early diagnosis; Esophageal cancer; Esophageal squamous cell carcinoma; Lugol's solution; Narrow-band imaging endoscopy

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INTRODUCTION

The cancers arising from the esophageal mucosa, including squamous cell carcinoma (SCCE) and adenocarcino-

ma (ADC), are the eighth most common cancers worldwide, with 482 000 new cases estimated in 2008, and are the sixth most common cause of death from cancer with 4 070 00 deaths in the same year[1]. The majority of new cases occur in developing countries accounting for 83% of cases and 86% of deaths, with incidence ratios varying 16-fold between high incidence regions, such as Southern and Eastern Africa and Eastern Asia, and low incidence regions like Western and Middle Africa and Central America[2]. SCCE is still the most frequent histological type worldwide, even after the 400% increase in the prevalence of ADC in the United States[3,4] and in some countries in Western Europe[5,6] where ADC accounts for more than 80% of new cases[7]. Indeed, the predominance of SCCE is due to its high prevalence in Eastern Asia, as it is observed in some provinces of China, Turkey and Iran, where as much as 120 to 175 new cases are diagnosed per 100 000 inhabitants each year[8]. Intermediate prevalence of SCCE has been observed in France[6], Southern and Eastern Africa[9], and in some countries of South America such as Uruguay, southeast Argentina and southern Brazil, where SCCE still accounts for more than 80% of esophageal cancers[10].

Esophageal cancers carry a high mortality mainly due to its late diagnosis, with a five-year survival of less than 10%[11]. More than 70% of diagnosis are made in patients presenting with dysphagia and weight loss, clinical findings frequently observed in patients in at least stage Ⅱ disease[12,13]. In developing countries more than 90% of diagnosis of esophageal cancers are at stage Ⅱ to Ⅳ with only 15% to 30% of patients elected for curative surgery[14]. Early diagnosis is uncommon even in developed countries such as France, Japan and the United States, where stage I accounts for just 4% to 25% of new diagnosis[13,15]. This negatively affects the 3- and 5-year survival of patients submitted to multimodality treatments, reaching between 8% to 40% and 5% to 15%, respectively[16]. Diagnosis of early stage lesions is still the best way to improve the chances of cure and survival.

The heterogeneity of risk factors, the differences in geographic distribution and the ethnic groups at risk, make it really difficult to rely on serologic markers for the diagnosis of SCCE. Some attempts have been made, but none of them can be used in clinical practice, due to their low sensitivity[17] or lack of confirmatory values for the diagnosis of early SCCE[18-21]. Since serologic tests are not clinically available yet, more invasive tests are still needed to diagnose SCCE.

Therefore, the aim of the current article is to review some of the most recent efforts that have been made to enhance early diagnosis of SCCE and its precursor lesions.

DEFINITION OF EARLY DIAGNOSIS

Invasive SCCE develops from intraepithelial neoplasia, such as dysplasia and carcinoma *in situ*, that reaches the lamina propria and extends beyond the submucosa[22]. In a recent Italian study by Ancona and colleagues[23], patients with lesions that were restricted to the esophageal mucosa did not present lymph node metastasis, while lymph node metastasis were observed in 8.3% of patients with tumors restricted to the first third of the submucosa (Sm1). In fact, the diagnosis and treatment of such early stage lesions can improve the survival rates of SCCE, reaching a five-year survival rate of more than 90% after endoscopic or surgical treatment[24].

For the purpose of this review, early esophageal SCCE will be considered high-grade dysplasia, carcinoma in situ, and tumors limited to the upper two thirds of the submucosa. These three types of lesions have a low rate of lymph node metastasis and present higher rates of cure and survival.

RISK FACTORS – WHO SHOULD BE SCREENED?

Early diagnosis of SCCE must not be based on symptoms, since they occur frequently in advanced disease, consequently, screening techniques must be used in asymptomatic individuals exposed to risk factors.

In high risk areas of the "esophageal cancer belt", such as northern Iran, some provinces of north-central China and north Afghanistan, the main risk factors are poor nutritional and socioeconomic status[25,26], exposure to polycyclic aromatic hydrocarbons (PAH)[27-30], low intake of vegetables and fruits[31], drinking hot beverages[32,33] and there is probably a role for genetic factors[34,35]. These risk factors affect the whole population in these high risk areas, and screening of SCCE in these populations must include the largest number of people that live in these places, with lower costs and less invasive devices.

In moderate and lower risk Western countries, the most important risk factors are the combination of tobacco smoking and excessive alcohol consumption[36-44]. A previous diagnosis of head and neck squamous cell carcinoma has been observed to have a significant impact on the incidence of SCCE[45-47]. Some areas of South America, such as southern Brazil, Uruguay, Paraguay and northwestern Argentina, have a moderate prevalence of SCCE which is influenced by ingestion of a hot beverage called *maté*. This hot beverage is an infusion of the leaves of Ilex paraguayensis that probably increases the risk of SCCE due to its high temperature[33,38,48-51] and its high content of PAH[52,53]. Some other risk factors that may contribute to SCCE are achalasia, previous radiotherapy for breast cancer, previous caustic injury to the esophagus and thylosis. SCCE screening in moderate and lower risk Western countries must be carried out in subjects exposed to the risk factors described above[54].

CYTOLOGICAL SCREEENING

In the late 1950s a new technique was developed in China to collect cells from the esophageal mucosa uti-

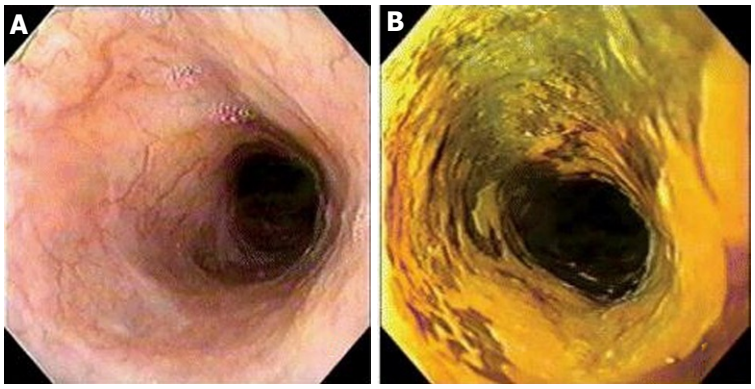

Figure 1 Conventional esophagoscopy and Lugol's chromoendoscopy. A: Conventional esophagoscopy presenting normal appearing mucosa; B: Lugol's chromoendoscopy disclosed an unstained areaafter multiple biopsies, the diagnosis was high-grade dysplasia.

lizing an inflatable balloon covered with a cotton web attached to the tip of a plastic catheter[55]. This device was swallowed and passed down the esophagus to the gastric cardia with the balloon deflated. Once it reached the gastric cardia, the balloon was inflated with air using a 20mL syringe attached to the proximal end of the catheter, and the inflated balloon was gently withdrawn until it reached the upper esophageal sphincter, deflated and then completely withdrawn. The "Chinese Balloon" was designed to be used in multiple patients after simple washing techniques. Other rubber and mechanical disposable balloons and other devices such as sponges have been developed and used in several studies conducted in China which reported that exfoliative cytology may allow early diagnosis of SCCE[55-59].

After collecting squamous cells using this method, slides are stained by the Papanicolaou technique and analyzed. Cytologic findings of atypical squamous cells of undetermined significance (ASCUS), low grade squamous intraepithelial lesions (LSIL), high-grade squamous intraepithelial lesions (HSIL) and carcinoma according to the Bethesda system for squamous cells[60] must undergo upper digestive endoscopy to determine the presence of SCCE.

Many studies in China and one study in Brazil have shown that exfoliative cytology is a good way to collect squamous cells from the esophagus, however, the results of conventional cytology in the diagnosis of SCCE has been discouraging with sensitivities between 39% and 66%[56-59,61-63].

Cytological samples collected using the methods described above are representative of the esophageal mucosa and it is possible that a molecular marker could increase the sensitivity of this inexpensive and simple technique. Immunocytochemical expression of p53 protein was tested recently in southern Brazil, but did not improve the yield of cytological analyses[64]. Two studies have been conducted in China to detect molecular markers that could increase the sensitivity and specificity of balloon cytology[65,66]. One of these studies, published by Adams and colleagues[65], evaluated the presence of methylation in eight genes in esophageal balloon cytology specimens from 147 patients with endoscopic biopsy diagnoses ranging from normal mucosa through to severe squamous dysplasia. This study suggested that evaluation of gene methylation in cytological samples may have utility for the early detection of esophageal squamous dysplasia and early SCCE, however, more sensitive methylation markers will be required for clinical use. The second study by McGruder and colleages[66] tested the telomerase activity measured by real time PCR in esophageal balloon samples in 8 patients from China, and the results seemed to enhance the accuracy of the cytological analysis, however, larger populations and different ethnic groups should be tested before this technique is used in clinical practice.

LUGOL'S DYE CHROMOENDOSCOPY – AN INEXPENSIVE AND SIMPLE SCREENING METHOD

Due to the low sensitivity of conventional endoscopy for the diagnosis of early SCCE[67], new methods were required to evaluate the esophageal mucosa of high risk patients. During the 1990s, multiple reports on Lugol' s dye chromoendoscopy were published and showed how easy, inexpensive and sensitive this method was for detecting early and late squamous cell neoplasia[68-70]. It is based on the lack of absorption of the iodine stain by abnormal squamous tissue, such as inflamed, dysplastic or neoplastic lesions. The esophageal mucosa evaluation occurs during conventional endoscopy, when 10mL to 40 mL of 0.5% to 3% Lugol's solution is sprayed onto the esophageal mucosa which results in a green-brown, dark-brown, or black discoloration of normal mucosa lasting up to 5 to 8 min (Figure 1). Absence of staining indicates abnormal mucosa that can be biopsied. Lesions with a diameter smaller than 0.5 cm rarely show neoplastic lesions[46].

One of the first reports of Lugol's dye chromoendoscopy was published by Misumi and colleagues in 1990[71] and demonstrated that this method could reveal esophageal cancer in normal appearing mucosa under conventional endoscopy. Since then, many studies have been published and the use of this method has increased worldwide. Of great interest is a study conducted in China by Dawsey *et al*[68], where the method showed great sensitivity in revealing early and late SCCE in a high risk population in Linxian province. The same study showed that iodine staining improved the visualization of the lateral margins of the lesions, which was important in

guiding endoscopic biopsies and treatment.

Lugol staining of the esophagus has been used in different populations. Studies from Japan and from Brazil which examined alcoholic patients confirmed the significant sensitivity of this chromoendoscopic method when compared with conventional endoscopy[69,72-74]. Patients with previous head and neck cancers were evaluated and similar results were obtained[46,47,75].

The largest series on the use of Lugol's chromoendoscopy was a multicenter study from France published in 2006 by Dubuc and colleagues[15]. This French study evaluated 1095 patients divided into 4 groups according to exposure to risk factors to SCCE as follows: group 1 –patients with previous diagnosis of head and neck or tracheobronchial squamous cell carcinoma; group 2 –patients with alcoholic pancreatitis; group 3 - patients with alcoholic cirrhosis; group 4 - alcohol and tobacco addicts. SCCE and/or dysplasia were observed in 9.9%, 0%, 7.3% and 2.9% in these groups, respectively. Conventional endoscopy detected only 35 esophageal lesions in these patients, while Lugol staining chromoendoscopy detected 67. The difference in diagnostic accuracy was more important for early lesions like low-grade dysplasia, since 77% of these lesions were observed only after spraying of the iodine dye. According to the authors, Lugol's chromoendoscopy must be used for SCCE screening of patients with previous head and neck or tracheobronchial squamous cell carcinoma.

The pitfalls in its use include increased duration of the procedure, the risk of allergic reactions to the iodine solution and chest pain in some patients[68,70]. The duration of endoscopy is between 5 min and 10 min longer than conventional endoscopy[68,70]. Chest pain and agitation during endoscopy are uncommon, and when they do occur they are easily managed. Indeed, these problems have been surpassed by the advantages of this simple, inexpensive, worldwide available and accurate method for diagnosing early squamous dysplasia and SCCE, when compared to conventional endoscopy[15,46,47,68-72,74-76] and esophageal capsule endoscopy[77].

NARROW-BAND IMAGING – A PROMISING OPTIC-BASED CHROMOENDOSCOPY

Narrow-band imaging (NBI) is a novel, noninvasive optical technique that uses reflected light to visualize the organ surface, and works as an optic-based chromoendoscopic method to detect early lesions[78]. A single-touch of the control knob on the grip of the endoscope allows switching from the standard endoscopy to the NBI filter, emphasizing capillary vessels in the endoscopic images, with image processing in real time[79], and identifying early squamous cell lesions as brownish, well demarcated lesions[80]. NBI when used without magnification has high sensitivity, but a high rate of false-positive lesions, with results similar to Lugol's chromoendoscopy[81].

Adding magnification to NBI increased the sensitivity and the specificity for the screening of early lesions due to identification of intraepithelial papillary loop (IPCL) patterns such as dilatation, tortuosity, caliber change and variety in shape suggestive of mucosal high-grade neoplasia as shown by Yoshida *et al*[79]. Ishihara and colleagues[82] identified, in a multivariate analysis, that brownish epithelium and brownish dots were independent factors for the identification of early squamous neoplastic lesions, with an odds ratio of 25.5 [95% confidence interval (CI): 2.4–268] for brownish epithelium and 19.3 (95% CI: 1.8–207.7) for brownish dots. Brownish epithelium and brownish dots had a moderate interobserver agreement in this study. In the same study, IPCL patterns such as dilatation, tortuosity, caliber change and variety in shape were not associated with high-grade dysplasia.

As for Lugol's chromoendoscopy, the majority of studies on NBI have been conducted in previous head and neck cancer patients. The results are impressive with a sensitivity greater than 90% in this population[80,81,83,84]. However, some pitfalls must be outlined: (1) endoscopes with the NBI system are more expensive than conventional endoscopes and Lugol's solution; and (2) the NBI technique requires expertise for application. Ishihara and colleagues[85], showed that NBI, when used by less experienced endoscopists, had a sensitivity of 53% in diagnosing high-grade dysplasia.

AUTOFLUORESCENCE IMAGING – AN OPTIC-BASED CHROMOENDOSCOPY FOR MULTIMODALITY APPROACH

Autofluorescence imaging (AFI) is another optic-based chromoendoscopic device designed to detect early lesions. AFI neoplastic areas, that usually involve a thickening of the mucosal layer and increased hemoglobin, emit weaker autofluorescence compared to non-neoplastic areas. In this technique, non-neoplastic areas appear green in color, whereas neoplastic areas are purple or magenta. Some studies have been conducted in the screening of early squamous esophageal lesions and showed that AFI had a higher sensitivity than white-light endoscopy to detect superficial lesions (79% *vs* 51%, respectively), however, its accuracy was worse than Lugol's chromoendoscopy or NBI[86,87].

CONCLUSION

Esophageal cancer is a common malignancy with a very poor prognosis. It represents a challenge in medical practice and in the field of public health. It is a devastating disease that continues to have a 5-year survival of less than 10% despite the advances in multimodality therapy. Since surgical and endoscopic resection offer the only possible cure for esophageal cancer, early detection via screening is appealing, particularly in high risk populations. However, so far, there are no guidelines for the screening of SCCE.

Esophageal balloon cytology is a patient-acceptable sampling technique, but the current methods are insufficient for primary screening due to sampling errors. Blind sampling of a large organ misses small lesions and morphologic evaluation of a small percentage of the cell sample misses rare abnormal cells. Molecular markers may be able to help, but the use of biomarkers has to wait for its validation and availability.

Currently there is no single test or testing series that screen for SCCE in a reliable and cost-effective manner, and 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 optic chromoendoscopy, magnifying endoscopy, and optical-based spectroscopic and imaging modalities.

Considering that esophageal cancer is a highly lethal disease, with about 80% of deaths occurring in developing countries, 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. In areas of medium and low risk, individual cases should be considered for screening only if the risk and costs to the individual warrant aggressive screening and follow-up evaluation, such as in certain groups of subjects at high risk of the disease such as alcoholics, smokers, *mate* drinkers, previous head and neck cancer, achalasia and lye stricture of the esophagus.

In ideal conditions, or in developed countries where expensive techniques such as NBI and AFI are available, it is reasonable to think that optimal detection will require a combination of techniques. For example, a suspicious area could be identified initially by NBI or Lugol' s chromoendoscopy, and then further characterized by a high resolution technique, such as confocal endoscopy. The diagnostic performance, availability and cost-effectiveness will determine whether these modalities will become part of standard endoscopy practice.

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