

Barrett's Esophagus: A Review of Biology and Therapeutic Approaches

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ABSTRACT

Despite advances in diagnosis and therapy, esophageal cancer remains a highly lethal disease. The incidence of esophageal adenocarcinoma (EAC) has risen faster than that of any other cancer in the western world, and Barrett's esophagus (BE) may be a significant contributing factor. In-depth knowledge of biology of cancer progression and cancer could lead to the identification of biomarkers that are the hallmark of BE's progression. By integrating validated biomarkers of progression into clinical practice, there is a possibility of identifying high-risk patient population for targeted surveillance, and such biomarkers may serve as novel therapeutic targets for chemoprevention and therapy. Clinical management of BE has improved considerably due to the improvements in endoscopic resection and ablation techniques. We discuss the current status of biology and therapeutic approaches to BE.

Gastrointest Cancer Res 5:49–57. © 2012 by International Society of Gastrointestinal Oncology

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Supported in part by Dallas, Park, Caporella, Sultan, Smith, and Cantu Family funds and by the Rivercreek Foundation. Also supported by the Multidisciplinary Research Program Grant from UT MD Anderson Cancer Center and NHI-NCI grants (CA142072, CA127672, CA129906, CA111922).

Submitted: December 8, 2010

Accepted: March 2, 2012

Esophageal cancer (EC) is an aggressive neoplasm and a major cause of cancer-related deaths worldwide.¹ A total of 16,470 new cases and 14,530 deaths were projected to occur in the United States in 2009.² Despite advances in diagnosis, 50% of patients present with advanced disease.³ Five-year relative survival rates are low (14%), and the improvement in comparison with 20 years earlier (10%) is not substantial.^{4,5} Moreover, systemic nature and the intrinsic resistance to therapy are hallmarks of EC.

The incidence of esophageal adenocarcinoma (EAC) is rising faster than that of any other cancer in the western world.⁶ Barrett's esophagus (BE) is a known premalignant condition of EAC and is characterized by the replacement of squamous stratified epithelium with a columnar metaplasia in distal esophagus.^{7,8} Whether the presence of intestinal-type differentiation is a requirement for its definition is still a matter of debate. The American Gastroenterological Association Chicago workshop required the presence of intestinal metaplasia, but meanwhile the British Society of Gastroenterology does not require it to diagnose BE.^{9,10}

In a Swedish study, the prevalence of BE in general population was approximately 1.6%,

but in a US study it was 5.5%.^{11,12} This may be due to the prevalence of obesity in US adults. Furthermore, 5–15% of patients with gastroesophageal reflux disease (GERD) are expected to have a diagnosis of BE.¹³ The risk of EAC in patients with BE is low, 0.15–0.5% per year, but the lifetime risk is 10- to 125-fold higher than the general population.^{14,15} Progression of BE to EAC is a stepwise process beginning with metaplasia and progressing to low-grade dysplasia (LGD) to high-grade dysplasia (HGD) and finally to EAC. However, the risks from LGD remain controversial with regard to its frequency to progress to HGD or EAC.^{16–18} This unpredictability could be the result of sampling error, inter- or intraobserver variability, or instability of the dysplastic lesion. HGD's natural history is better defined and understood with a progression to EAC of almost 6.6% per year.¹⁹ It is important to underline that a multifocal or nodular HGD designation raises the risk of EAC progression even higher.²⁰

Since BE tissue is relatively easily accessible, BE can serve as a model to study molecular alterations associated with its progression to EAC.

RISK FACTORS

BE is correlated with GERD.²¹ White, elderly men have an increased risk of BE diagno-

sis.²² Hiatal hernia and central obesity (rather than diffuse obesity) as well as the presence of acid and bile in the refluxate have also been considered as strong risk factors for development of BE.^{23,24} In contrast, smoking and alcohol appear to be low-risk factors.²⁵ Contradictory results have been published regarding the damage that bile without acid could cause to the esophageal tissue.^{26,27}

PATHOGENESIS OF METAPLASIA

Histogenesis Stem Cell Theory

When squamous mucosa is damaged in the presence of extrinsic factors such as cytokines, gastric acid, and bile-stem cells could be involved in BE pathogenesis. Their location in the esophagus is not yet identified. Three main theories exist for BE histogenesis: (1) Stem cells are in the papillae in squamous mucosa (de novo meta-

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plasia therapy). An analogous model is identified and described in vaginal mucinosis.²⁸ (2) Stem cells exist in the neck regions of glands of esophageal ducts (duct cell metaplasia theory). A similar model (ulcer-associated cell lineage) occurs next to ulceration in the gastrointestinal tract.²⁹ (3) Stem cells are located at the gastroesophageal junction (GEJ) (transition zone metaplasia theory). This model is identified in cervical metaplasia.³⁰ One hypothesis suggests that the bone marrow stem cells could seed to the area of epithelial injury and subsequently differentiate to columnar cells. This hypothesis is supported by a case report and in experiments done in an animal model.^{31,32}

Stem cell theory has become more popular in recent days for cancer development. It is stated that the inflammatory milieu in the esophagus exposed to chronic GERD would result in animation of stem cells for repair. This repeated call for repair that demands proliferation would lead to mistakes in the DNA of stem cells. These mistakes (mutations) are sometimes not repaired, leading to clone formation. Several clones are generated over time, and some clones will survive the stressful environment to form cancer.

Familial Barrett's Esophagus (FBE)

Over the past few decades, accumulated results suggest that BE may be a multifactorial condition where genetic predisposition may result in susceptibility that leads to inadequate detoxification of enzymes and cell-cycle regulators.³³⁻³⁵ Currently little is known regarding the genes that lead to genetic predisposition. Moreover, previous reports on familial aggregation of BE and its associated cancers that is termed FBE are interesting and shed light on this issue.³⁶⁻³⁸ However, familial clustering may indicate either genetic predisposition or common exposure to environmental agents. Chak et al reported that FBE can occur in 7% of patients with BE, EAC, and adenocarcinoma of GEJ.³⁹ In FBE, 20% of the relatives have BE compared to 10% in sporadic BE.⁴⁰ Despite the fact that no genes responsible are yet identified, several reports suggest that FBE is a complex genetic disease inherited in an autosomal dominant fashion.^{41,42}

Epigenetic Molecular Alterations

On the other hand, the epigenetic mechanisms associated with the development of BE are better studied. Caudal homeobox gene 1 (CDX 1) and 2 (CDX 2) are involved and are critical points in this process.⁴³ Nuclear factor kappa b (NF-Kb), fibroblast growth factor (FGF), bone morphogenetic protein 4 (Bmp-4), and hedgehog and wnt pathways are related with CDX gene regulation.⁴⁴⁻⁴⁸ Furthermore, p63 suppression that is a determinant of squamous phenotype may also be an important factor.⁴⁹

NEOPLASTIC PROGRESSION

Linear models of multistage carcinogenesis may not be ideal to define progression of BE to EAC. One of their limitations is that they cannot sufficiently deal with genetic heterogeneity. It should be emphasized that in the study by Smith et al a linear model of colorectal carcinogenesis applied only to 6.6% of cases.⁵⁰

Interestingly, normal stem cells and certain cancer cells share properties. They both have the ability to self-renew, to differentiate, to migrate, to interact with stroma (niche), and to activate antiapoptotic pathways.⁵¹ Because of this evidence and because stem cells are subject to mutations when repeatedly called to repair under highly chronically inflammatory conditions, a cancer stem cell hypothesis could be central to unraveling the biomarkers of progression from BE to EAC. This hypothesis postulates that tumors may originate from adult tissue stem cells or their immediate progenitor cells.⁵² Cancer stem cells would then organize themselves as an organ (cancer mass). These cells can self-renew and give rise to differentiating progeny. A deregulated self-renewal process due to several mutations on genes that regulate this process could be important to neoplastic progression. Hedgehog, Wnt, Bmi-1, and Notch pathways are implicated to self-renewal process, and their deregulation could lead to tumorigenesis.⁵³⁻⁵⁶ Various studies conducted in leukemia, breast cancer, and brain cancers appear consistent with this model of carcinogenesis.⁵⁷⁻⁵⁹ For normal human esophageal epithelial cells, a candidate stem/progenitor cell fraction is characterized by the expression of the low-affinity p75 neurotrophin receptor (p75NTR).⁶⁰

Further studies on esophageal squamous cell cancer specimens and cell lines have demonstrated that p75NTR expression was related with cancer stem cells characteristics, such as self-renewal and chemotherapy resistance.^{61,62}

During the 1970s, Nowell presented his clonal evolution hypothesis.⁶³ The evolutionary theory describes that during progression, clonal expansions occurred. These are intermittent selective sweeps of clones with advantageous mutations. Various mutations could happen in a cell without defining a distinct change (neutral mutations). Only when they occur before or after an advantageous mutation (hitchhiked mutation) will they be selected and dominate the neoplasm (fixation).

In BE it appears that loss of heterozygosity (LOH), promoter hypermethylation, or sequence mutations of p16 are the initial and main events that drive and select the sweep of clones necessary for clonal expansion through the tumor.⁶⁴ This hypothesis was developed upon the observation that the identical p16 mutations or LOH patterns are identified in large areas of BE lesions, thus suggesting that p16 inactivation is associated with selective sweeps.⁶⁵ Subsequent inactivation of p53 by LOH or mutation drives aneuploidy and cancer progression.⁶⁶

Genomic Instability

In epithelial tumors during neoplastic progression tumor genome acquires extensive chromosomal changes. The degree of genetic instability increases during the multiple displacement amplification sequence.⁶⁷ These alterations are also extensive and multifocal, indicating the field cancerization effect. Genomic instability mainly consists of genome-wide copy losses, gains, and LOH. Whole-genome single-nucleotide polymorphism (SNP) and comparative genomic hybridization (CGH) -based technologies have been used for biomarker discovery in premalignant lesions that are not well characterized yet, such as BE.⁶⁸ Li et al analyzed 42 samples of patients in different stages from BE to EAC using a SNP platform.⁶⁹ They found that chromosomal instability was increased between early- and late-stage BE ($P < .001$). SNP alterations highly correlated with DNA aneuploidy and were suitable to identify EAC patients. Lai et

al studied copy number alterations (CNAs) in six patients using a high-resolution CGH platform.⁷⁰ They found that genomic instability increases in severity during neoplastic progression. In addition, Paulson and co-workers using a CGH array examined 98 patients with BE or EAC.⁷¹ They showed that CNAs were more frequent in late stages of carcinogenesis and highly correlated with DNA content aneuploidy. Tissues with CNAs involving >70 Mbp indicated patients at increased risk of progression to DNA changes or EAC (HR = 4.9, 95% confidence interval [CT], 1.6–14.8, *P* = .0047).

Recent studies on genetic diversity and BE heterogeneity presented intriguing results that need further validation. Genetic clonal diversity's impact was described by Maley et al⁷² Using three measures of clonal diversity, i.e., number of clones per lesion, divergence between samples, and Shannon index of diversity, this group analyzed 268 patient samples with BE with a median follow-up of 4.4 years. It was shown that clonal diversity predicts further progression to adenocarcinoma development and is a greater risk factor rather than a clonal expansion. It seems that diversity drives transformation in a multilineage rather than a sequential events and there may be barriers that prevent frequent selective sweeps.

Leedham et al genetically studied individual crypts.⁷³ Their results proposed that BE heterogeneity arises from multiple independent clones that probably expand during adenocarcinoma development but not from a single founder mutation sweeping through an entire area to fixation.

The marked heterogeneity observed in BE lesions underline the suggestion that multiple molecular pathways are involved and interact through tumor development. To that direction, a panel of prediction factors could be more useful than single factors alone. Galipeau et al showed that a combination of p53 and p16 LOH, aneuploidy, and tetraploidy provided better risk prediction.⁷⁴ Unfortunately, this panel required a combination of techniques that are difficult to implement in the clinic. Advanced modern technology such as SNP-based technologies and high-resolution comparative genomic hybridization arrays

seem to be promising options that could be clinically useful.

Table 1 lists the altered genes in BE and EAC.

CURRENT CLINICAL MANAGEMENT

The appropriate management of BE patients depends on the presence of dysplasia and the type of dysplasia that occurs (Figure 1). Because of the small proportion of BE patients that progress to EAC, the value of surveillance programs is a matter of debate. However, in a high-risk group of patients surveillance programs have significant impact.⁷⁵ BE is so prevalent that it is crucial to identify a high-risk population for targeted surveillance.

Histologic designation should be made by an experienced gastrointestinal (GI) pathologist. For LGD, esophago-gastro-duodeno-scopy (EGD) should be repeated after six months and then annually until two serial EGDs are negative for dysplasia. In the case of HGD, histology needs confirmation by a second GI pathologist. The risk of concomitant early EAC also should be investigated. The options offered at this

stage (BE/HGD) are aggressive surveillance through endoscopy and biopsies every three months as well as ablation therapy followed by surveillance or esophagectomy.⁷⁵

Esophagectomy

A high concordance that reaches 30–50% of the cases with HGD is observed between HGD and occult EC.^{76,77} Because of this, esophagectomy was traditionally the standard treatment for BE with HGD. However, with increasing sophistication and favorable results from endoscopic approaches, surgery is not always recommended as an immediate first option. Esophagectomy in patients with EAC without muscularis mucosa involvement confers 5-year survival rates >80%.⁷⁸ Despite advances in surgical techniques, esophagectomy can result in significant mortality, ranging from 1% to 10% depending on the volume of the center.⁷⁹ Furthermore, morbidity rates can range from 30% to 50%.⁸⁰ Although minimally invasive approaches of esophagectomy have been found to be safe with better perioperative outcomes, randomized trials

Table 1. Altered genes/pathways in BE and EAC (these genes may not represent all genes that may be involved)

BE	EAC
<i>CDX1, CDX2</i>	
NF-κB targets	NF-κB targets
Genes related to hedgehog signaling	Genes related to hedgehog signaling
Genes in the mTOR pathway	Genes in the mTOR pathway
Notch pathway genes	Notch pathway genes
<i>BMP4</i>	—
Rb pathway genes	—
<i>p53</i>	<i>p53</i>
Ras pathway	Ras pathway
VEGF-related genes	VEGF-related genes
Telomerase-related pathway	Telomerase-related pathway
Cell-cycle-related pathway genes	Cell-cycle-related pathway genes
<i>STAT-3</i>	<i>STAT-3</i>
<i>Sox 9</i>	<i>Sox 9</i>
<i>MMPs</i>	<i>MMPs</i>
Wnt signaling	Wnt signaling
—	<i>Rho</i>
c-MET pathway	c-MET pathway

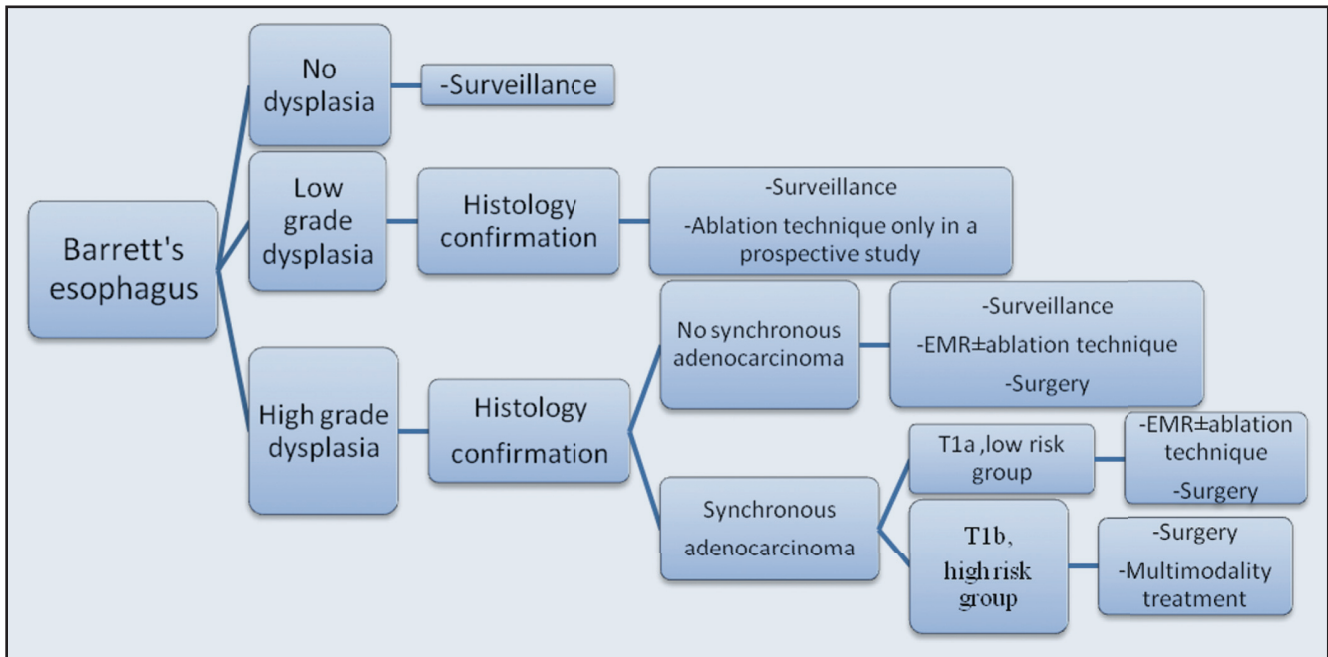


Figure 1. Therapeutic recommendations for various categories of Barrett's esophagus.

are needed to evaluate them in comparison with open procedures.⁸¹

Ablation Techniques

Mucosal adenocarcinomas result in a low rate of lymph node involvement (<2%).⁸² This observation provides the basis that less invasive local approaches, such as ablation techniques, could be performed as curative strategies in this group of patients with expectations of equivalent effectiveness but with a significant decrease in mortality and morbidity rates (Figure 2).

Prior to the ablative techniques, esophageal endoscopic ultrasound and computed tomography scanning should be performed to evaluate the size, length, depth of lesion, lymph node enlargement, and distal metastases.

Lasers

A light amplification by stimulated emission of radiation (LASER) beam is directed against the lesion and destroys it. There are various types of lasers: argon, neodymium:yttrium-aluminum-garnet (Nd:YAG), potassium titanyl phosphate (KTP), and KTP:YAG with different wavelength emissions. Gossner and colleagues studied 10 patients (LGD = 4, HGD = 4, early EC=2) using a (Nd:YAG) KTP laser system.⁸³ After a mean follow-up of 10.6 months a complete response was observed in all. In two patients Barrett's

submucosa was identified. Weston et al also presented the results of 14 patients with BE and HGD/IMC treated with a Nd:YAG contact laser.⁸⁴ They reported successful elimination of HGD and or cancer in all patients. Eleven of 14 achieved complete histological ablation of Barrett's tissue, and no buried columnar epithelial tissue was observed. Odynophagia and early dysphagia were reported in 30.6% and 16.3% of the patients, respectively.

Photodynamic Therapy (PDT)

The basis for PDT is the administration of a photosensitizer [porfimer sodium (iv), 5-aminolevulinic acid (per os)] that has properties to bind the neoplastic area through an unknown mechanism. After an exposure to intense laser light, vascular thrombosis and cell necrosis is caused. Overholt and colleagues studied 100 patients (LGD = 14, HGD = 73, IMC = 13) with a mean follow-up of 19 months.⁸⁵ Elimination of BE and HGD was observed in 43% and 88% of the patients, respectively. Progression or failure was found in 21 patients. Complications observed were stricture (34%) and subsquamous Barrett's esophagus (6%). An international randomized phase III trial was also conducted by Overholt et al⁸⁶ that studied 208 patients to compare PDT using porfimer sodium (POR) plus omeprazole (n = 138) vs.

omeprazole only (n = 70). There was a significant difference (P < .0,001) in favor of PORPDT compared with omeprazole [39% (27/70)] in complete eradication of HGD at any time during the follow-up period. The occurrence of EAC in the PORPDT group was 13% and significantly lower compared with the omeprazole group, being 28% (P < .006).

Multipolar Electrocoagulation (MPEC)

Two or more electrodes of MPEC probe allow the delivery of thermal energy to the desired area and destroy tissue. In a multicenter trial, 58 patients were studied, and after a follow-up of six months, 78% of the patients had a complete response. Residual BE was identified in 4 of 58 patients. One patient developed stricture and the most common side effect was chest pain (19/58).⁸⁷ Kovacs et al studied 27 patients with BE treated with MPEC and lansoprazole with an intention to reverse histology.⁸⁸ Twenty-two patients had successful reversal, and the most common side effect was dysphagia (41%).

Argon Plasma Coagulation (APC)

Through the flow of ionized argon gas, a high-frequency monopolar current is directed to the neoplastic tissues. Attwood et al studied 29 patients with HGD with a mean follow-up of 37 months.⁸⁹ The me-

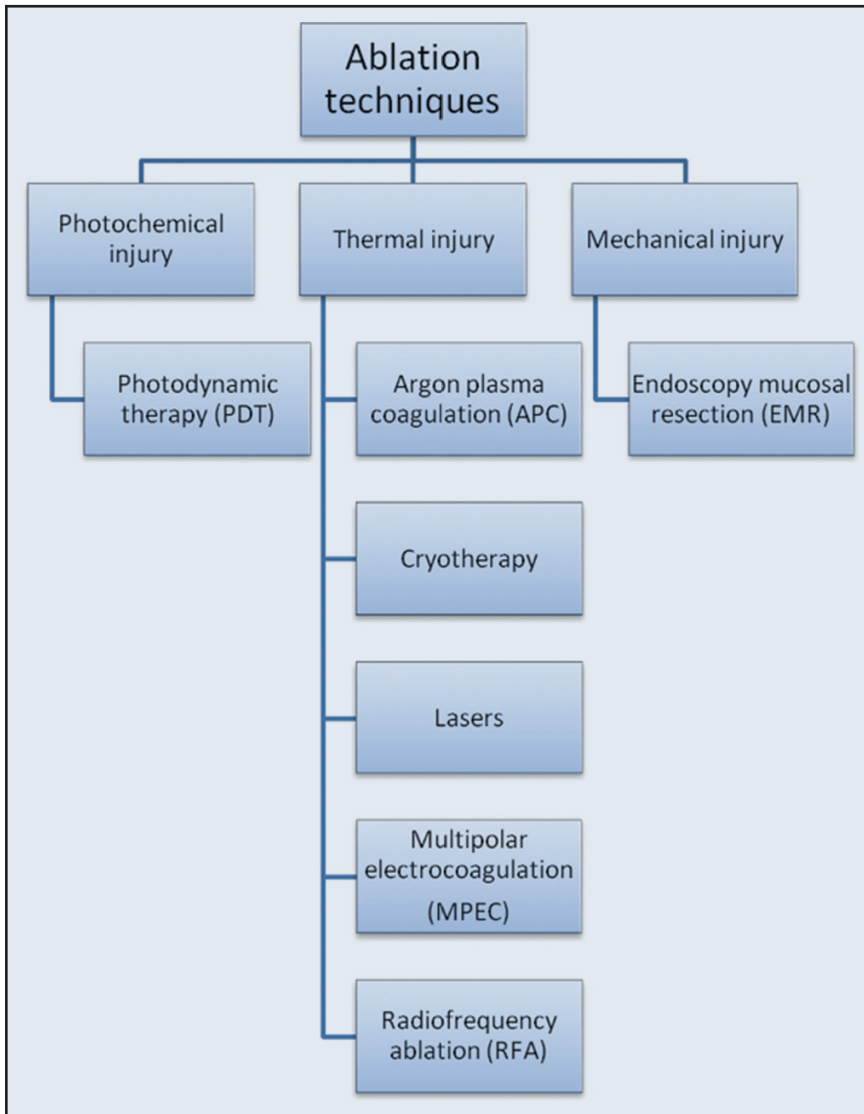


Figure 2. Types of ablative approaches available.

dian number of treatments was two, and complete regression was observed in 25 out of 29 patients (86%). Recurrence was identified in four out of 25 patients (16%). Ackroyd and coresearchers randomized patients with BE to intervention with APC (n = 20) vs. surveillance (n = 20).⁹⁰ After a five-year follow-up 14/20 patients treated with APC achieved >95% BE regression vs. 5/20 in the surveillance arm. No patients in the intervention group progressed to HGD. On the contrary, 2/20 in the surveillance group progressed. Two patients treated with APC developed a stricture but could be managed endoscopically.

Radiofrequency Ablation (RFA)

This technique requires the application of a balloon with circular electrodes delivering

radio-frequency energy in circumferential way (HALO³⁶⁰). In addition, for focal lesions, a plate device can be used (HALO⁹⁰). Roorda et al studied 13 patients (6 with BE, 4 with LGD, and 3 with HGD).⁹¹ After a mean follow-up of 12 months, eradication of BE was observed in 6 patients (46%) and eradication of dysplasia in 5 out of 7 (71%). Fleischer et al presented their data on 61 patients with intramucosal carcinoma.⁹² A complete remission was observed in 98% of patients after a median follow-up of 30 months. In both studies no complications were reported. Shaheen and co-researchers reported on a randomized, multicenter prospective trial comparing RFA with a sham procedure in BE with dysplasia.⁹³ One hundred and twenty-seven patients (LGD = 64, HGD = 63) with

a 12-month follow-up were studied. Complete eradication of LGD and HGD occurred in 90.5% and 81% in the ablation group ($P < .001$). On the other hand, complete elimination of LGD and HGD occurred in 22.7% and 19% in the control group ($P < .001$). A clear superiority for RFA was observed. Furthermore, this superiority was also significant for eradication of BE with 77.4% (RFA group) as compared with 2.3% of those in the control group ($P < .001$). Patients in the ablation group had fewer cancers (1.2% vs. 9.3%, $P = .045$) and less disease progression (3.6% vs. 16.3%, $P = .03$). Six percent of patients treated with RFA developed a stricture, and one had gastrointestinal bleeding.

Endoscopic Mucosal Resection (EMR)

In EMR, local, endoscopic resection is performed after the injection of fluid to separate the mucosal and muscle layers. Ell et al reported their experience with EMR in BE patient with dysplasia or IMC.⁹⁴ They studied 64 BE patients with HGD or IMC. Thirty-five patients belonged to the low-risk group and 29 to the high-risk group according to histological grade, lesion size, and macroscopic appearance. BE eradication was observed in 97% and 59% in low- and high-risk groups, respectively, after a mean follow-up of 12 months. Recurrence or metachronous lesions incidence was 13.6% and 17.1%, respectively.

Larghi et al also reported their results with this technique in 24 BE patients with HGD or IMC after a mean follow-up of 28 months.⁹⁵ Complete eradication was observed in 87.5% of the patients (21 out of 24). Complications were observed in five patients (two with bleeding and three with stricture). Persistence or de novo BE, developing underneath the newly formed squamous mucosa (subsquamous), was identified in two patients (8%).

Cryo-Spray Ablation (CSA)

Through the application of liquid nitrogen gas or CO₂, cold temperatures (−196°C, −70° respectively) generated can freeze the tissues, and ischemic necrosis can occur. Furthermore, cryo-ablation induces apoptosis and immune stimulation. A prospective trial evaluating safety and efficacy of CSA in patients with BE and HGD or

IMCA by Dumot and colleagues was reported in 30 patients with a median follow-up of 12 months. At the last follow-up, responses persisted in 68% for HGD and 80% for IMCA.⁹⁶ Greenwald et al presented results of parallel prospective treatment studies at four tertiary care medical centers.⁹⁷ Seventy-seven patients (BE = 7, BE with HGD = 45, BE with IMCA = 13, EC = 10, and severe squamous dysplasia = 2) were treated. Out of 23 patients completing therapy, in 17 patients with HGD, there was a complete response in 94% and complete elimination of BE in 53%. In all four patients with IMC, a complete response was noted for cancer and 75% of BE eradication. In all three patients with esophageal cancer (inoperable or refused surgery, ineligible or refused radiation or systemic therapy) a complete response was observed for cancer and 67% of BE elimination. One major complication occurred during their study, consisting of a gastric perforation caused by gastric distention due to nitrogen gas. The most common side effect in procedures was chest pain (17.6%) and dysphagia (13.3%).

Optimal management strategy of BE remains in flux, and large prospective trials are needed. In three retrospective studies comparing esophagectomy vs. endoscopic therapy in BE with HGD or IMC outcomes in terms of overall survival were similar.⁹⁸⁻¹⁰⁰ Each approach has its disadvantages and limitations. It should be underlined that all but EMR ablation techniques have the major disadvantage in that they destroy tissue, and histopathologic evaluation is not possible. Furthermore, the risk of buried BE under the re-epithelized surface remains a concern because of risk of carcinoma development. Bronner et al found that this was not a safety concern for patients who underwent PDT therapy.¹⁰¹ The multimodality endoscopic approach, combining EMR and RFA, CSA, or other ablative interventions for eradicating the remaining high-risk tissue is a promising option to optimize treatment.

FUTURE DIRECTIONS

Questions to Be Addressed

Today none of the biomarkers reported have been introduced into daily clinical practice. According to the Early Detection

Research Network, five phases are needed to confirm preliminary results from case studies and develop cancer-screening biomarkers.¹⁰² Many questions still need to be addressed; GERD is so prevalent, therefore, we should be able to identify who is susceptible to BE. Furthermore, in patients with BE, we should be able to identify individuals highly susceptible to developing dysplasia and EAC.

Pathways to the Target

Better understanding of tumor biology and the need for a more efficacious therapy has led to the development of specific agents to target carcinogenesis/neoplastic progression. Given the success of monoclonal antibodies and tyrosine kinase inhibitors against solid or hematologic tumors there is optimism that some of these approaches could be applied to premalignant conditions such as BE.

Cyclin D1

Cyclin D1 proto-oncogene is a regulator of the G1-S phase cell cycle transition is found to be expressed in 46% of BE and in 64% of esophageal or gastroesophageal junction adenocarcinomas.^{103,104} Various studies suggest a role in esophageal tumorigenesis.^{105,106} Furthermore, in our previous study, Cyclin D1 A870G polymorphism was related with younger age of onset of EAC, greater frequency of distant metastasis, and increased levels of nuclear Cyclin D1 expression.¹⁰⁷ Nuclear CD1 alternate form drives cellular transformation and cancer progression. This polymorphism was also related with genomic instability and poor outcome in EAC.³⁴

Nuclear Factor Kappa B (NF- κ B)

NF- κ B is an important transcription factor that regulates important functions such as proliferation, cell survival, apoptosis, invasion, angiogenesis, and metastasis. Normally it is inactivated and is located in cell cytoplasm in a heterotrimer form consisting of p50-p65 and I κ B α subunits. Upon activation, the p50-p65 heterodimer is translocated into the nucleus and binds to the promoters of NF- κ B-related genes.¹⁰⁸ NF- κ B is activated and overexpressed along M-D-A sequence and associated with CD1 nuclear expression.¹⁰⁹ NF- κ B is an adverse prognostic factor for chemo-radia-

tion efficacy in EC and overall a poor prognosis factor.^{110,111}

Gastrin Signaling

Gastrin is a hormone that mainly regulates gastric acid secretion. Various studies have shown that in patients with BE treated with proton pump inhibitors an elevation of fasting and postprandial serum gastrin levels is assessed.¹¹² Gastrin could have a role in carcinogenesis promotion initially binding to the cholecystokinin receptor (CCK2R).¹¹³ Through CCK2R stimulation and subsequent epidermal growth factor (EGF) expression COX-2 expression could be induced.¹¹⁴ COX-2 is expressed in 75% in patients with BE without dysplasia and 100% in HGD and EC patients and is related with neoplastic progression.¹¹⁵ Furthermore, CCK2R activation also participates in proapoptotic factors' inactivation.¹¹⁴ Gastrin-signaling activity in tumorigenesis promotion has been previously described in *in vitro* experiments; however, clear clinical evidence does not yet exist. Whether PPIs could counterbalance the effect of hypergastrinemia with their ability to suppress acid-reflux signaling is a matter of conjecture. The combined use of gastrin's signaling inhibitors along with PPIs might be an interesting option.

Growth Factors—Receptors

Epidermal growth factor is overexpressed in BE's progression to EAC and is related with matrix metalloproteinase production.¹¹⁶ Its gene amplification is observed as a late event in esophageal carcinogenesis and is related to poor prognosis.^{117,118} ErbB-2 gene amplification is also a late event in disease progression related to aggressive phenotype.¹⁰⁶ Vascular endothelial growth factors (VEGFs) and VEGF receptors are observed in BE and neoplastic lesions and are associated with angiogenesis process.¹¹⁹ Their prognostic role in EC is not yet identified.¹⁰⁸ Furthermore, HGF receptor c-Met is overexpressed during this process, in BE with dysplasia and EA, compared to normal esophagus epithelium.^{120,121} Herrera et al also showed that c-Met dysregulation can occur as an early event in EAC tumorigenesis.¹²² These findings suggest that it may be an attractive target for chemoprevention or targeted

therapy against EAC. In addition, inhibition of COX-2 has been shown to downregulate c-Met expression and decrease the frequency of BE malignant transformation and could be an option for preventive therapy.¹²³

Future efforts should be directed toward defining the high-risk population through biomarkers.

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Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.