WJGO World Journal of Gastrointestinal Oncology

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DOI: 10.4251/wjgo.v6.i8.275

World J Gastrointest Oncol 2014 August 15; 6(8): 275-288
ISSN 1948-5204 (online)

REVIEW

Endoscopic assessment and management of early esophageal adenocarcinoma

Ghassan M Hammoud, Hazem Hammad, Jamal A Ibdah

Ghassan M Hammoud, Hazem Hammad, Jamal A Ibdah, Division of Gastroenterology and Hepatology, University of Missouri, Columbia, MO 65212, United States
Author contributions: Hammoud GM and Hammad H participated in writing the manuscript; Ibdah JA edited the manuscript.
Correspondence to: Jamal A Ibdah, MD, PhD, Professor, Director, Division of Gastroenterology and Hepatology, University of Missouri, 3635 Vista Avenue, St. Louis, Columbia, MO 65212, United States. ibdahj@health.missouri.edu
Telephone: +1-573-8820482 Fax: +1-573-8844595
Received: November 29, 2013 Revised: April 8, 2014
Accepted: July 17, 2014
Published online: August 15, 2014

Abstract

Esophageal carcinoma affects more than 450000 people worldwide and the incidence is rapidly increasing. In the United States and Europe, esophageal adenocarcinoma has superseded esophageal squamous cell carcinoma in its incidence. Esophageal cancer has a high mortality rates secondary to the late presentation of most patients at advanced stages. Endoscopic screening is recommended for patients with multiple risk factors for cancer in Barrett's esophagus. These risk factors include chronic gastroesophageal reflux disease, hiatal hernia, advanced age, male sex, white race, cigarette smoking, and obesity. The annual risk of esophageal cancer is approximately 0.25% for patients without dysplasia and 6% for patients with high-grade dysplasia. Twenty percent of all esophageal adenocarcinoma in the United States is early stage with disease confined to the mucosa or submucosa. The significant morbidity and mortality of esophagectomy make endoscopic treatment an attractive option. The American Gastroenterological Association recommends endoscopic eradication therapy for patients with high-grade dysplasia. Endoscopic modalities for treatment of early esophageal adenocarcinoma include endoscopic resection techniques and endoscopic ablative techniques such as radiofrequency ablation, photodynamic therapy and cryoablation. Endoscopic therapy should be precluded to patients with no evidence of lymphovascular invasion. Local tumor recurrence is low after endoscopic therapy and is predicted by poor differentiation of tumor, positive lymph node and submucosal invasion. Surgical resection should be offered to patients with deep submucosal invasion.

Key words: Esophageal adenocarcinoma; High grade dysplasia, endoscopic ultrasound; Gastroesophageal reflux; Barrett's esophagus; Chromoendoscopy; Narrow band imaging; Endoscopic mucosal resection; Radiofrequency ablation

Core tip: This review provides an up-to-date summary of the recent published studies on the use of endoscopic diagnosis and endoluminal management in patients with early esophageal adenocarcinoma, including endoscopic mucosal resection and local ablative techniques. Moreover, the review highlights the significance of this disease and the rising incidence of adenocarcinoma in the United States and western world.

Hammoud GM, Hammad H, Ibdah JA. Endoscopic assessment and management of early esophageal adenocarcinoma. *World J Gastrointest Oncol* 2014; 6(8): 275-288 Available from: URL: http://www.wjgnet.com/1948-5204/full/v6/i8/275.htm DOI: http://dx.doi.org/10.4251/wjgo.v6.i8.275

INTRODUCTION

The incidence of esophageal cancer has been increasing steadily in the United States and the western world, with a remarkable 7-fold increase in incidence in the last 30 years[1]. In fact, it has been the most rapidly increasing cancer in white male population[2]. Unfortunately, the overall 5-year survival for early esophageal adenocarcinoma (EAC) has not improved and remains lower than 15%[3].

According to the National Cancer Institute (NCI), it is estimated that 17990 new cases of esophageal cancer will be diagnosed in the United States in 2013, of which approximately 60% will be adenocarcinomas[4].

The other type of esophageal cancer, esophageal squamous cell cancer continues to be the predominant type of esophageal cancer worldwide, but its incidence has been decreasing in the western countries[5]. Although genetic factors play a role in the pathogenesis of esophageal adenocarcinoma[6]. The recent dramatic increase in the incidence of esophageal adenocarcinoma is likely related to increased prevalence of gastroesophageal reflux disease (GERD)[7], increased obesity[8,9] and *Helicobacter pylori* eradication[10,11].

Reflux injury to the lower esophagus resulting in Barrett's esophagus (BE) seems to be the main precursor for EAC. This usually begins with inflammation (esophagitis), which could result after a period of time into intestinal metaplasia (BE) with increased risk to progress to dysplasia and eventually EAC[12]. In addition to acid reflux, bile acid reflux may also play an important role in the progression from Barrett esophagus to esophageal adenocarcinoma. Bile acids are synthesized from cholesterol and down-regulate caveolin-1 in esophageal epithelial cells through sterol responsive element-binding protein[13]. Caveolin-1 protects squamous epithelial cells. Moreover, bile acids increase reactive oxygen species production and cell proliferation *via* activation of PI-PLCgamma2, ERK2 MAP kinase, and NADPH oxidase NOX5-S, thereby contributing to the development of esophageal adenocarcinoma[14].

BE is two to three times more common in men than in women, and is more common in Caucasians. It is less common in African American and is extremely uncommon in Asians[15]. The risk of progression to adenocarcinoma in nondysplastic BE appears to be small. A recent population based study from the Denmark that followed 11028 patients with BE for a median of 5 years reported an annual risk of EAC of 0.12%[16].

The risk of progression to cancer increases in the presence of dysplasia and is up to 6% in patients with high grade dysplasia (HGD)[17].

Risk factors for progression of BE into cancer include low grade dysplasia (LGD), abnormal DNA ploidy and certain lectin binding patterns. Other biomarkers for progression include aberrant DNA methylation changes, expression of microRNAs, as well as overexpression or loss of expression of p53[18].

Endoscopic therapy with curative intent can only be undertaken when the risk of lymph node metastasis is negligible. It is estimated that the rate of lymph node spread is 0% in case of HGD and 1%-2% in case of intramucosal cancers (IMCs). The rate increases to 22% in case of submucosal invasion[19,20].

Table 1 Paris classification of superficial lesions

Type	Lesion
0- I	Protruding/polypoid
0- I p	Pedunculated
0- I s	Sessile
0- II	Non-protruding/non-excavated
0- II a	Slightly elevated
0- II b	Flat
0- II c	Slightly depressed
0- III	Excavated

Protruding (0- I), depressed (0- II c) and excavated (0- III) lesions have been identified as carrying a higher risk of submucosal invasion[118].

ENDOSCOPIC DIAGNOSIS OF BE AND EARLY EAC

The diagnosis of BE is usually suspected on forward viewing upper endoscopy and is confirmed with histologic examination. Careful examination by high-resolution forward-viewing white-light endoscopy is recommended[21,22]. In a study by Gupta *et al*[23] post hoc analysis of an enriched study population and experienced endoscopists at tertiary referral centers. The authors showed that Longer time spent inspecting the BE segment (BIT) is associated with increased detection of HGD/EAC. Endoscopists who had an average BIT > 1 min per centimeter of BE detected more endoscopically suspicious lesions. Multiple random biopsies should be obtained from the four quadrants every 2 cm in non-dysplastic BE segments and every 1 cm if there is suspicion or history of dysplasia (Seattle protocol). Any visible nodule or lesion is usually suspicious for dysplasia or malignancy and should be sampled separately. Accurate description of the location, size and endoscopic appearance of the lesion is necessary for planning future therapy. Endoscopic description of lesions is usually done using the Paris classification of superficial neoplastic lesions (Table 1), which can help predict submucosal invasion in the digestive tract[24].

When confirmed histologically, the current standard of care for BE surveillance involves careful inspection using high resolution white light endoscopy with random biopsies of the BE segment according to the Seattle protocol and targeted biopsies of any suspicious areas. Multiple studies have shown that the random biopsy protocol has low sensitivity for the detection of early neoplastic changes in BE and has low adherence among endoscopists (50%)[25,26]. Furthermore, a cost-utility analysis by Gordon *et al*[27] concluded that the endoscopic surveillance of patients with non-dysplastic BE is unlikely to be cost-effective for the majority of patients and depends heavily on progression rates between dysplasia grades unless new technologies improve the quality adjusted survival benefit from the surveillance[27].

Resorting to a "random" biopsy protocol reflects the difficulty to recognize early neoplastic changes in BE. One of the reasons for this is the fact that flat lesions (such as Paris 0- II a and 0- II b lesions, Table 1) are by far

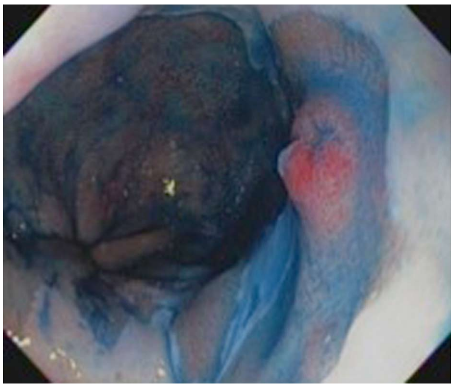

Figure 1 Chromoendoscopy with indigo carmine showing dysplastic nodule in a background of Barrett's mucosa.

the most frequent macroscopic type of neoplastic lesion in BE, and these lesions are typically hard to detect using the standard while light endoscopy[28].

Therefore, there has been major development in image enhancement techniques to improve the detection of early neoplastic lesions in BE. These techniques include detection techniques "red flag" that cover a wide area and help detect a suspicious lesion, and characterization techniques that provide detailed information about a specific area.

DETECTION TECHNIQUES

Dye-based chromoendoscopy

Dye-based Chromoendoscopy consists of spraying the Barrett's mucosa with a dye to better evaluate the microarchitecture of the mucosa to detect early neoplastic changes. Methylene blue was used in the past for this purpose[29-31]; however, it had largely fallen out of favor due to many reasons including difficulty of use and concerns on mutagenesis[32,33]. Indigo carmine is a contrast stain that permeates into the mucosal surface pits and crevices which helps to accentuate any mucosal irregularities[34] (Figure 1). Since it is not absorbed by cells, it does not have safety concerns like methylene blue. A study of 80 patients with suspected BE using high magnification chromoendoscopy with indigo carmine. The yield of intestinal metaplasia (IM) on target biopsies was 97% and 100% for HGD. However, it was not able to distinguish LGD from non-dysplastic intestinal metaplasia[35].

Acetic acid has also been used and provides magnified aspect of the mucosal architecture to help differentiate neoplastic tissue[36]. Curvers *et al*[37] demonstrated that the addition of indigo carmine and acetic acid didn't actually improve the diagnostic yield for early neoplastic lesions in BE compared to high resolution white light endoscopy. Dye-based chromoendoscopy can be labor intensive and is operator dependent and may prolong the procedure. Moreover, it has not been shown to consistently improve the detection of early neoplasia in BE.

Virtual (Dye-less) chromoendoscopy

This includes narrow band imaging (NBI) which uses optical filter to limit the white light illumination to narrow bands of light wavelengths (blue and green), which is predominantly absorbed by hemoglobin and can highlight the capillary network. This results in enhancement of the mucosal vascular and pit patterns and allows visualization of any subtle mucosal irregularities and alteration in vascular patterns concerning for early neoplastic changes[38]. Using pooled data from five studies, Curvers *et al*[39] showed promising results with NBI for detection of early neoplasia in BE with sensitivity of 97%, specificity of 94% and overall diagnostic accuracy of 96%. However, other studies showed a much lower accuracy (71%)[40].

Other virtual chromoendoscopy techniques include Pentax i-Scan and Fujinon intelligent color enhancement. These techniques use post-acquisition image computer reconstruction to enhance mucosal and vascular patterns.

At this time, there is little evidence that chromoendoscopy techniques (both dye-based and dye-less) provide improvements in the characterization and detection of early neoplasia in BE.

Autofluorescence imaging

This technique uses fluorescence radiation following excitation of tissue using light of short wavelengths, which allows differentiation of neoplastic and normal tissue. Autofluorescence imaging (AFI) has been shown to significantly improve the detection of neoplasia in BE; however, the false positive rate is very high (up to 80%)[41]. AFI has also been studied in combination with high resolution endoscopy and NBI, so called Endoscopic Trimodal Imaging (ETMI). In a multicenter randomized trial, ETMI improved the targeted detection of early neoplastic lesions compared to standard video endoscopy. However, the overall histologic yield was not different[42].

Optical coherence tomography and volumetric laser endomicroscopy

Optical coherence tomography produces high quality cross-sectional images of the mucosa based on measuring the rate of backscattering of near-infrared light. This is usually achieved using a probe that is passed through the operative channel of the endoscope. Evans *et al*[43] developed a scoring system for optical coherence tomography (OCT) and reported a sensitivity of 83% and specificity of 75% in the detection of early neoplasia in BE.

Volumetric laser endomicroscopy, the second generation from of OCT, was shown to image the esophageal mucosa at a higher speed and obtain a better quality images[44]. The recent improvements in OCT technology make it a promising technique that can achieve the goal of wide field scanning (detection) as well as characterization of a specific area of concern.

CHARACTERIZATION TECHNIQUES

Endoscopic ultrasound

Endoscopic ultrasound (EUS) may play a little role in the evaluation of patients with HGD or early adenocarcinoma and is not routinely recommended for evaluation of flat BE segments with HGD[45,46]. A systematic review by Young *et al*[47] showed that the diagnostic accuracy for EUS staging in early EAC was only 65%. A subsequent larger meta-analysis showed better accuracy for EUS in staging T1a and T1b lesions with the area under a receiver operating characteristic curve $\geqslant$ 0.93[48]. The use of high-frequency ultrasound catheter probe (miniprobe) can provide a significant better T staging than conventional radial EUS; however, the accuracy is low with both techniques (64% and 49% respectively)[49]. Nevertheless, the National Cancer Comprehensive Network recommends EUS staging prior to proceeding with mucosal resection in the setting of esophageal carcinoma.

Confocal laser endomicroscopy

This is an imaging technique that obtains real-time 1000-fold magnified view of the mucosa, and provides histological information of the target areas (so called virtual histology). Confocal laser endomicroscopy (CLE) could be performed using a dedicated CLE endoscope or miniprobes that can be used with regular large working channel endoscopes (probe-based CLE). A recent study showed that a combination of CLE and while light endoscopy increased the sensitivity for detection of early neoplastic changes compared to white light endoscopy (76% *vs* 34%)[50]. Disadvantages to this technique include that it is expensive, time consuming and requires intensive training.

Spectroscopy

This technique relies on the principle of light interaction with esophageal mucosa to generate a biochemical profile that reflects the cellular architecture. Early results appear to be promising for the real-time detection and diagnosis of esophageal adenocarcinoma with an accuracy of 96%[51]. More recently, Almond *et al*[52] used a novel probe-based endoscopic Raman spectroscopy in *ex vivo* esophageal tissue samples and showed sensitivity of 86% and specificity of 88% for detecting early neoplasia in BE.

The above mentioned enhanced imaging techniques are not widely used in clinical practice due to the limited diagnostic accuracy, high inter-observer variability and high cost. It is also unlikely that these techniques will replace standard high resolution white light endoscopy and random biopsies for surveillance in BE; however, they could play an important role in further characterization and grading of suspicious lesions detected during surveillance exams.

Histopathologic diagnosis

Neoplastic changes in BE can be classified as LGD, HGD, *in situ* (or intraepithelial) carcinoma, IMC and invasive carcinoma[53].

Mucosal lesions are further divided into M1 lesions (or *in situ* carcinoma) when the lesion is limited to the epithelial layer, M2 lesions when the lesion invades the lamina propria and M3 when the lesion invades into but not through the muscularis mucosa layer. Lesions that invade into the submucosal are labeled SM lesions. SM lesion can be further divided into SM1 lesions when the lesion invades into the upper one third of the submucosal, SM2 lesions when the lesion invades the middle third and SM3 lesions when the lesion invades the deep one third of the submucosal layer[54].

Pathologists should carefully evaluate biopsy or resection specimens of esophageal neoplasms to provide details about tumor depth of invasion, tumor differentiation (well, moderate and poorly differentiated), lymphovascular invasion and the presence of tumor invasion at the resection margin. Lymphovascular invasion and poorly differentiated histology increases the risk of lymph node metastasis and these patients should ideally be referred for surgical resection[55].

HGD

HGD is characterized by marked cytological atypia and distorted architecture. Architectural distortion changes include marked crypt crowding, crypt budding and branching. Cytologically, HGD shows cells with marked nuclear pleomorphism, increased N/C ratio, and an increased number of atypical mitoses, particularly in the upper levels of the crypts. Goblet and Paneth cells are usually scarce or absent. Adenomatous (intestinal) dysplasia is the most common subtype but non-adenomatous (foveolar) dysplasia has also been described[56].

Immunohistochemistry staining could help in the diagnosis of HGD. Promising markers include p53 and α-methylacyl coenzyme A racemase but these are not widely used yet[57,58]. Given the significant intraobserver and interobserver variability in the diagnosis of LGD and HGD in BE, most gastrointestinal (GI) societies recommend that a second experienced gastrointestinal pathologist confirm the diagnosis[59]. It is noteworthy that the Japanese and some European pathologists don't use the term HGD and prefer to use the term *in situ* carcinoma for these lesions[60].

Intramucosal carcinoma

IMC invades through the basement membrane to the lamina propria and the muscularis mucosa. It is characterized by atypical cells or complex glands invading into the lamina propria. It is extremely important to differentiate between IMC (or T1a lesion) and carcinoma invading into the submucosa (T1b) as the distinction carries significant implications for the risk of lymph node metastasis and therapy. Such distinction is often difficult to make on biopsy specimens and larger resection specimens such as that resulting from endoscopic mucosal resection (EMR) are more helpful to distinguish between T1a and T1b lesions. In one study, 45% of patients had their final pathological stage changed after EMR compared to pre-EMR forceps biopsies[61]. It also known that most BE usually has double muscularis mucosa layer but this has no impact on the classification or the treatment of Barrett's adenocarcinoma[62].

STAGING OF EARLY ESOPHAGEAL ADENOCARCINOMA

Several modalities have been used to stage esophageal adenocarcinoma. These include EUS, endoscopic mucosal resection with histological assessment and computed tomography/positron emission tomography (CT/PET). EUS and EMR are currently applied as staging tools for early esophageal adenocarcinoma. Early cancer is defined as T1sm1, as beyond this point metastases increases from 1% to 10% for T1sm2 based on a recent consensus[63]. Stage T1a malignancies include lesions confined to the mucosa: M1 (intraepithelial), M2 (lamina propria invasion), or M3 (muscularis mucosa invasion). Submucosal or T1b malignancies are classified into Sm1 (superficial submucosa invasion), Sm2 (invasion to center of submucosa), or Sm3 (invasion to deep submucosa). Mucosal (T1a) malignancies have extremely low risk of local lymph node progression while submucosal invasion (T1b) markedly increases the risk of lymph node metastases[64,65].

EUS

The clinical utility of EUS for staging patients with BE and high-grade dysplasia or intramucosal carcinoma prior to endoscopic therapy has a limited accuracy. The principal role of EUS in evaluating patients with Barrett's-associated dysplasia is to identify patients who may be candidates for endoscopic ablative therapy such as endoscopic mucosal resection and/or photodynamic therapy. EUS has been shown to be superior to computed tomography or magnetic resonance imaging for preoperative staging in patients with high-grade dysplasia and carcinoma. EUS is considered the best tool for T and N staging of esophageal cancer, however, its performance in early Barrett's neoplasia is suboptimal for tumor depth assessment. In a meta-analysis by Puli *et al*[66] the pooled sensitivity of EUS in T1 disease was (88.1%), T2 (82.3%), T3 (89.7%) and T4 (99.2%). EUS can identify nodal spread (N1) or deep tumor invasion (T3) for which it precludes surgical resection. The risk of nodal involvement in early esophageal cancer confined to the mucosa (T1a) ranges between 0% and 3%, and when the lesion extends into the submucosal layer (T1b) this risk approaches up to 30%-50%[67-69]. Tumor size (OR = 1.35 per centimeter, 95%CI: 1.07-1.71) and lymphovascular invasion (OR = 7.50, 95%CI: 3.30-17.07) were the strongest independent predictors of lymph node metastasis[70]. In a retrospective analysis of 135 with HGD (79%) or IMC (21%) who had staging by EUS. Pathologic lymph nodes or metastases were not found by EUS. There were no endosonographic abnormalities noted in any patient with non-nodular mucosa (0/79). However, abnormal EUS findings were present in 14% with nodular neoplasia (five IMC, three HGD)[71]. For patients with nodular neoplasia, endoscopic mucosal resection of the nodule with histological examination had greater utility than staging by EUS. The use of high frequency ultrasound catheter probe (HFP) have been studied in two large studies included 94 and 106 subjects[72,73]. Both studies revealed that HFP is significantly better for lesions localized in the tubular esophagus than the gastroesophageal junction. Moreover, the performance of HFP in assessing submucosal involvement is poor. At this time EUS and HFP staging technique is inadequate for predicting T1-2N0 disease in esophageal adenocarcinoma[74].

Endoscopic mucosal resection

Endoscopic mucosa resection (EMR) has taken a central role in the staging and treatment modality for patients with early esophageal adenocarcinoma, as it allows the pathologist to provide tumor-staging information necessary for an appropriate clinical management decision process. In fact, it is the most accurate staging procedure to assess depth of invasion if full submucosa is provided in the specimen. By providing full thickness of the resected submucosa, pathologists are able to provide a clear histologic depth of the tumor (T staging) and evaluate for lymphovascular invasion. EMR provides better staging for visible lesions than do biopsies alone. Moreover, endoscopic mucosal resection may result in changing the histologic diagnosis in patients with BE with visible and flat neoplasia. In a multicenter study which evaluated 138 patients with BE-related neoplasia who undergone endoscopic eradication therapy showed EMR resulted in a change of the histologic diagnosis in 31.1% patients (upgrades 10.1%; downgrade 21%) with or without visible lesions[75]. At this time, EMR appears to be superior to biopsy for diagnosing and staging superficial esophageal tumors and can substantially modify the diagnostic grade of a lesion. Therefore EMR may facilitate optimal therapeutic decisions by avoiding undertreatment and overtreatment based on inaccurate grading and staging[76].

CT/PET

Early use of PET in the staging of patients with esophageal cancer could facilitate treatment planning and identifying unsuspected distant metastases in up to 20% of patients with a negative metastatic survey by conventional staging[77]. Positron emission tomography detects more distant lymph node and organ metastases compared with conventional diagnostics, allowing a more accurate selection of the most appropriate treatment. CT/PET has inadequate assessment in the superficial esophageal adenocarcinoma. Moreover, the addition of PET to a complete EUS examination did not alter regional-node or celiac-node staging in patients with esophageal cancer[78]. SUVmax ratio was only associated with tumor invasion depth on CT/PET. A recent study evaluated the use of CT/PET in early esophageal adenocarcinoma using a cut-off of 1.48, the sensitivity and specificity of SUVmax ratio for identification of T1a lesions were 43.3% and 80.9%, respectively[79]. Thus more data is needed on the role of CT/PET in early EAC.

ENDOSCOPIC MANAGEMENT OF EARLY ESOPHAGEAL ADENOCARCINOMA

The management of patients with early esophageal cancer

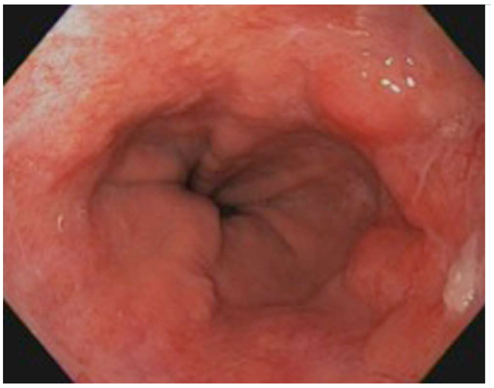

Figure 2 Barrett's esophagus with nodularity concerning for dysplasia or malignancy between 1 and 5 o'clock.

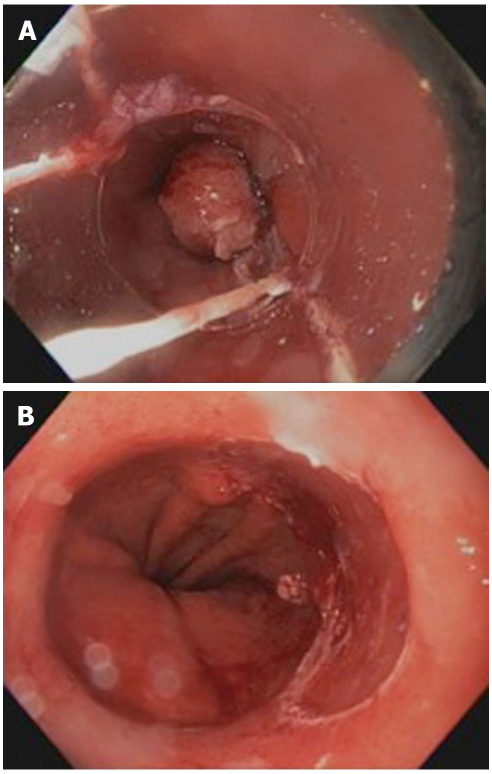

Figure 3 Endoscopic mucosal resection. A: Using Band ligation of Barrette's esophagus nodule; B: Defect after endoscopic mucosal resection using band ligation and resection of Barrett's esophagus nodules.

considered for treatment should take place in a specialty multidisciplinary team including GI pathologist, esophageal surgeon, therapeutic endoscopist, radiologist and oncologist. The endoscopic treatment should commence in high volume tertiary referral centers with availability and expertise in the multiple modalities of endoscopic therapy of BE. Moreover, the center must possess expertise in the management of complications of each modality. The British Society of Gastroenterology recommended a minimum of 30 supervised cases of endoscopic resection and 30 cases of endoscopic ablation should be performed to acquire competence in technical skills, management pathways and complications. Patients with EAC should be informed about the benefits, risks and alternatives of endoscopic and surgical approach. Initially, endoscopic mapping of the Barrett's segment with intestinal metaplasia should be undertaken prior to any endoscopic therapy. The American Gastroenterological Association (AGA) recommends endoscopic eradication therapy for patients with high-grade dysplasia. Risk stratification based on histopathologic assessment should be performed and any nodularity seen on white-light forward viewing upper endoscopy should undergo resection prior to any local ablative therapy (Figure 1). Lymph node metastasis should be excluded. Endoscopic therapy appears to be a good alternative to esophagectomy for patients with low risk pT1b sm1 EAC, on the basis of macroscopic and histologic analyses[55,80]. Data obtained from the Surveillance Epidemiology and End Results database of the NCI to compare cancer-free survival in patients with early esophageal cancer who were either treated with endoscopic therapy (n = 99) or surgical resection (n = 643) did not reveal a difference in esophageal cancer-specific mortality between the two groups[81]. In a population-based analysis, the use of endoscopic therapy for superficial EAC tended to increase from 1998-2009 and the long-term survival of patients with EAC did not appear to differ between those who received endoscopic therapy and those treated with surgery[82]. Several curative modalities are available for local treatment of BE with HGD. Among these modalities are radiofrequency ablation, argon plasma coagulation, thermal laser therapy, cryotherapy and photodynamic treatment. Here we review the efficacy and risks of each modality. Long term outcome of patients with BE and HGD who underwent endoluminal therapy revealed recurrence of intestinal metaplasia occurs in one-third of cases and supports continued endoscopic surveillance even after complete eradication[83].

EMR

Endoscopic mucosal resection provided a primary role in the endoscopic therapy of patients with early EAC (HGD, T1a). EMR should not be attempted if lymph node invasion is suspected. EMR should be performed by an expert therapeutic endoscopist. The principle of EMR is to capture the entire mucosa and submucosa using a suction cup fitted on the tip of the endoscope (Cap-assisted suck and cut or band and cut technique) or lifting the submucosa from the muscularis propria through submucosal injection of saline or indigo carmine (freehand technique). The entire specimen is then excised *en bloc* using a diathermy snare resection or performing multiband mucosectomy[84] (Figures 2 and 3). Total *en bloc* resection is preferred to reduce risk of recurrence and provide accurate histologic assessment. The distinct advantage of EMR over ablative therapy is providing large specimen of resected tissue for histopathologic assessment. One must understand the limitations of EMR include the assessment of base and lateral margin of the tumor resected specimen. The depth of infiltration is better assessed using quantitative micrometric measure in microns

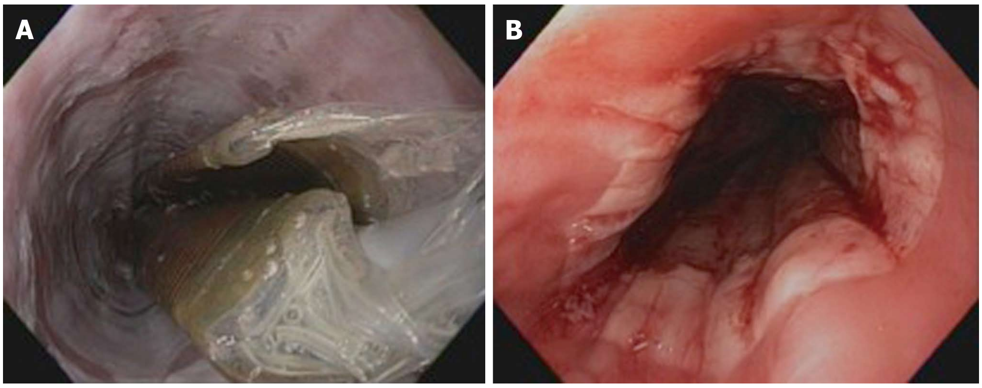

Figure 4 Barrett's esophagus. A: Ablation of Barrett's esophagus using the circumferential balloon catheter; B: Barrett's esophagus after the first round of ablation using the circumferential balloon ablation catheter.

of the depth of submucosal invasion from the bottom of muscularis mucosae. This is deemed to be more accurate than classifying tumor invasion based on depth of submucosal involvement (sm1, sm2, and sm3) as the entire submucosa may not be available in the specimen of all cases[85]. EMR can also be performed in patients with early esophageal adenocarcinoma with previous antireflux surgery[86]. Risk of recurrence after EMR appears low. In one study evaluating 22 patients (16 with HGD), 82% had no evidence of HGD or cancer after a median follow-up of two years[87]. Another long-term follow up study carried in 7 patients for more than 10 years, in 43 for 5-10 years, in 31 for 3-5 years and in 66 for less than 3 years after endoscopic resection. Of the 11 patients who died during the follow up, 10 died of other diseases, only 1 of recurrence of tumor. The 5-year survival rate was 96.2% for early-stage esophageal cancer[88]. Risks of EMR include bleeding, perforation and stricture formation which can occur in up to 37% of cases[61].

Endoscopic submucosal dissection

Endoscopic submucosal dissection is an advanced endoscopic procedure to resect early gastrointestinal neoplasms. It is technically more difficult, carries a high risk when used to treat early esophageal tumors and currently is not widely available in the United States. Studies have been published and reported its efficacy and safety in patients with early EAC[86,89]. In a phase Ⅱ study of endoscopic submucosal dissection for superficial esophageal neoplasms to assess the efficacy and safety of endoscopic submucosal dissection (ESD) in 56 lesions, the *en bloc* resection rate and R0 resection rate were 100% and 94.6%, respectively. The median treatment time for completing the procedure was 69 min (24-168 min)[90]. The rates of adverse events during and after ESD were 22.2% and 53.8%, respectively, but most events were mild. Another study evaluated ESD in combination with radiofrequency ablation in 30 patients with biopsy-proven mucosal adenocarcinoma. Endoscopic follow-up (median 17 mo) showed complete remission of neoplasia in 27/28 (96.4%) patients who underwent successful ESD using waterjet-assisted system[90]. A Meta-analysis by Cao *et al*[91] of endoscopic submucosal dissection *vs* endoscopic mucosal resection for tumors of the gastrointestinal tract showed higher *en bloc* and curative resection rates (OR = 13.87, 95%CI: 10.12-18.99; OR = 3.53, 95%CI: 2.57-4.84) irrespective of lesion size. Subgroup analysis showed higher *en bloc* and curative resection rates with ESD for esophageal, gastric, and colorectal neoplasms, and for lesions of size < 10 mm, 10 mm < 20 mm, and > 20 mm and lower local recurrence. However, ESD was more time-consuming than EMR and showed high procedure-related bleeding and perforation rates (OR = 2.20, 95%CI: 1.58-3.07; OR = 4.09, 95%CI: 2.47-6.80). Similarly, in a previous study evaluating the role of ESD in comparison to EMR in 171 lesions ≤ 20 mm of esophageal cancer (168 were squamous-cell carcinoma and 3 were adenocarcinoma), the curative resection rate of ESD was 97% significantly higher than endoscopic mucosal resection cap-assisted (87%)[92]. However, EMR would be an alternative to lesions < 15 mm in diameter. One must note that ESD in the esophagus has been associated with perforation rates of 2% to 5% and stricture rates between 5% and 17.2%[90,93]. More data is needed to evaluate the utility of ESD for early esophageal adenocarcinoma in the United Stated.

Radiofrequency ablation

Radiofrequency ablation of BE with HGD is the most commonly used therapy, which has been shown to produce reproducible superficial injury in the esophagus (Figure 4). Its ease of use and better safety profile makes it a favorable therapy for flat lesions with HGD. The system generator is capable of delivering 10 to 12 J at a setting of 40 W/cm² with a depth of ablation between 500 and 1000 mm. Two delivery systems are currently available in use. A 3-cm-long balloon ablation catheter (HALO 360) intended to treat long-segment circumferential BE, and an endoscope-mounted targeted device (HALO 90) to treat short segments and tongues of BE. In a recent large series of 335 patients with BE and neoplasia (72% with HGD, 24% with IMC, 4% with low-grade dysplasia) in the United Kingdom who underwent RFA for BE-related neoplasia. The authors found that by 12 mo after treatment, dysplasia was cleared from 81% of patients. Shorter segments of BE respond better to radiofrequency ablation (RFA)[94]. In another study of 70 patients who were treated. Seventy-four per cent had dysplasia (44 LGD, 8 HGD). Complete response was accomplished in 81% of patients[95]. A United Kingdom registry that follows the outcomes of 335 patients with BE who have undergone RFA for neoplasia and received endoscopic mucosal resection if nodules are found revealed HGD was cleared from 86% of patients, all dysplasia from 81%, and BE from 62% at the 12-mo time point, after a mean of 2.5 (range, 2-6) RFA procedures[94]. Of interest, endoscopic mucosal resection before RFA did not provide any benefit. Moreover, RFA appears to have a higher rate of complete histologic resolution response in comparison to photodynamic therapy (PDT) without any serious adverse events and was less costly than PDT for endoscopic treatment of Barrett's dysplasia[96]. Complications of RFA include chest and cervical pain, abdominal pain, dysphagia and stricture formation. Subsquamous neoplasia have been reported to develop after RFA for BE[97]. Currently, RFA is reserved for patients with BE with high-grade dysplasia with no visualized nodules. Its application for patients without dysplasia is debatable giving risks of complications and cost[98].

Photodynamic therapy

Photodynamic therapy has been used to photochemically eliminate abnormal mucosa. Porfimer sodium (POR) PDT use has been limited by serious side effects including prolonged cutaneous photosensitivity and stricture formation. In a randomized phase Ⅲ trial using POR and photodynamic therapy for ablating HGD in conjunction with omeprazole, POR PDT appears to be an effective therapy for ablating HGD in patients with BE and in reducing the incidence of esophageal adenocarcinoma[99]. PDT is associated with increased risks of stricture formation and of buried intestinal metaplasia or malignancy underneath neosquamous epithelium. In a study by Weiss *et al*[100] on 17 patients treated with PDT. High-grade dysplasia or early adenocarcinoma was completely eliminated in nine of 60% patients. Complications included stricture, sunburn, urticaria, small pleural effusions, esophageal spasm and transient atrial fibrillation. A recent randomized controlled trial of 5-Aminolaevulinic acid (ALA) *vs* Photofrin photodynamic therapy for high-grade dysplasia arising in BE showed no difference in complete reversal of HGD between the two groups. On sub-group analysis for BE $\leqslant$ 6 cm, complete reversal of HGD was significantly higher with ALA-PDT than Photofrin-PDT. Strictures and skin photosensitivity were significantly more common after treatment with Photofrin-PDT than ALA-PDT (33% *vs* 9% and 43% *vs* 6%, respectively, $P < 0.05$)[101].

Argon plasma coagulation

Argon plasma coagulation is a noncontact thermal tissue coagulation in which argon gas provides the medium for the delivery of an electric current[102]. This is accomplished with passing a probe through the working channel of the endoscope. The general setting for ablation of Barrett's mucosa is a high power setting 60-90 W at 1-2 L/min. Earlier study showed complete eradication of HGD and *in situ* adenocarcinoma was achieved after a mean number of 3.3+/-1.5 V. Argon plasma coagulation (APC) sessions in (80%)[103]. In a randomized controlled trial of 35 patients who received ablation of BE with multipolar electrocoagulation (16) *vs* argon plasma coagulation (19), the authors concluded complete reversal of BE can be maintained in approximately 70% of patients, irrespective of the technique[104]. Similarly, previous studies showed similar outcome with eradication of BE and restoration of squamous epithelium[105]. However, progression to HGD can still occur despite APC ablation[106]. Thus APC is effective ablative therapy for BE but the long term benefits are unknown. More data is needed on its use in early EAC.

Cryotherapy

Cryoablation is a relatively new technique with studies focusing on high-grade dysplasia and early-stage cancer in high-risk patients. It has an acceptable safety profile, and early results show response in a significant number of patients in whom other modalities have failed[107]. Its ease of use and lower chance of complication make it an attractive procedure. Although cryoablation is a non-tissue acquiring procedure that requires liquid nitrogen spray application it is not devoid of potential risk of gastric perforation due to gas insufflation. Data on its use in early EAC is limited. In a multicenter, retrospective cohort study of 79 patients with esophageal carcinoma in whom conventional therapy failed, refused and/or were ineligible for conventional therapy[108]. The study included all T staging and showed complete response of intraluminal disease in 31 of 49 subjects (61.2%), including 18 of 24 (75%) with mucosal cancer with an overall follow up of 10.6 months. No serious adverse events were reported. A recent study by Gosain *et al*[109] evaluated 32 patients with BE-HGD of any length who were treated with liquid nitrogen spray cryotherapy every 8 wk until complete eradication of HGD and intestinal metaplasia. Complete eradication of HGD achieved in 100% (32/32), and IM in 84% at 2-year follow-up. Recurrent HGD occurred in 18% with HGD. BE segment length $\geqslant$ 3 cm was associated with a higher recurrence of IM but not HGD. No serious adverse events occurred although stricture was seen in 9% of cases. Thus, cryoablation therapy appears comparable to other treating modality in BE and in early EAC, spray cryotherapy appears to have a unique role, eliminating mucosal cancer in 75% of patients[110].

A recent meta-analysis of seven studies involving 870 patients who underwent endotherapy (n = 510) or surgery (n = 360) concluded that endotherapy has similar efficacy to surgery but with lower adverse event rates. However, endotherapy was associated with a higher neoplasia recurrence rate[111]. Limitation to this study included small number of retrospective studies and different types

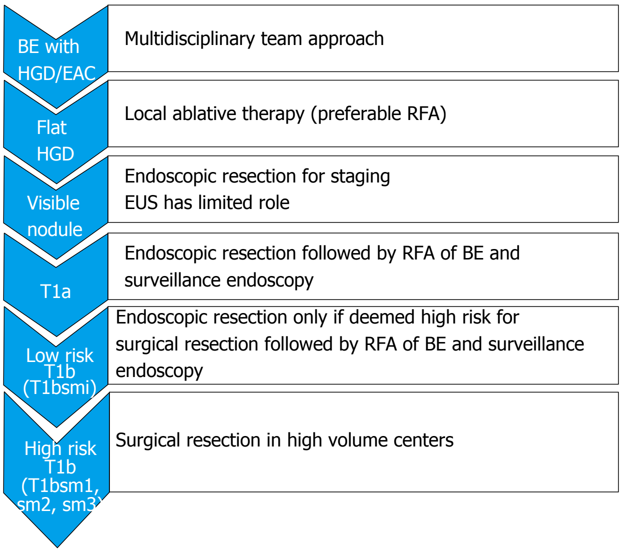

Figure 5 The current practical approach for patients with early esophageal neoplasia. BE: Barrett's esophagus; HGD: High grade dysplasia; EAC: Esophageal adenocarcinoma; EUS: Endoscopic ultrasound.

of endoscopic treatments used. Figure 5 shows the current practical approach to the management of patients with early EAC.

ROLE OF CHEMOPREVENTION

Esophageal adenocarcinoma is characterized by increasing incidence, male predominance and lack of preventive measures. Future preventive therapy might include the treatment of gastroesophageal acid reflux, obesity and/or chemoprevention with nonsteroidal antiinflammatory (NSAIDs) drugs or statins. Today, there is no evidence-based preventive measures are currently available for patients with EAC. Proton pump inhibitors are effective in reducing esophageal acid exposure and improve reflux symptoms however, they are not recommended for use as chemopreventive agents in EAC. Weight loss, exercise and bariatric surgery may potentially improve obesity. Studies have shown up-regulation of cyclooxygenase (COX)-2 in BE-metaplastic and dysplastic tissue and in Barrett's adenocarcinoma[112-114]. Others showed conflicting results[115]. NSAIDs and COX inhibitors have been proposed and shown to reduce risk of metaplasia in BE and EAC[116]. Statins have been suggested to induce anti-cancer effects against a variety of cancers in several studies[117]. Agents targeting the vascular endothelial growth factor and epidermal growth factor receptor pathways are currently in progress. The AGA recommendation for the chemoprevention of cancer in patients with BE is screening patients to identify cardiovascular risk factors for which aspirin therapy is indicated and against the use of aspirin solely to prevent esophageal adenocarcinoma in the absence of other indications[22].

CONCLUSION

Esophageal cancer is one of the most serious gastrointestinal cancers worldwide, owing to its rapid development and fatal prognoses in most cases. Major risk factors for EAC include BE, GERD, smoking, and obesity. Improved survival is achievable when the disease is confined to the more superficial mucosal layers and treated. Endoscopic luminal therapy is feasible and proven useful in BE with HGD and early esophageal adenocarcinoma.

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P- Reviewer: Bustamante-Balen M, Lisotti A
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