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History, Molecular Mechanisms, and Endoscopic Treatment of Barrett's Esophagus

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Abstract

This report is written as an adjunct to the American Gastroenterological Association Institute's medical position statement and technical review on the management of Barrett's esophagus, which will be published in the near future. Those documents will consider a number of broad questions on the diagnosis, clinical features, and management of patients with Barrett's esophagus, and the reader is referred to the technical review for an in-depth discussion of those topics. In this report, we review historical, molecular, and endoscopic therapeutic aspects of Barrett's esophagus that are of interest to clinicians and researchers.

History of Barrett's Esophagus

Barrett's esophagus is a condition named for the late Norman Rupert Barrett, an influential esophageal surgeon who was born in Adelaide, Australia in 1903.[1] Barrett worked for most of his career as a consultant surgeon at St. Thomas' Hospital in London. He was a pioneer in the field of thoracic surgery and a charismatic academic leader who served for more than 25 years as editor of *Thorax*. By all accounts, Norman Barrett was an outstanding surgeon, scholar, and teacher. However, Norman Barrett was not the first to describe the condition that now bears his name; in fact, his original contentions about the nature and pathogenesis of the condition were incorrect. The eponym "Barrett's esophagus" continues to evoke confusion and controversy, and authorities still dispute the definition of the disorder.[2] To appreciate these controversies, it is helpful to consider some key events in the relatively brief history of Barrett's esophagus.

In 1950, Barrett published a treatise proposing that the esophagus should be defined as "that part of the foregut, distal to the cricopharyngeal sphincter, which is lined by squamous epithelium".[3] He commented on earlier reports describing patients with ulcerations in a tubular organ that grossly appeared to be the esophagus, but whose distal, ulcerated portion was lined by columnar epithelium. Since Barrett had defined the esophagus by its squamous lining, he

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argued that the ulcerated, columnar-lined viscus described in those reports was a tubular segment of stomach that had been tethered within the chest by a congenitally short esophagus. To support that contention, Barrett noted that the ulcerated columnar lining always was identified as "histologically gastric in type".

Barrett himself claimed that peptic ulcer of the esophagus was first reported in 1839 by the German pathologist Albers.[3] However, credit for describing the columnar-lined esophagus probably should go to Wilder Tileston, a pathologist who, while working in Boston in 1906, described 3 cases of "peptic ulcer of the oesophagus", and noted "the close resemblance of the mucous membrane about the ulcer to that normally found in the stomach".[4] Tileston wrote that "the first requisite for the formation of the peptic ulcer of the oesophagus is an insufficiency of the cardia" (i.e. gastroesophageal reflux). Thus, almost a half-century before Barrett, Tileston described the columnar-lined esophagus and correctly attributed the pathogenesis of the associated ulceration to gastroesophageal reflux.

In 1953, Allison and Johnstone described 7 patients who had reflux esophagitis involving an "oesophagus lined with gastric mucous membrane".[5] In this report, they refuted Barrett's contention that the tubular, intra-thoracic, columnar-lined viscus was stomach. They noted that, unlike the stomach, the columnar-lined organ lacked a peritoneal covering, harbored islands of squamous epithelium, and had submucosal glands and a muscularis propria typical of the esophagus. In deference to Barrett, the editor of the journal to which they had submitted their report, Allison and Johnstone suggested that ulcerations in the columnar-lined esophagus should be called "Barrett's ulcers". Barrett eventually accepted Allison and Johnstone's arguments and, in a report published in 1957, suggested that the condition should be called "lower oesophagus lined by columnar epithelium".[6] Whether justified or not, the eponym Barrett's esophagus has been retained.

In another influential report published in *Thorax* in 1961, an Australian surgeon named John Hayward elaborated his opinions on the histological features of the distal esophagus.[7] He contended that the distal 1– 2 cm of the esophagus is normally lined by a mucus-secreting, junctional epithelium (also called gastric cardia-type epithelium). Hayward argued that "…if squamous epithelium joined gastric epithelium of fundal [acid-secreting] type directly, it would be liable to digestion at the junction. The buffer zone of junctional epithelium, which does not secrete acid or pepsin but is resistant to them, has to be interposed." Hayward provided no data to support his contentions and Barrett remarked that Hayward's report contained "a lot of nonsense".[1] Nevertheless, Barrett published the report essentially unaltered, and it has had substantial influence on the course of studies on Barrett's esophagus.

The histology of the columnar-lined esophagus remains a controversial issue to this day. Barrett, and virtually all of the investigators who wrote about the condition before he did, described an acid-secreting, gastric type of columnar epithelium lining the esophagus.[3] In 1951, Bosher and Taylor were the first to describe intestinal-type goblet cells in the columnar-lined esophagus.[8] In 1952, Morson and Belcher reported a patient who had an adenocarcinoma in an esophageal mucosa that had "atrophic changes with a tendency towards intestinal type containing many goblet cells".[9] Still other investigators described cardia-type epithelium in Barrett's esophagus.[10]

This confusing situation was clarified somewhat in 1976, when Paull *et al*. reported a systematic study of 11 patients with Barrett's esophagus who had esophageal biopsy specimens taken above the lower esophageal sphincter using manometric guidance.[11] Those patients were found to have as many as 3 types of columnar epithelia lining the distal esophagus: 1) a junctional (cardia-type) epithelium that comprised mucus-secreting cells, 2) a gastric fundic-type epithelium with parietal and chief cells, and 3) intestinal-type metaplasia, which the

authors called specialized columnar epithelium, with prominent goblet cells. The 3 epithelial types occupied different zones in the columnar-lined esophagus, with intestinal-type metaplasia adjacent to squamous epithelium in the most proximal segment, followed by cardia-type epithelium, with gastric fundic-type epithelium lining the most distal esophageal segment.

By the 1970's, it was well established that Barrett's esophagus was associated with severe gastroesophageal reflux disease (GERD) and hiatal hernia,[12-14] conditions that can obscure the endoscopic landmarks used to identify the gastroesophageal junction (GEJ). Endoscopists intent on collecting biopsy samples from the distal esophagus of patients with these disorders could mistakenly take those specimens from the proximal stomach, resulting in a spurious diagnosis of Barrett's esophagus lined by gastric-type epithelium. Further complicating diagnostic issues, Hayward had contended that even the normal esophagus could be lined by up to 2 cm of cardia-type epithelium.[7] Therefore, analysis of biopsy samples from this "normal" columnar mucosa also might result in a spurious diagnosis of Barrett's esophagus. These factors created major problems for investigators, because accurate diagnostic criteria are a prerequisite for a meaningful study of a disease.

In the early 1980's, investigators intent on avoiding the problem of spurious diagnoses established diagnostic criteria for Barrett's esophagus based on an arbitrary extent of esophageal columnar lining above the GEJ. For example, Skinner *et al*. chose 3 cm as the extent of esophageal columnar lining required for patients to be enrolled in studies of Barrett's esophagus.[15] These arbitrary, investigative criteria were eventually used by clinicians as diagnostic criteria. As a result, endoscopists often dismissed columnar epithelium limited to the distal few centimeters of the esophagus as normal, and obtained biopsy specimens to confirm a diagnosis of Barrett's esophagus only when columnar lining extended some arbitrary distance (e.g. >3 cm) above the GEJ. Furthermore, endoscopists sought to identify Barrett's esophagus almost exclusively in patients who had symptoms and endoscopic signs of severe GERD. By adhering to such diagnostic guidelines, physicians minimized the problem of mis-diagnosis, but failed to identify short segments of metaplastic epithelium in the distal esophagus.

By the 1980s, it was well established that adenocarcinoma was associated with Barrett's esophagus.[16-18] When reports of esophageal adenocarcinomas in patients with Barrett's esophagus provided a description of the associated Barrett's epithelium, they almost invariably identified that epithelium as intestinal-type metaplasia, usually with dysplastic features.[19] By the late 1980's, intestinal metaplasia was widely regarded as both the most common type of Barrett's epithelium and the epithelial type associated with cancer development.[20,21] Barrett's esophagus had little clinical importance outside of its malignant predisposition, and intestinal metaplasia was distinct in its histologic appearance (and unlike the gastric types of Barrett's epithelia, clearly abnormal when located at the GEJ). Consequently, some researchers chose to define Barrett's esophagus by the presence of intestinal metaplasia.[22,23] This diagnostic criterion, arguably based more on convenience than on science, also was adopted into clinical practice.

An esophageal biopsy specimen showing intestinal-type metaplasia had become virtually a *sine qua non* for the diagnosis of Barrett's esophagus by the early 1990s.[22] Nevertheless, in the early 1990s, most endoscopists would not take esophageal biopsy specimens to seek a diagnosis of Barrett's esophagus unless their patients had GERD with some minimal extent of esophageal columnar lining (e.g. at least 3 cm). That practice was challenged in 1994, when Spechler *et al*. showed that 18% of consecutive patients in a general endoscopy unit who had columnar epithelium that involved <3 cm of the distal esophagus also had intestinal metaplasia.[24] Futhermore, they showed that symptoms and endoscopic signs of GERD were not reliable markers for intestinal metaplasia in the distal esophagus. Numerous subsequent studies

confirmed that short segments of intestinal metaplasia frequently line the distal esophagus of individuals with no signs or symptoms of GERD.[25-27] Since the late 1990s, therefore, Barrett's esophagus has been categorized as long-segment (when the metaplastic epithelium extends at least 3 cm above the GEJ) or short-segment (when there is <3 cm of metaplastic epithelium lining the esophagus).[28] Thus, 5 decades after the publication of Norman Barrett's treatise, the diagnostic criteria for Barrett's esophagus had evolved from an esophagus lined extensively by gastric epithelium in patients with severe GERD to an esophagus lined by any extent of intestinal epithelium in patients who might not have GERD.

A recent issue of contention is whether the presence of gastric cardia-type epithelium in the distal esophagus warrants a diagnosis of Barrett's esophagus.[29] The British Society of Gastroenterology's recent guidelines specifically state that only "columnar lined oesophagus on histology" (i.e. cardia- or intestinal-type epithelium) is needed for the diagnosis of Barrett's esophagus.[30] Data indicate that cardia-type epithelium is not normal, as Hayward had contended, but rather a metaplastic lining that develops as a consequence of GERD.[31] Histochemical and genetic studies of cardia-type epithelium have revealed molecular abnormalities, similar to those found in intestinal metaplasia, that could predispose patients to carcinogenesis,[32,33] and recent clinical studies support the concept that cardia-type epithelium has malignant potential.[34-36] This issue and others related to diagnostic criteria for Barrett's esophagus are discussed in detail in the AGA Institute's technical review on Barrett's esophagus, which recommends that Barrett's esophagus should now be defined as "the condition in which any extent of metaplastic columnar epithelium that predisposes to cancer development replaces the stratified squamous epithelium that normally lines the distal esophagus."

Physicians should consider how and when the diagnostic criteria for Barrett's esophagus changed when evaluating reports on the disorder. Short-segment Barrett's esophagus was not widely recognized until 1994,[24] and the vast majority of studies reported before that year included patients with only long-segment disease. More recent studies, however, include a substantial proportion of patients with short-segment Barrett's esophagus. Patients with short- and long-segment Barrett's esophagus can differ considerably in the severity of their associated GERD and risk for developing esophageal adenocarcinoma. It is therefore not appropriate to extrapolate the results of older studies on the epidemiology and natural history of Barrett's esophagus to patients with short-segment disease.

Molecular Events that Underlie Metaplasia and Cancer in Barrett's Esophagus

GERD and metaplasia

Long-segment Barrett's esophagus is associated with GERD, and the epithelial metaplasia characteristic of Barrett's esophagus is widely regarded as a consequence of GERD (Fig. 1, panels A,B). Early investigators proposed that Barrett's esophagus developed from gastric columnar cells that migrated from the stomach into the esophagus to reconstitute GERD-damaged squamous epithelium.[5] This hypothesis did not account for the intestinal metaplasia typical of Barrett's esophagus, however. The prevailing hypothesis now is that Barrett's esophagus forms when GERD damages the esophageal squamous epithelium, thereby exposing multipotential stem cells in the basal layers to refluxed gastric juice that stimulates abnormal differentiation.[37-39] These progenitor cells may also be present in the ducts of esophageal mucosal glands.[40] One recent study has suggested that circulating stem cells of bone marrow origin might contribute to the development of Barrett's esophagus.[41] Although the progenitor cell for Barrett's esophagus remains unknown, metaplasias must arise from changes in cellular gene expression and, in Barrett's esophagus, those changes appear to be induced by GERD.

Recent studies have reported molecular events in esophageal squamous epithelium that might be triggered by gastroesophageal reflux to cause Barrett's metaplasia. In esophageal squamous cell lines, for example, acid and bile induce the expression of caudal homeobox genes such as *CDX1* and *CDX2*.[42-45] The word homeobox originates from the Greek *homeosis*, meaning a shift in structural development; homeobox genes encode transcription factors that regulate cell differentiation during embryogenesis. In adult cells, alterations in homeobox genes might alter cellular phenotypic features.[46,47] Homeobox gene expression in adult cells can be regulated epigenetically, such as through alterations in gene promoter methylation, or via cell signaling pathways regulated by factors like bone morphogenetic proteins (BMPs) or fibroblast growth factors.[45,48]

Compared to normal esophageal squamous epithelium, BMP4 expression is increased in Barrett's metaplasia; in a rat model of reflux-induced Barrett's esophagus, BMP4 expression is increased in the stroma that underlies the Barrett's metaplasia.[49] Cultures of human esophageal squamous cells treated with BMP4 express cytokeratins that are characteristic of columnar cells.[49] Bile acids, at neutral and acidic pH levels, cause a cancer cell line to express CDX2 through ligand-dependent transactivation of the epidermal growth factor receptor.[50] It was therefore proposed that GERD induces the expression of Cdx genes through BMP4 and, perhaps, EGFR activation, and that GERD-induced Cdx expression might partially mediate the development of Barrett's metaplasia.[47]

GERD and Carcinogenesis in Barrett's esophagus

Tumor initiation is the process in which cells are changed so that they are able to form tumors. Although GERD clearly plays a role in the pathogenesis of Barrett's metaplasia, it is not clear whether gastroesophageal reflux can initiate tumor formation in the metaplastic cells. Studies have shown that esophageal cells exposed to acid develop DNA double-strand breaks that might contribute to tumor initiation.[51,52] In addition, deoxycholic acid (a bile acid) induces DNA damage in a dose-dependent, but nonlinear fashion.[53,54] These DNA injuries appear to be mediated by reactive oxygen species, so antioxidants could have chemopreventive effects in patients with Barrett's esophagus.

In addition to its potential role in initiating tumor development, GERD might also promote the growth of established neoplasms in Barrett's esophagus (a process called tumor promotion). Acid and bile exposure alter Barrett's cell kinetics[55-58] so as to enable cells that have sustained DNA damage to resist apoptosis via activation of the nuclear factor (NF)-κB pathway.[59] Other studies have shown that acid and bile salts increase NF-κB activity[60] and have effects on molecules involved in inflammation and proliferation.[61-63] For example, the farnesoid X receptor (FXR), a nuclear receptor that regulates inflammation, is up-regulated by deoxycholic acid *in vitro*.[64] Tuberous sclerosis complex 1 (TSC1) is a tumor suppressor that regulates the mammalian target of rapamycin (mTOR) pathway; in neoplastic Barrett's cells, bile acids deregulate the TSC/mTOR pathway.[65] There are therefore several potential mechanisms by which gastroesophageal reflux of acid and bile might initiate and promote tumors in Barrett's esophagus.

Obesity, metabolic syndrome, and Barrett's esophagus

Obesity is a risk factor for Barrett's esophagus and Barrett's adenocarcinoma,[66,67] especially an abdominal pattern of obesity, which has been associated both with GERD and Barrett's esophagus.[68] The mechanical effects of intra-abdominal fat might adversely affect the anatomical anti-reflux barrier.[69] Metabolic syndrome is also frequently observed in patients with Barrett's esophagus;[70] the adipocytokines associated with the metabolic syndrome and central adiposity have been proposed to contribute to the development of GERD, Barrett's esophagus and cancer.[71] For example, adipose tissues secrete inflammatory cytokines like

tumor necrosis factor-alpha and interleukin-6, as well as pro-proliferative hormones like leptin and insulin-like growth factor-1 that might promote carcinogenesis. Obesity is also associated with low levels of the anti-proliferative hormone adiponectin and low plasma levels of adiponectin have been described in patients with Barrett's esophagus.[72] Nevertheless, the precise nature of the relationships among the metabolic syndrome, GERD, Barrett's esophagus, and cancer remains to be established.

Diet and Barrett's esophagus

The role of specific dietary factors in the pathogenesis of Barrett's esophagus is not clear. In patients with GERD, the distal esophagus can be exposed to high concentrations of nitric oxide and other nitrosating species, which are generated from the nitrate in green, leafy vegetables in the diet.[73] Those nitrosating species are capable of causing DNA double-strand breaks, which are potentially carcinogenic.[51] These types of oxidative injuries to DNA might be prevented by dietary antioxidant compounds such as polyphenols. Modest wine intake has been associated with a lower risk for Barrett's esophagus and esophageal adenocarcinoma, possibly from the reduction in oxidative stress provided by polyphenols in wine.[74]

Iron also might have a role in the development of esophageal cancer. After the surgical induction of reflux in rats, the rate of development of esophageal adenocarcinoma is substantially higher in animals that receive iron supplementation.[75] One study described overexpression of iron transport proteins in the progression of Barrett's metaplasia to adenocarcinoma, and cultured cancer cells loaded with iron increased proliferation.[76] Reduced iron levels in premenopausal women might underlie the delayed onset of adenocarcinoma in women with Barrett's esophagus.[77] However, no link has been found between hemochromatosis (excess iron storage) genes and Barrett's esophagus, so the relationship between iron metabolism and this condition is complex.[78]

Genetics, Carcinogenesis, and Barrett's esophagus

Unlike the well-characterized sequence of genetic alterations that lead to some forms of colon cancer, no well-defined pathway has been shown to mediate the pathogenesis of adenocarcinoma in Barrett's esophagus. There is considerable genetic heterogeneity among the adenocarcinomas that develop in patients with Barrett's esophagus, which frequently involve alterations in tumor suppressor genes.[79,80] A number of the many molecular changes that have been described in Barrett's-associated cancers are so-called "hitchhiker mutations" that do not directly contribute to carcinogenesis, but are retained in the cancer cell genome because they are linked to oncogenic mutations.[81] It is not clear which of the many genetic changes described in Barrett's esophagus are required for oncogenesis; when these are identified, they might be used in diagnosis and as therapeutic targets.

In general, both alleles of a tumor suppressor gene must be silenced to contribute to carcinogenesis. The first silencing event (allele 1) usually involves a DNA nucleotide sequence change mutation (e.g. a nucleotide base excision or deletion). The second silencing event (allele 2) can also be a sequence change mutation, but more commonly involves loss of a chromosome segment after a faulty cell division (so-called loss of heterozygosity or LOH). Methylation of DNA cytosine residues in the gene promoter region is another common gene silencing mechanism.

Alterations in genes that encode the tumor suppressors p16 (*CDKN2A*) and TP53 are frequently found in cells from Barrett's esophagus samples. Loss of expression of a *CDKN2A* allele, usually through methylation of its promoter, is found in non-dysplastic Barrett's metaplasia in 85% of cases (Figure, panel B).[82-84] The *CDKN2A* mutations found in Barrett's metaplasia appear to have been caused by oxidative damage in areas of chronic inflammation.[85] LOH has

been observed in *CDKN2A* in dysplastic regions of Barrett's esophagus (Fig. 1, panel B,C).[82,83,86,87] *CDKN2A* abnormalities do not always alter esophageal cell proliferation and the affected cells can remain diploid, so these defects might cause not histological abnormalities.[85,88] However, there is little point in testing for loss of p16 expression to predict adenocarcinoma risk because it occurs with such high frequency that it is not a useful biomarker.[81]

In addition to being part of the coding sequence of p16, exon 2 of *CDKN2A* is also part of the region that encodes p14ARF (alternate reading frame). P14ARF is a tumor suppressor that prevents degradation of TP53. Because p16 expression is downregulated so frequently in Barrett's metaplasia, there has been interest in whether p14ARF expression is also lost. p14ARF expression appears to be lost in approximately 30% of Barrett's cancers. Data indicate that p14ARF loss is a relatively late event that is independent of the loss of p16 expression in Barrett's metaplasia. The loss of p14ARF expression appears to occur primarily as the result of CpG or histone methylation, rather than LOH.[89]

The appearance of low-grade dysplasia in Barrett's esophagus often coincides with the loss of *TP53* expression, through methylation of the gene promoter, mutations, or LOH in cells that have already lost p16 expression (Fig. 1, panel D). LOH at *TP53* is associated with a 16-fold increase in the rate of progression to cancer.[90] Certain mutations in TP53 result in nuclear accumulation of the resulting non-functional p53 protein that can be detected by immunohistochemistry. A large, nested, case-control study found that TP53 staining was increased in biopsies from patients who developed esophageal adenocarcinoma compared with controls, with an odds ratio of 11.7 [91,92]

Cells that lose TP53 expression often acquire an abnormal content of DNA (tetraploidy or aneuploidy) that can be detected by flow cytometry. These DNA changes correlate with increased proliferation and expansion of the proliferative compartment towards the mucosal surface.[93-95] The increased proliferation is associated with an increase in the proportion of cells in the S phase of the cell cycle and increased expression of cell cycle-related proteins such as cyclins.[85,92,96] These molecular changes and the associated proliferative abnormalities are often accompanied by histological changes in tissues recognized as high-grade dysplasia (Fig. 1, panel E). Widespread LOH at *TP53* and cytogenetic abnormalities are associated with increased cancer risk, perhaps because these changes increase sensitivity to mutagens.[96-99]

Aneuploidy has diverse effects on cell metabolism, proliferation, and immortalization.[100] Chromosomal copy number changes (a manifestation of aneuploidy) do not appear to be random events in Barrett's cells. Aneuploidy at chromosomes 4 and 7 usually occurs early in carcinogenesis, followed by aneuploidy at chromosomes 8 and 17 and then by the loss of the Y chromosome in cells from male patients.[101,102] The presence of ploidy abnormalities in esophageal cells increases the risk for cancer among patients with Barrett's esophagus (relative risks (RR)=4.4 and 11 for tetraploidy and aneuploidy, respectively; RR=20 when both are present).[103]

At advanced stages of neoplastic progression, the Barrett's esophagus often harbors multiple distinct clones that exhibit variable degrees of expansion (Fig.1 panel F),[104] and the level of clonal diversity correlates with the risk of adenocarcinoma development.[97,105] One study found that samples of adenocarcinoma in Barrett's esophagus had such high levels of genomic heterogeneity that even neighboring crypts had distinct genetic profiles.[106] This genomic heterogeneity results from local variations in the microenvironment of different regions of the esophagus (so-called microenvironmental niches) or from genetic instability.[105] However, microsatellite instability, which often underlies colorectal carcinomas, does not seem to contribute importantly to carcinogenesis in Barrett's esophagus.[107]

The number of molecular abnormalities identified in Barrett's esophagus has greatly increased with advances in high-throughput screening techniques for genomic and epigenetic alterations. Unfortunately, our understanding of the functional implications of these abnormalities and how they might be used to improve patient care lags behind. Application of concepts from other disciplines, such as evolutionary biology and bioinformatics, should facilitate progress in understanding causality. This information might be used to develop non-invasive tests for determining which patients will benefit most from the exciting new endoscopic techniques available for treatment of patients with Barrett's esophagus.

Endoscopic Therapy for Barrett's Esophagus

Endoscopic ablative therapy for Barrett's esophagus is based on the principle that, when gastroesophageal acid reflux is controlled by medical or surgical means, squamous epithelium replaces ablated metaplastic epithelium. This principle was first validated more than 20 years ago in subjects whose Barrett's epithelium was ablated by endoscopic laser treatment.[108,109] Since then, endoscopic ablation has advanced from an experimental approach to a valid therapeutic option that is endorsed by professional societies.[110,111] Large cohort studies with long durations of follow up have documented the durability of endoscopic therapies and the comparability of their outcomes to those of traditional surgical treatment for neoplasia in Barrett's esophagus.[112-114] The efficacy of endoscopic ablation has been confirmed in multicenter, randomized controlled trials.[115-117] Nevertheless, many questions remain regarding which patients are appropriate candidates for endoscopic therapy and which endoscopic eradication technique is most effective in preventing cancer.[118,119]

Techniques of endoscopic therapy for Barrett's esophagus can be categorized broadly into those that provide tissue for histological examination (endoscopic mucosal resection and endoscopic submucosal dissection) and those that do not (ablative therapies). The ablative therapies can be further classified as heat-generating thermal techniques (radiofrequency ablation, multipolar electrocoagulation, and argon plasma coagulation), photochemical techniques (photodynamic therapy), and cryotherapy. Multimodal endoscopic therapy, which uses a resection technique to remove visible abnormalities followed by an ablation technique to eradicate the remaining Barrett's epithelium, is considered to be the most comprehensive endoscopic management of neoplasia in Barrett's esophagus. Table 1 summarizes the evidence for efficacy, advantages, and limitations of each technique.

Endoscopic mucosal resection

Endoscopic mucosal resection (EMR) involves the removal of mucosal and submucosal tissue, usually after the targeted mucosal segment is elevated by the submucosal injection of fluid.[120,121] The most commonly used EMR technique is the "suck and cut" method, wherein the mucosal lesion is sucked into a cap on the tip of the endoscope and then resected using a diathermic snare. There is also a "band and snare" method that uses a band ligating device, similar to that used for endoscopic variceal ligation, which deploys elastic bands around the suctioned mucosal segment. The banded segments are then removed with a snare. The band ligation method allows multiple resections to be completed in a single intubation and does not always require submucosal fluid injection before banding. The 2 EMR techniques have been compared; the suck and cut method provides larger tissue samples whereas the band ligation technique is faster and less expensive for multiple resections.[122] EMR can be applied focally (to resect only a visible lesion) or circumferentially (to remove the entire segment of Barrett's metaplasia).[113,114,123]

Compared to conventional endoscopic biopsy methods, EMR allows for more precise characterization of neoplasia, less inter-observer variation among pathologists, and more accurate assessments of dysplasia grades and the depths of invasion.[124,125] In addition, the

pathologist can provide information about neoplastic involvement in the margins of the resection specimens.[126] All of this information is invaluable in determining whether endoscopic therapy is adequate or whether surgical resection is required to cure neoplasias in patients with Barrett's esophagus. Results of the 2 approaches are summarized in table 1.

Accurate T staging of the depth of neoplastic involvement is required to determine whether endoscopic therapy can be considered definitive. Esophageal resections performed on patients with intramucosal carcinomas, which do not penetrate the muscularis mucosae, have revealed a low rate of metastases to lymph nodes (less than 5%). [127-130] Thus, endoscopic therapy might be curative for most patients with neoplasms confined to the mucosa. For tumors that involve the submucosa, however, the rate of metastasis to the lymph nodes exceeds 20%.[126,131] Therefore, endoscopic therapy is generally not considered definitive for patients with submucosal neoplasia, despite reports documenting successful endoscopic therapy for some patients with tumors that invaded only the upper third of the submucosa.[132] Non-invasive procedures like endoscopic ultrasonography have relatively poor accuracy for staging early esophageal neoplasia.[133] Consequently, EMR has a major role in staging early esophageal neoplasms and determining whether endoscopic therapy is feasible.

Endoscopic submucosal dissection

Endoscopic submucosal dissection (ESD) has been used primarily in Japan, predominantly for the treatment of gastric neoplasia. ESD starts with injection of fluid into the submucosa, followed by incision around the mucosal segment to be removed using a cutting device (e.g. ceramic tip knife, triangle tip knife, flex knife, hook knife, standard needle knife) and, finally, submucosal dissection of the segment.[121] This technique requires meticulous endoscopic control and the use of a cap to help with the submucosal dissection.

The major proposed advantage of ESD over EMR is the ability to remove a neoplastic lesion *en-bloc*, which provides more precise determination of its vertical and lateral margins and, perhaps, greater potential for the complete removal of all neoplastic cells. However, ESD is a technically challenging and lengthy procedure that sometimes requires hours to complete, and serious complications such as perforation are frequent. In the esophagus, furthermore, GERD-induced inflammation and fibrosis in the submucosa can make ESD difficult and even more hazardous. These concerns have limited the use of ESD in the treatment of Barrett's esophagus.

Multipolar electrocoagulation

Multipolar electrocoagulation (MPEC) involves the application of thermal energy to the mucosa using an electrode-tipped, 7F or 10F catheter that is advanced through the working channel of the endoscope.[134,135] The technique is time consuming and not practical for ablating large mucosal areas; there are no published data on the efficacy of MPEC for treating neoplasia in Barrett's esophagus. Because MPEC is a bipolar device, however, it might be used to eradicate residual areas of intestinal metaplasia for patients who have implanted cardiac devices.

Argon Plasma Coagulation

Unlike MPEC, argon plasma coagulation (APC) is a non-contact technique in which monopolar energy is delivered to tissue using ionized argon gas. Energy settings from 40W to 90W have been used to ablate Barrett's metaplasia and dysplasia, with short-term success rates ranging from 70% to 90%. However, some studies have reported recurrence rates as high as 66% and frequently found metaplastic glands underlying squamous epithelium (so-called "buried metaplasia"). This might reflect the relatively superficial injury inflicted by APC.[136] In addition, reports of serious complications such as perforation, pneumomediastinum, and major bleeding have reduced endoscopists' enthusiasm for APC ablation of Barrett's esophagus.

[137,138] Newer ablation techniques (see below) have rendered both APC and MPEC largely obsolete for the eradication of Barrett's esophagus, although APC and MPEC could still be used to eliminate small islands of Barrett's metaplasia.

Photodynamic therapy

Photodynamic therapy (PDT) is an ablation technique that destroys Barrett's epithelium using photochemical energy generated through the interaction between endoscopically delivered light and a photosensitizer that is concentrated in the tissue. This interaction leads to the generation of toxic, singlet oxygen molecules that damage tissue. The photosensitizers used for PDT include porfimer sodium, which is administered intravenously, and 5-aminolevulinic acid (ALA), which can be administered orally.[139] The most data on efficacy, durability, and long-term outcome are available for the use of PDT with porfimer sodium.[115,140,141] Common side effects of PDT using porfimer sodium include photosensitivity reactions in more than 60% of patients, a high rate of esophageal stricture formation (as much as 36%), and substantial short-term morbidity.[115, 142] PDT with ALA is associated with a shorter duration of photosensitivity and less esophageal structuring than with porfimer sodium, but ALA appears to be less efficacious and has been associated with vascular instability and at least 1 death.[143,144]

Radiofrequency ablation

Radiofrequency ablation (RFA) uses radiofrequency energy, which is delivered by an endoscopic balloon catheter (Halo[360] system) or a focal ablation device (Halo [90] system), to destroy Barrett's epithelium. To perform RFA, the endoscopist first determines the esophageal diameter using a balloon measuring device. The mucosa is sprayed with 1% N-acetyl cysteine solution to remove mucus that might interfere with energy delivery to the mucosa, and a 3cm-long ablation balloon (whose diameter is determined by the aforementioned measurement) that is lined by circumferential electrodes is positioned in the esophageal segment to be ablated. If there is evidence of fibrosis in the wall of the esophagus, an ablation balloon with a diameter smaller than that determined by the measuring balloon is used to prevent esophageal tears; RFA is not recommended for patients with esophageal strictures because inflation of the treatment balloons (typical diameters of 28 to 31 mm) could cause perforations. Radiofrequency energy is delivered through the electrodes to produce heat that destroys the metaplastic tissue. Patients return 2–3 months after initial RFA treatment for endoscopic evaluation, and any residual metaplastic tissue is ablated using the focal ablation device (which measures 20 mm in its longest dimension).

Initial dose-finding and phase II studies showed the efficacy and safety of RFA for ablating non-dysplastic Barrett's epithelium.[145,146] By using a combination of the balloon-based and focal RFA devices, an uncontrolled study has described complete eradication of Barrett's epithelium in 60 of 61 patients (98%) during a follow-up period of 30 months.[116] A recent multicenter, randomized, sham-controlled study demonstrated the ability of RFA to eradicate dysplasia and intestinal metaplasia in patients with Barrett's esophagus.[147] Adverse events included esophageal stricture formation (6%), gastrointestinal bleeding (1%) and chest pain requiring hospitalization (2%); these rates of serious complications were substantially lower than those reported for PDT with porfimer sodium. Esophageal mucosal tears and perforations with RFA have been reported infrequently to the FDA MAUDE database (www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfMAUDE/search.CFM). Although these results are encouraging, the long-term durability of RFA remains to be determined. Furthermore, the randomized controlled trial enrolled patients who had high-grade dysplasia without associated nodularity, so only a small proportion had undergone EMR before RFA (7 of 84 patients in the ablation arm of the study). Moreover, the EMR was performed by

endoscopists with substantial expertise, so it is not clear whether the results could be reproduced by community endoscopists.

Cryotherapy

Cryotherapy involves the use of an endoscopically delivered cryogen (liquid nitrogen or carbon dioxide) to inflict tissue injury. One of the 2 cryotherapy systems available (CryoSpray Ablation system) uses a 7F catheter passed through the working channel of the endoscope to spray liquid nitrogen onto the metaplastic epithelium. The other system (GI Supply) delivers cold carbon dioxide gas to the mucosa through a spray catheter. Tissue destruction from cryotherapy occurs in 2 phases: an immediate phase, caused by freezing of the cell and its organelles, followed by a delayed phase, in which cells undergo apoptosis.[148] Cryotherapy is delivered by spraying without the need for mucosal contact with the catheter, which might be useful for application to uneven surfaces. Problems encountered with cryotherapy include over-distention with perforation (in a patient with Marfan's syndrome), and fogging of the endoscope lens (with the liquid nitrogen device). Though initial results with cryotherapy are promising and its adverse-event profile seems reasonable, long-term data are lacking.[149-151] Initial results are summarized in table 1.

Buried Metaplasia

A major concern for all of the endoscopic ablative procedures is that partially-ablated Barrett's epithelium might heal with an overlying layer of squamous epithelium that "buries" metaplastic tissue (with neoplastic potential) and hides it from the endoscopist. Although some studies suggest that buried metaplasia has a low risk of malignant transformation,[152] case reports of dysplasia and adenocarcinoma in buried metaplastic glands continue to cause concern.[153,154]

A recent study that explored the prevalence of buried metaplasia in a large, randomized trial of PDT for patients with high-grade dysplasia in Barrett's esophagus has allayed some concerns about buried metaplasia.[155] A systematic review of more than 33,000 esophageal biopsy specimens revealed that the frequency of buried metaplasia increased after PDT (from 5.8% to 30%). However, a similar increase in the frequency of buried metaplasia was noted for patients treated with PPIs alone (from 2.9% to 33%). In addition, the highest grade of dysplasia detected during any given endoscopic examination was not found exclusively in the buried metaplasia in any patient.

In the aforementioned sham-controlled trial of RFA for dysplasia in Barrett's esophagus, the frequency of buried metaplasia decreased in the group treated with RFA and PPIs (from 25% to 5%) and increased in the control group who received sham therapy and PPIs (from 25% to 40%).[147] Another study of 22 patients treated with RFA found no buried metaplasia 2 months after the procedure in biopsy specimens of neo-squamous epithelium taken using a "keyhole" technique designed to obtain deep specimens.[156] Nevertheless, the importance of buried metaplasia remains controversial, and large, well done, long-term studies are needed to determine its risk for malignancy.

Factors that influence choice of endoscopic therapy

The choice among treatment options for patients with dysplasia in Barrett's esophagus requires consideration of patient, esophageal, and institutional factors. Patient factors include age, fitness for therapy, and personal preferences.[157] The risks of esophagectomy might be prohibitive for older patients with substantial co-morbidities. Before endoscopic therapy is chosen, patients should be informed of the failure rates of the procedure and of the need for careful endoscopic follow-up.[158] Patients who choose endoscopic therapy should be willing to comply with follow-up requirements and be aware of the uncertainty regarding the long-term efficacy of endoscopy in preventing cancer. Esophageal factors include the length of the

Barrett's segment, the presence of visible lesions like nodules that can be targeted for EMR, and the presence of multifocal lesions.[142,159,160] Extensive metaplasia involving long segments of the esophagus can be difficult to eradicate with ablative therapies. The absence of a visible lesion to target by EMR makes it difficult to stage the depth of the neoplasia or determine whether endoscopic therapy can be successful. Dysplasia that is focal might be easily resected or ablated, whereas multi-focal dysplasia can be much harder to eradicate with a reasonable degree of certainty. Institutional factors include the levels of expertise of the surgeons and endoscopists. Surgical volume has been repeatedly shown to be an important determinant of esophagectomy outcome.[161] Undoubtedly, an endoscopist's level of experience will affect results as well. An approach to choosing endoscopic therapy for neoplasia in patients with Barrett's esophagus is illustrated in Figure 2.

There are number of unresolved issues in the endoscopic treatment of Barrett's esophagus. Dysplasia is an imperfect marker for cancer risk, and the identification of biomarkers to select patients who would benefit most from endoscopic or surgical treatments would represent a major advance. Although data from retrospective studies have shown that complete elimination of all metaplasia decreases the recurrence rate, prospective studies on this issue are needed. Predictors of recurrent dysplasia following ablation need to be defined to design interventions to limit that recurrence. New imaging techniques such as narrow band imaging, laser confocal endomicroscopy and endocytoscopy have the potential to improve the detection neoplasia in Barrett's esophagus, and to direct endoscopic therapies. Finally, long-term data on the recurrence of metaplasia and dysplasia following ablation are required to determine the need for post-ablation surveillance and select appropriate surveillance intervals.

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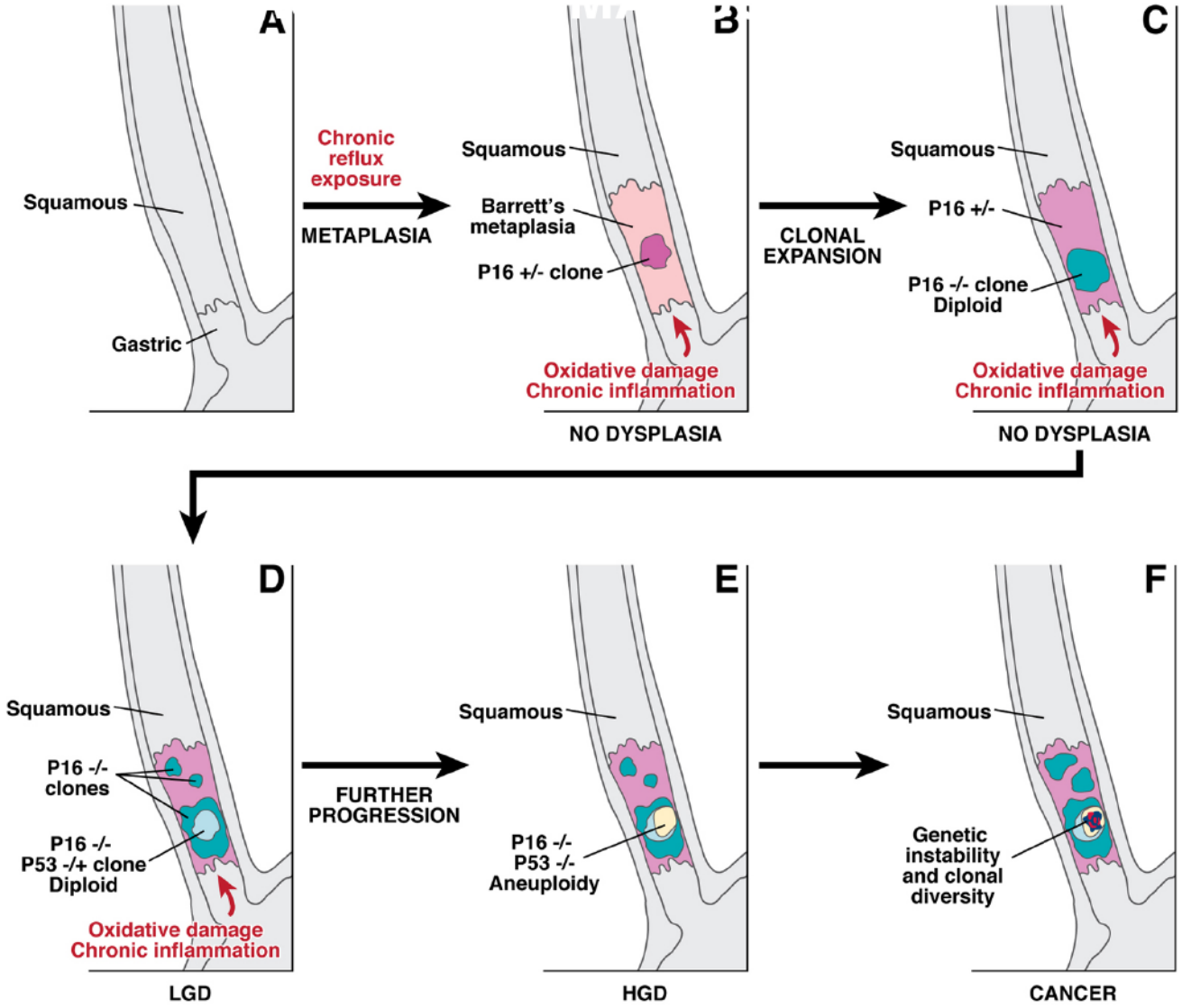

Figure 1.

A schematic illustrating the sequential somatic genetic changes in the progression from the squamous esophagus to Barrett's esophagus to adenocarcinoma. The normal squamous esophagus (A) undergoes a metaplastic transformation with the oxidative damage and chronic inflammation that accompanies chronic gastroesophageal reflux. The initial metaplastic change is followed early on by the loss of one p16 allele (B); this clone may then expand (pink area panel C), followed by loss of the 2nd p16 allele and the formation of some p16 null clones (blue area, C). The subsequent loss of p53 may be associated with morphological changes of low grade dysplasia (LGD), (D). Genetic instability may lead to aneuploidy, which is commonly seen with high grade dysplasia (HGD), (panel E). Numerous clones may develop, and there may be heterogeneity within clones especially as the degree of genetic instability increases and invasive adenocarcinoma develops (F).

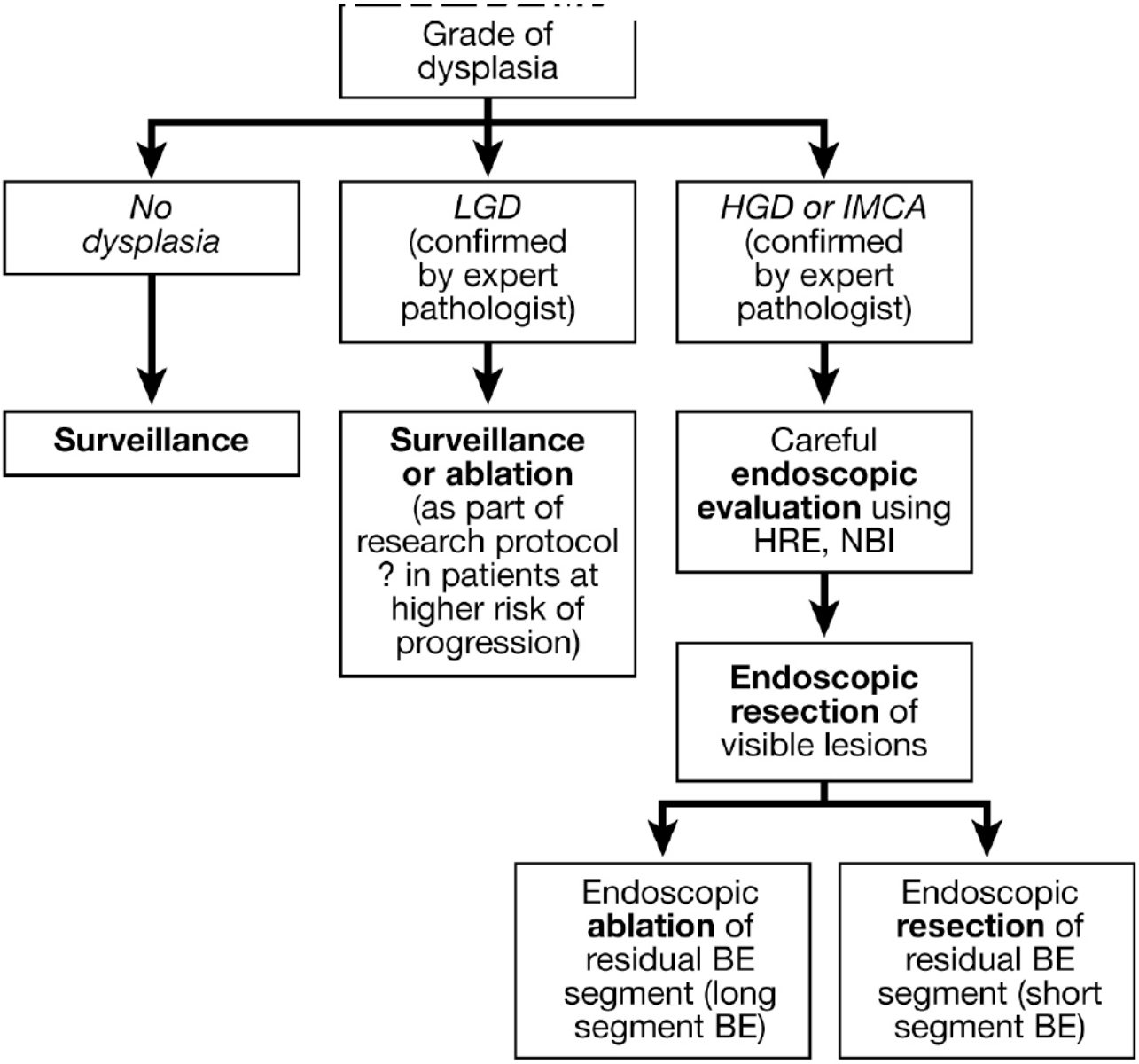

Figure 2.
Algorithm for the endoscopic management of dysplasia in Barrett's esophagus.

Table 1

Technique	Study	Study Design	Dysplasia grade included (sample size)	Outcomes	Advantages	Limitations
Endoscopic resection techniques						
Focal Endoscopic resection	Pech et al[$] 113	Single center cohort	HGD (61) IMCA (288) Median follow up 63months	CR–D: 97% Recurrence of HGD/ IMCa: 21.5% Overall 5 year survival : 84%	Allows precise determination of depth of invasion and assessment of margins Less variability in pathological assessment	May need multiple sessions to achieve remission Focal EMR alone may be associated with higher recurrence rates and positive margins Bleeding (0.6% to 6%) Perforation (0% to Stricture (4%)
	Prasad et al [#] 114	Single center cohort study (endoscopic : PDT/EMR and surgical cohorts)	IMCa (178) Median follow up Surg 64m Endo 43m	CR-D: 94% Recurrent Ca : 12% Overall 5 year survival: 83% in the Endo group and 95% in Surg group		
Circumferential endoscopic resection	Gondrie et al 162	Multicenter cohort study	HGD/IMCa (149) Median follow up 18months	CR-IM : 97% Recurrent neoplasia 3% 2-3 sessions needed to achieve CR	Low rate of recurrence by removing all at-risk mucosa With availability of EMRL easier to perform	Perforation 1% High stricture rate 52% Bleeding 1-4%% Ridges of tissue persist between EMR sites which may contribute to recurrence Buried metaplasia (8%)
	Larghi et al 123	Multicenter cohort study	HGD/IMCa (26) Median follow up 28months	CR-IM : 88% Recurrent neoplasia 4% (IMCa)		
Submucosal Dissection	Yoshinaga et al 163	Single center cohort study	GE junction adenoCa (24) Median follow up 30m	CR : 72% No recurrence in those with CR	En bloc resection allows clear margins to be obtained May be more suitable in lesions > 2 cm in diameter	Long procedure times Strictures
Endoscopic ablation techniques						
Thermal						
Multipolar electrocoagulation	Sampliner et al 135	Multicenter cohort study	No dysplasia (58) Median follow up 6m	CR-IM : 78%	Technically easy Relatively inexpensive Well tolerated (1/58 developed stricture, 1/58 hospitalized for chest pain) Persistent reversal of IM at 24 m in 68%	Difficult to treat longer segments (study used 10F probe via therapeutic endoscope) Not used for treatment of HGD Short follow up

Technique	Study	Study Design	Dysplasia grade included (sample size)	Outcomes	Advantages	Limitations
	Sharma at al 164	Multicenter randomized controlled trial (comparing MEPC and APC)	No dysplasia and LGD (35) Median follow up 24 m	CR-IM : 83% (75% MPEC, 63% with APC) CR-IM at 24 m : 68%		
Argon Plasma Coagulation	Attwood et al 165	Single center cohort study	HGD (29) Median follow up 37m	CR-D :86% CR-IM: 76% 4 patients progressed to EAC 1 esophageal perforation	Technically easy to perform	Dosimetry variable across studies Superficial effect leads to high prevalence of buried metaplasia Perforation reported Limited evidence in HGD
	Ferraris et al 166	Multicenter cohort study	No dysplasia (96) Median follow up 36 m	CR-IM 96% Recurrence 18%		
Radiofrequency Ablation	Shaheen et al 147	Multicenter, sham controlled RCT	HGD (64) LGD (63)	CR-IM (12 m): 77% vs. 2.3% CR-D (12m) HGD : 81% vs. 19% LGD: 90% vs. 23% Progression to Ca: 19% vs. 2%	Well tolerated by most patients Low stricture rate (6%) Low rate of subsquamous BE (5%)	Ablation requires multiple steps Long term data on durability of ablation and recurrence not available
	Fleischer et al 116	Multicenter, cohort study	No dysplasia (100)	CR-IM (12m) : 70% CR-IM (30m): 96%		
Photochemical						
Porfimer PDT	Overholt et al 115	Multicenter, partially blinded controlled RCT	HGD (208)	CR-HGD (24m): 77% Vs 38% CR-IM (24m) : 52% Vs 7% CR-D (24m): 59% Vs. 14%	Easy to administer Results of RCT durable at 5 years[33]	Photosensitivity (60%) Strictures (27-39%)[5] Significant post procedure morbidity
	Prasad et al 141	Single center cohort study (endoscopic : PDT/EMR and surgical cohorts)	HGD (199)	Overall survival comparable at 5 years between endoscopic and surgical cohorts. No death from esophageal carcinoma in both groups	Compares favorably to esophagectomy[36]	
ALA PDT	Pech et al 167	Single center cohort study	HGD (35) IMCA (31)	CR-D : 100% CR-D : 97% Median follow up 37m	Oral administration of 5-ALA Limited photosensitivity	Minor adverse effects 40% No strictures reported 29% recurrent carcinoma
	Peters et al 144	Single center cohort study	Residual HGD or IMCA after EMR (23)	CR-D : 75% CR-IM: 0% Median follow up 30m	Oral administration of 5-ALA	Major adverse effects : arrhythmia, hypotension, hematemesis

Technique	Study	Study Design	Dysplasia grade included (sample size)	Outcomes	Advantages	Limitations
				Recurrent HGD : 27%		Buried metaplasia in 33% High recurrence rate Death has been reported
Cryotherapy						
Liquid N_2 spray	Greenwald et al [150]	Multicenter cohort study	IMCA, HGD, Non dysplastic BE, severe squamous dysplasia (77)	CR-D : 88% (in HGD) CR-IM: 53% 1 perforation (in patient with Marfan Syndrome) 3 esophageal strictures Adverse effects: chest pain (17%), dysphagia (13%)	No mucosal contact required Well tolerated by most patients	Dosimetry not well established No controlled data available Technically challenging : need for accompanying decompression tube, visibility impaired due to freezing
CO_2 spray	Canto et al [151]	Single center cohort study	HGD/IMCA (44) Median follow up 12m	CR-IM 86% (after median of 6 procedures)	Initial promising results in patients who failed other forms of ablation (n=25) including EMR	Additional decompression tube not needed. May be option for patients who fail RF ablation, PDT

RCT : randomized controlled trial

CR-IM : complete remission – intestinal metaplasia

CR-D : complete remission – dysplasia

IMCA : intramucosal carcinoma

$: Additional ablative therapy used : PDT used in 64 patients, APC in 136 patients

#: Additional ablative therapy used : PDT used in 43 patients