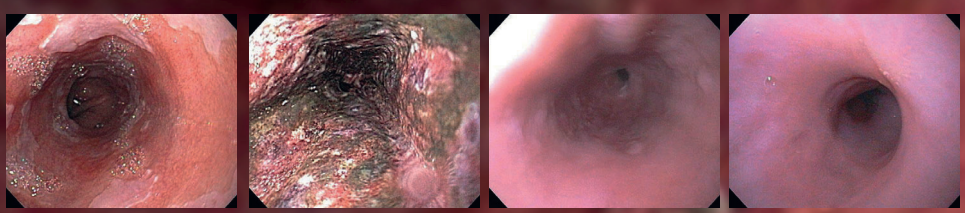
Endoscopic Therapy for Barrett's Esophagus

Edited by

Richard E. Sampliner, MD



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Richard E. Sampliner, MD

University of Arizona
College of Medicine, USA

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Editor
Richard E. Sampliner
College of Medicine
University of Arizona
P.O.Box 245028
Tucson AZ 85724-5028
AHSC 6406
USA
richard.sampliner@va.gov
samplinr@email.arizona.edu

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Preface

Endoscopic therapy for Barrett's esophagus (BE) has come of age. This is documented by the publication of a randomized controlled trial of one modality and an abstract of a randomized sham-controlled trial of another. The goal of this book is to highlight and detail the differing techniques of ablation for the elimination of neoplasia and intestinal metaplasia in BE. The authors are all experts in the utilization of endoscopic therapy for BE. The latest developments in technology and the most recent clinical data are reviewed.

Additional chapters on endoscopic imaging modalities to detect dysplasia, decision making in the clinical arena, and cost-effectiveness of ablation round out this approach to the management of BE.

High-grade dysplasia and early (intramucosal) adenocarcinoma should not lead to automatic esophagectomy in the current era. Familiarity with the availability of ablation techniques is essential for every clinician dealing with patients with Barrett's esophagus.

Richard E. Sampliner, MD

Contents

Contributors

STEPHEN E. ATTWOOD, MD, FRCSI • *Department of Surgery Newcastle University, Newcastle upon Tyne, United Kingdom*

JACQUES J.G.H.M. BERGMAN, MD, PHD • *Department of Gastroenterology and Hepatology, Academic Medical Center, Amsterdam, the Netherlands*

KENNETH J. CHANG, MD • *H.H. Chao Comprehensive Digestive Disease Center, School of Medicine, University of California, Irvine, Orange, CA*

SUVADIP CHATTERJEE, MB, MRCP • *Department of Gastroenterology, North Tyneside Hospital, Northumbria Healthcare, Tyne and Wear, United Kingdom*

CHRISTIAN ELL, MD • *Department of Internal Medicine, HSK Wiesbaden, Wiesbaden, Germany*

GARY W. FALK, MD, MS • *Department of Gastroenterology and Hepatology, Cleveland Clinic, Cleveland, OH*

CHIN HUR, MD, MPH • *Gastrointestinal Unit and Institute for Technology Assessment, Massachusetts General Hospital, Harvard Medical School, Boston, MA*

MICHAEL J. KRIER, MD • *Division of Gastroenterology/Hepatology, Stanford University School of Medicine, Stanford, CA*

HENDRIK MANNER, MD • *Department of Internal Medicine, HSK Wiesbaden, Wiesbaden, Germany*

V. RAMAN MUTHUSAMY, MD • *Department of Veterans Affairs Medical Center, Division of Gastroenterology, Kansas City, MO*

PANKAJ JAY PASRICHA, MD • *Division of Gastroenterology/ Hepatology, Stanford University School of Medicine, Stanford, CA*

OLIVER PECH, MD • *Department of Internal Medicine, HSK Wiesbaden, Wiesbaden, Germany*

ROOS E. POUW, MD • *Department of Gastroenterology and Hepatology, Academic Medical Center, Amsterdam, the Netherlands*

PRATEEK SHARMA, MD • *Department of Veterans Affairs Medical Center, Division of Gastroenterology, Kansas City, MO*

YUTAKA TOMAZAWA, MD • *Research Associate, Barrett's Esophagus Unit, Mayo Clinic, Rochester, MN*

MICHAEL B. WALLACE, MD, MPH • *Professor of Medicing, Mayo Medical School, Rochester, MN*

KENNETH K. WANG, MD • *Professor of Medicine, Barrett's Esophagus Unit, Mayo Clinic, Rochester, MN*
HERBERT C. WOLFSEN, MD • *Consultant, Division of Gastroenterology and Hepatology, Mayo Clinic, Jacksonville, FL; Associate Professor, Mayo Medical School, Rochester, MN*
PATRICK YACHIMSKI, MD, MPH • *Gastrointestinal Unit, Massachusetts General Hospital, Harvard Medical School, Boston, MA*

New Technologies for Imaging of Barrett's Esophagus

Herbert C. Wolfsen, MD
and Michael B. Wallace, MD, MPH

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Summary

Several important endoscopic imaging modalities have recently been approved for use and are commercially available. This chapter briefly reviews these developments and the implication for patients with Barrett's esophagus, especially advanced dysplasia and mucosal carcinoma. Important developments in biophotonics have been moving from the experiment laboratory to the gastrointestinal endoscopy unit. Narrow band imaging, auto-fluorescence, confocal fluorescent microscopy, spectroscopy and optical coherence tomography are reviewed. Unresolved issues for most of these technologies include regulatory approval, commercial availability and demonstration of clinical utility. This chapter reviews recent developments in endoscopy-based imaging modalities in patients with Barrett's esophagus.

Key Words: Narrow band imaging, Auto-fluorescence, Confocal microscopy, Spectroscopy, Optical coherence tomography

INTRODUCTION

Several important endoscopic imaging modalities have recently been approved for use and are commercially available. This chapter briefly reviews these developments and the implications for patients with Barrett's disease, especially advanced dysplasia and mucosal carcinoma. The history of Barrett's esophagus features several important milestones. Norman Barrett initially described a congenital short esophagus with ulcerations in the gastric cardia. Later, others determined that Barrett's esophagus represented acquired glandular ulcerations of the distal esophagus [1, 2] related to severe gastroesophageal reflux disease [3], with increasing rates of dysplasia and adenocarcinoma [4]. Subsequently, much of the interest in Barrett's esophagus has focused on the utility of standard resolution white light surveillance endoscopy, with random mucosal biopsies to detect dysplasia and early carcinoma [5]. Recently, important developments in biophotonics have been moving from the laboratory to the gastrointestinal endoscopy unit. Unresolved issues for most of these technologies include regulatory approval, commercial availability, demonstration of clinical utility, securing reimbursement for the required additional time and imaging equipment, as well clarifying the medical–legal issues associated with image interpretation and data storage. This chapter reviews recent developments in endoscopy-based imaging modalities in patients with Barrett's esophagus.

WHITE LIGHT ENDOSCOPIC IMAGING FOR BARRETT'S ESOPHAGUS

Barrett's disease is suspected when endoscopy detects salmon-colored mucosa in the distal esophagus. North American guidelines require mucosal biopsies to document the specialized intestinal metaplasia of Barrett's disease and differentiation from fundic or cardiac forms of gastric metaplasia. Beyond the initial diagnosis, the role of surveillance endoscopy, using standard resolution white light surveillance endoscopy, has not proven reliable for the visualization of dysplasia and early neoplasia. Therefore, surveillance endoscopy biopsy protocols, dependent upon quadrantic mucosal biopsies, have been adopted despite their expense, time consumption, associated sampling error, and the high inter- and intra-observer variability found in the histologic analysis [5, 6]. In the recent past, video endoscopes have largely replaced the fiber optic instruments around the world. A video endoscope utilizes a charge-coupled device (CCD) – an integrated electrical circuit made of photosensitive silicone semiconductors. The CCD surface is made up of photosensitive elements (pixels) that generate an electrical charge in proportion to light exposure and then generate an analog signal that is digitalized by the computer video processor. CCDs in standard video endoscopes have 100,000–300,000 pixels, and the image resolution, the ability to discriminate between two adjacent points, varies accordingly (Fig. 1). These endoscopes have a focal distance of 1–9 cm, and images will appear out of focus if they are beyond this range. Endoscopes with high-density CCDs (600,000–1,000,000 pixels per CCD), referred to as high-resolution endoscopes (HRE),

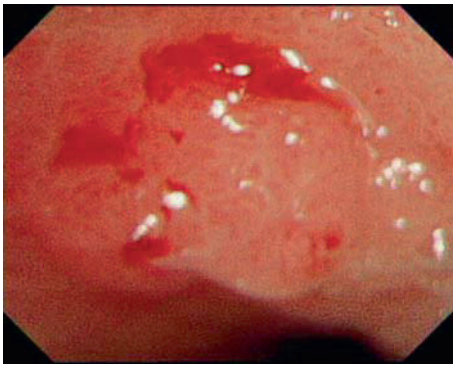

Fig. 1. High-resolution white light imaging of the same nodule. Despite the improved image quality the fine mucosal details are somewhat obscured by the *red light*.

are capable of producing high-magnification images, with increased spatial resolution for the detection of microscopic abnormalities in mucosal glandular and vascular structures. In conjunction with a movable lens for magnification endoscopy, the focal distance may be controlled to allow detailed examination of the mucosal surface at close range (< 3 mm).

CHROMOENDOSCOPY AND BARRETT'S ESOPHAGUS

It is laborious and impractical to use high-resolution endoscopy with high-magnification endoscopy over a large mucosal surface area. Therefore, HRE and magnification endoscopy have been combined with the use of chromendoscopy (vital dye staining) in an attempt to improve detection of mucosal abnormalities. Researchers recently reviewed chromendoscopy (vital dye staining with agents such as Lugol's iodine solution, methylene blue, indigo carmine, crystal violet, and acetic acid), for the enhanced detection of the specialized intestinal metaplasia of Barrett's esophagus [7]. Lugol's solution, a 0.5–3.0% aqueous solution of potassium iodide and iodine, has been used to improve the detection and delineation of the squamous cell carcinoma and dysplasia in the aerodigestive tract via absorption by glycogen-containing cells. Lugol's is often used with endoscopy procedures in patients at an increased risk of squamous cell carcinoma (heavy smokers, alcoholics, and prior lye ingestion patients). Methylene blue, 0.1–1.0% solution after mucolysis, is used for the detection of Barrett's esophagus as it is taken up by intestinalized mucosa, but not squamous or gastric mucosa. Methylene blue, indigo carmine, and acetic acid combined with magnification endoscopy have been found to identify mucosal glandular patterns. Guelrud et al. described four pit patterns using acetic acid and magnification endoscopy (round, reticular, villous, and ridged) and found ridged and villous to be associated with intestinal metaplasia [8]. Sharma et al. described three mucosal patterns visualized with indigo carmine in patients with Barrett's esophagus (ridged/villous, circular, and irregular/distorted), with the ridged or villous patterns found to be associated with intestinal metaplasia, while the irregular or distorted pattern was noted with Barrett's high-grade dysplasia or superficial adenocarcinoma [9]. A review of seven prospective and controlled studies using methylene blue-targeted biopsies found a higher yield for the detection of Barrett's disease compared with a random biopsy protocol [8, 10–15]. Sharma et al. studied 80 Barrett's esophagus patients using indigo carmine dye and determined the presence of the ridged or villous pattern which had high sensitivity, specificity, and positive predictive

value (97%, 76%, and 92%, respectively) [9]. The distorted or irregular glandular pattern was also detected in six patients with Barrett's high-grade dysplasia. However, subsequent studies have failed to demonstrate a detection benefit for either Barrett's metaplasia or dysplasia [16, 17]. There has also been a report that raises the issue of DNA damage resulting from methylene blue staining and white light illumination [18]. Similar conflicting results have been found with studies using acetic acid, a mucolytic agent that alters cellular protein structure, and crystal violet staining [19–21]. These initial enthusiastic results have subsequently been found to vary widely, perhaps because of differences in technique, operator experience, and a patient population with the prevalence of Barrett's esophagus [22, 23]. Four expert gastrointestinal endoscopists in Europe analyzed blinded evaluations of magnification chromendoscopy images of Barrett's esophagus, using acetic acid or methylene blue. The interobserver agreement was poor (kappa = 0.40) for all parameters studied including the mucosal patterns, methylene blue positive staining, and the presence of specialized intestinal metaplasia. These inconsistencies, along with safety issues, increased cost, and procedure time, have prevented the widespread use of vital dye-staining chromendoscopy techniques [24].

NARROW BAND IMAGING AND BARRETT'S ESOPHAGUS

Narrow band imaging (NBI) is currently the best studied advanced endoscopic imaging technique for the detection of Barrett's dysplasia. In addition, NBI has received regulatory approval and is a commercially available method of optical chromendoscopy that improves detection of mucosal abnormalities, without the messy, time-consuming problems associated with vital dye-staining chromoendoscopy (Fig. 2). NBI was developed by Gono et al. in 1999 as a joint project of the Japanese National Cancer Center Hospital East and Olympus Corporation (Tokyo, Japan) [25]. Their team of bio-optical physicists studied variations of conventional endoscopy that potentially could visualize early changes of angiogenesis (increased density of microvessels), associated with the development of dysplasia and superficial neoplasia. Using light filters, the contribution of blue light is increased by narrowing the band widths of the red, green, and blue components of the excitation light, reducing the amount of green light, and eliminating the red light. The resulting "narrow band" blue-green light improves imaging of mucosal patterns because of the limited optical scattering and shallow penetration depth. This blue light is also absorbed by hemoglobin [since the

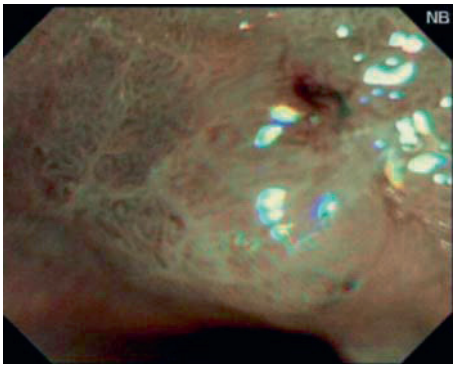

Fig. 2. This view of the same nodule with narrow band imaging allows better appreciation of mucosal glandular and vascular irregularities.

hemoglobin absorption band (Soret band) lies at 415 nm] for optimal detection of mucosal glandular, vascular patterns, and the presence of abnormal blood vessels that are associated with the development of dysplasia [26]. Olympus, Tokyo, Japan, produces two versions of the NBI system. The Evis Exera II system is available in North America, with a high-resolution white light endoscope and narrow band imaging using a color charge-coupled device to detect the reflected red, green, and blue light, with several diminutive band-pass color filters in each pixel for 530–550 nm green light and 390–445 blue light. The Lucera system uses a monochromatic CCD system and is available predominantly in Japan and Europe. Both of these systems feature an electronic switch on the handle of the endoscope to permit rapid switching between high-resolution white light and narrow band imaging modes. While these systems are technically distinct, they are functionally equivalent.

Several single center studies have correlated the appearance of mucosal glandular and vascular patterns with metaplasia. Kara et al. studied magnified images in Barrett's esophagus patients and found that regular mucosal and vascular patterns were associated with intestinal metaplasia, whereas irregular mucosal and vascular patterns and the presence of abnormal blood vessels were associated with Barrett's high-grade dysplasia [27, 28]. These mucosal and vascular patterns have been the basis of a series of studies from several advanced endoscopy centers, demonstrating the utility of NBI in evaluating Barrett's dysplasia patients. Kara et al. compared HRE with indigo carmine chromendoscopy or NBI in 14 patients with Barrett's high-grade dysplasia

(HGD). The aim of the study was to test and compare these combinations for the detection of Barrett's high-grade dysplasia or superficial carcinoma. HRE alone found HGD in 11 patients (79%), while NBI detected it in 12 patients (86%), and indigo carmine chromendoscopy detected it in 13 patients (93%). One patient had HGD that was not detected with any imaging modality, but it was found with random biopsies (7%). NBI found an additional four HGD lesions in three of these 12 patients. The efficacy of both techniques was found to be similar, and NBI was preferred over vital dye staining for its ease of use, although white light resolution endoscopy detected all cases of high-grade dysplasia, suggesting that NBI improved detailed inspection of suspicious lesions, rather than for their primary detection. As a historical comparison, a previous study performed by this group detected HGD in 62% of patients using targeted standard resolution endoscopy (SRE) biopsies, and in 85% of patients with SRE targeted plus random quadrantic biopsies [29, 30]. Anagnostopoulos found similar results in a study of 344 lesions in 50 patients using magnified endoscopic microstructural and vascular features of Barrett's disease. Regular microstructural patterns were associated with sensitivity, specificity, positive, and negative predictive values of 100%, 79%, 94%, and 100%, respectively, for intestinal metaplasia. The sensitivity, specificity, positive, and negative predictive values for patients with high-grade dysplasia was 90%, 100%, 99%, and 100%, respectively [28]. Interestingly, a recent publication from Curvers et al. studied the use of high-resolution endoscopy with vital dye-staining techniques, using acetic acid and indigo carmine as well as NBI, in 14 patients with 22 suspicious lesions, including 8 areas of high grade dysplasia, 1 area of low grade dysplasia, 1 area indefinite for dysplasia, and 12 areas of non-dysplastic Barrett's disease. In a blinded study, seven community and five expert gastrointestinal endoscopists evaluated standard images from these lesions for glandular and vascular patterns, and any association with dysplasia. The yield for detecting dysplasia or neoplasia, with high-resolution white light endoscopy, was 86% overall (90% for experts and 84% for non-experts), and the addition of enhancement techniques (vital dye staining or NBI) did not improve the diagnostic yield [31].

A prospective, blinded, tandem endoscopy study from our group, in press at *Gastroenterology*, compared SRE and HRE-NBI in 65 patients referred for evaluation of Barrett's dysplasia. As commercially available HRE-NBI systems in North America do not have high-magnification capability, the determination of areas suspicious for dysplasia or cancer was made with standard endoscopic techniques, in an attempt to reproduce a realistic clinical practice setting. This study

found that NBI-targeted biopsies found dysplasia in more patients (37 patients, 57%), compared with SRE with targeted plus random biopsies (28 patients, 43%; $p < 0.001$). NBI also found higher grades of dysplasia in 12 patients (18%), compared to zero cases where SRE, with targeted plus random biopsies, detected a high grade of histology (0%; $p < 0.001$). In addition, more biopsies were taken using SRE with targeted plus random biopsies (mean 8.5 biopsies per case), compared with NBI-directed biopsies (mean 4.7 biopsies per case; $p < 0.001$). The ability of HRE, combined with NBI to find dysplasia in significantly more patients with Barrett's esophagus with greater efficiency, using significantly fewer biopsy samples, illustrates the importance of this technology for the surveillance evaluation of Barrett's esophagus patients. Further studies, however, will be required to document this increased efficiency and cost savings for surveillance endoscopy and also to determine the impact of HRE-NBI on the results of endoscopic screening for BE and surveillance programs for dysplasia detection in BE [32, 33].

AUTO-FLUORESCENCE IMAGING, TRI-MODAL IMAGING, AND BARRETT'S ESOPHAGUS

Auto-fluorescence imaging (AFI) is a technique that differentiates tissue types based on their differences in fluorescence emission. When tissues are exposed to short wavelength light, endogenous biological substances (fluorophores) are excited, causing emission of fluorescent light of a longer wavelength (auto-fluorescence). The molecules responsible for tissue auto-fluorescence include collagen, NADH, elastin, flavin, porphyrins, and aromatic amino acids – each with a characteristic excitation and emission spectral pattern. AFI detects differences in the natural, endogenous fluorescence of normal, dysplastic, and neoplastic mucosa using blue light illumination, producing a low-intensity auto-fluorescence that is detected through highly sensitive CCDs, along with reflectance imaging detected through non-intensified CCD [34] (Fig. 3). The image processor incorporates the CCD signals into a real-time pseudo-color image of normal mucosa (green color) and dysplasia or neoplasia (varying tones of red/purple color). Previously, the use of AFI was with fiber optic endoscopes, which provided relatively poor white-light images. Early studies with this limited technology could prove no benefit for the use of AFI over white light endoscopy, including a randomized, crossover study from the Academic Medical Center in Amsterdam [29, 35, 36]. In a single center, uncontrolled study, Kara et al. evaluated using AFI after high-resolution white light

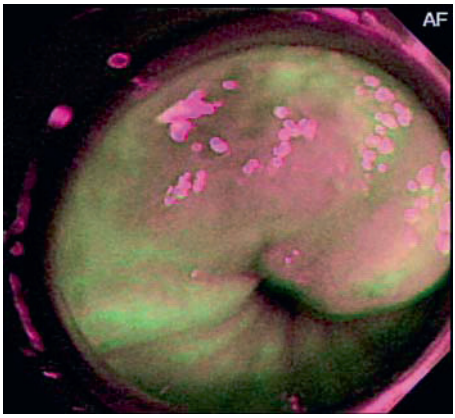

Fig. 3. Endoscopic tri-modal imaging utilizes an imaging system with auto-fluorescence imaging (AFI), high-resolution white light (HRE), and narrow band imaging (NBI). This image visualized a distal esophageal nodule with auto-fluorescence imaging where a pseudo-image is created based on the fluorescence spectrum with the dysplastic mucosa represented in *purple color*, in contrast to the normal mucosa that is *green color*.

endoscopy in 60 patients with Barrett's esophagus. High-grade dysplasia was detected in 22 patients including 6 patients where white light endoscopy did not identify lesions, but were only found with AFI. Therefore, AFI detected a significant number of patients with high-grade dysplasia, who had no visible lesions on high-resolution white light endoscopy, increasing the target detection rate from 63 to 91%. However, the use of AFI was associated with a 51% false positive rate, as 41 of 81 suspicious areas by AFI did not have dysplasia at biopsy. AFI endoscopy, then, offers the promise of wide-area imaging for Barrett's surveillance, but is associated with poor specificity [37].

Subsequently, tri-modal imaging endoscopes have been developed that combine the use of wide-field endoscopic imaging (high-resolution white light endoscopy), a wide-field sensitive method for the detection of dysplasia and carcinoma (so-called "red flag" technique; AFI), and a virtual chromendoscopy technique, to enhance and improve the combined accuracy of these techniques for the detection of mucosal dysplasia and neoplasia (NBI) [38]. Again, the initial single center study came from Bergman's group in Amsterdam where 20 patients were evaluated for 47 suspicious areas found with AFI. Of these 47, 28 were found to be abnormal based on NBI, and subsequently, biopsy confirmed the diagnosis of high-grade dysplasia in each case. However,

14 of 19 areas detected with AFI appeared normal with NBI, thereby reducing the number of false positive lesions from 40 to 10% (of 47 lesions, total). The positive predictive value of AFI alone for Barrett's disease with high-grade dysplasia was only 60%, but it improved to 85% when used in combination with NBI [39]. Curvers et al. published the results using tri-modal imaging in four expert endoscopy imaging centers in Europe and the United States, for the evaluation of 84 patients referred with Barrett's dysplasia [31]. The study outcomes were the number of patients and lesions of HGD detected with HRE and AFI plus the reduction of false positive AFI findings after NBI. The AFI algorithm utilized total auto-fluorescence after blue light illumination and green reflectance. At endoscopy, HRE was first used to examine the Barrett's segment for the presence of esophagitis or visible lesions. Then, AFI was used to identify areas suspicious for the presence of dysplasia (violet-purple pseudo-color). NBI was then used to describe the vascular and mucosal pattern of these suspicious lesions, in order to determine if they were suspicious for the presence of dysplasia or not. Random quadrantic biopsies were obtained after the image-targeted biopsies.

Overall, 30 patients were diagnosed with Barrett's high-grade dysplasia, 16 were detected with HRE, 11 were detected only with AFI, and 3 were diagnosed only by random biopsies. The use of AFI, therefore, increased the number of patients found to have HGD from 53% (16/30 patients) to 90% (27/30 patients). The use of NBI reduced the false positive rate of AFI from 81 to 26%, and the false positive rate of HRE was reduced from 67 to 44%, but mis-classified two lesions that were found to contain HGD. The utility of random quadrantic biopsies in addition to HRE, AFI, and NBI is unknown. Thus far, the published experience with these prototype systems, combining the use of HRE, AFI, and NBI in one endoscope, has come from academic centers with expert endoscopists evaluating a highly selected group of Barrett's patients with dysplasia and carcinoma. The application of this technology has not yet been studied in other practice settings, and these devices have not been approved for use in the United States.

CONFOCAL FLUORESCENT MICROSCOPY AND ENDOCYTOSCOPY FOR BARRETT'S ESOPHAGUS

The development of probe-based and endoscopic devices for real-time, in vivo microscopic imaging of Barrett's mucosa represents another milestone in advanced imaging technology [40]. Confocal microscopy uses blue laser light to stimulate mucosal cells, which reflect back

through a pin-hole opening to eliminate out-of-focus light. Laser scanning with computer generated cross-sectional images permits real-time microscopic imaging of Barrett's mucosa. The miniature confocal microscope, developed by OptiScan with Pentax, Japan, permits magnification beyond 1,000× with cellular and sub-cellular resolution of crypt and cellular architecture to a depth of 250 microns (level of the lamina propria). Improved images, however, require the use of a contrast agent, such as topical acriflavine or intravenous fluorescein sodium, for resolution of cellular structures and microvasculature. Image production tends to be relatively slow, one frame per second, creating lengthy procedure times. Initial studies using this system have reported very high accuracy (85–94%) for the detection of high-grade dysplasia in Barrett's esophagus [41, 42]. However, these results reflect the expert use of this technology in a single referral center. Importantly, this microscopy analysis was performed in patients with visible lesions detected on white light endoscopy. It is unclear if this experience would produce similar results for lesions that were not visible with white light endoscopy, or if this technology could produce similar or significantly better results when compared with tri-modal imaging with HRE, AFI, and NBI.

The second approach to in vivo microscopic imaging involves a small confocal microscope probe developed by Mauna Kea Technologies, France, which can be used with any endoscope to provide real-time endoscopic microscopy to varying depths from 50 to 200 microns [43]. This system features post-procedure image reconstruction for video mosaicing, the combination of dynamic single-frame images into a static, mosaic image over a broad field, without reduction in image resolution [44]. Larger studies from more centers are awaited to determine the role and utility of confocal microendoscopy systems in the evaluation of patients with Barrett's disease.

Endocytoscopy allows visualization of cells and nuclei using high-magnification probes or endoscopes for the detection of dysplasia, neoplasia, inflammation, and infection involving the gut mucosa, with initial reports describing findings in 12 esophageal squamous cell cancer patients [45]. For use in Barrett's disease, this method requires a dye or contrast agent, such as methylene blue or NBI for cellular imaging to evaluate the cell size, shape, and nuclear characteristics. A recent ex vivo study of 166 biopsy sites from 16 patients with 450× and 1,125× magnification, with investigators blinded to endoscopic and histologic findings, found adenocarcinoma 4.2% of biopsy sites, high-grade intraepithelial neoplasia in 16.9% and low-grade intraepithelial neoplasia in 12.1%. However, adequate assessment of endocytoscopy images was not possible in 49% of the target areas at the

450× magnification, and in 22% of the target areas at 1,125× magnification. At most, 23% of images with lower magnification and 41% of higher magnification images could be interpreted in order to identify characteristics of dysplasia and neoplasia. Interobserver agreement was less than fair (kappa from < 0 to 0.45), with positive and negative predictive values for high-grade dysplasia or carcinoma of 0.29 and 0.87, respectively, for 450× magnification and 0.44 and 0.83, respectively, for 1,125× magnification [46]. The real-time, in vivo use of these systems is likely to be limited by image stabilization problems, with motion artifact and image distortion.

SPECTROSCOPY

Optical spectroscopy may provide the means to detect mucosal abnormalities in real-time, using molecular and microstructural information in light–tissue interactions such as fluorescence, reflectance, Elastic scattering, and Raman (inelastic scattering) [47]. The behavior of light provides information about tissue composition, oxygenation, degree of inflammation, and dysplasia for histological-like characterizations of gut mucosa. Different spectroscopic techniques can be used to provide information about tissue biochemistry and oxygenation. However, currently available clinical studies are limited to single center feasibility studies. Reflectance spectroscopy quantitatively measures the color and intensity of reflected light after tissue illumination, to discriminate normal, dysplastic, and neoplastic mucosa. Unlike autofluorescence spectroscopy, this reflected light maintains the same wavelength, although varying degrees of light wavelengths are absorbed and reflected. Hemoglobin is the primary molecule that absorbs light, providing a marker of angiogenesis and dysplasia based on tissue oxygenation. Light scattering spectroscopy is a type of reflectance spectroscopy that studies elastic scattering (light not changed by the tissue interaction). Each wavelength of light is scattered differently depending on the density of the mucosal and cellular structures it encounters. By measuring which light wavelengths are scattered, and which are not, the size and characteristics of the mucosal and cellular structures, such as the size and density of nuclei, may be determined. Since endogenous fluorophores produce weak fluorescence signals, exogenous fluorophores, such as porphyrin compounds, are used to enhance the fluorescence effect. Exogenous fluorophores are thought to be relatively specifically retained in dysplastic and neoplastic tissues, and they exhibit a much higher intensity-induced fluorescence signal. Among different sensitizers, porphyrins have been best studied for application

in fluorescence spectroscopy. Porphyrins are heme products associated with prolonged photosensitivity (porfimer sodium), or other potentially serious adverse events such as nausea and hypotension (aminolevulinic acid). The advantage of drug-induced fluorescence is that the fluorescent signal generated by these exogenous fluorophores is typically stronger than auto-fluorescence and can be detected by simpler and cheaper instruments. Among exogenous fluorophores, 5-aminolevulinic acid (5-ALA) is the best studied photosensitizer that converts intracellularly to the photoactive compound protoporphyrin IX (PPIX). PPIX is associated with a significantly higher tumor selectivity compared to other exogenous fluorophores used in fluorescence imaging [48]. Furthermore, compared to other exogenous fluorophores, skin sensitivity is reduced to 24–48 h, although cardio-vascular side effects including severe hypotension and sudden death have been reported [49, 50]. An issue in the measurement of fluorescence spectra is the background generated by scattering and absorption. In this case, the fluorescence spectra may be analyzed, with information from the corresponding reflectance spectra, to permit subtraction of this background and produce a measure of intrinsic fluorescence [51]. Different fluorophores are excited by different wavelengths of light, and the optimal excitation wavelength for detecting dysplasia is unknown. A significant technical advance in fluorescence spectroscopy was made with the development of a fast multiexcitation system, capable of rapid tissue excitation with up to 11 different wavelengths, providing information to optical probes and allowing collection of many different fluorescence spectra for the determination of the optimal excitation wavelength [51, 52]. In addition to specific excitation and emission wavelengths, different fluorophores fade or decay their fluorescence at different rates. This difference between normal and abnormal tissue can be enhanced by measuring stimulated fluorescence at different intervals. This technique, termed "time-resolved fluorescence," has been used to increase the accuracy of dysplasia detection in patients with Barrett's esophagus [53].

Light propagation in tissue is governed by scattering and absorption. Light-scattering spectroscopy measures the extent to which the angular path of photons of light is altered by the size and number of cellular components (scatterers) they encounter. The primary scatterers are collagen fibers in the extracellular matrix, mitochondria, cellular nuclei, and other intracellular structures. By mathematical modeling, the number, size, and optical density of cellular structures (such as nuclei), can be determined by measuring the diffuse reflected light from epithelial surfaces [54]. This phenomenon has been exploited during endoscopic procedures to determine the number of nuclei, the size of

nuclei, and the degree of crowding of nuclei in patients with dysplastic changes in Barrett's esophagus [55, 56]. These studies have demonstrated that light scattering can accurately determine nuclear size, detect abnormally enlarged nuclei, as well as characterizing different grades of dysplasia, with less interobserver variability than routine pathology. Unlike fluorescence, light scattering spectroscopy uses a broad range of light to detect changes over the entire visible spectrum. Reflectance spectroscopy, laser-induced auto-fluorescence spectroscopy, and light scattering spectroscopy provide quantitative information to characterize either biochemical or morphological aspects of tissue, which can be significantly altered during the development of neoplasia. This improves the distinction of dysplastic and normal tissue by combining the information provided by each of the spectroscopic techniques, which are obtained simultaneously with tri-modal spectroscopy.

Raman spectroscopy detects scattered light that has been slightly shifted in wavelength (inelastic scattering), resulting from energy transfer between light and mucosa molecules. These shifts correspond to specific vibrations of molecular bonds. Since some of the light energy is transferred to the molecule in this process, the light emitted back from the tissue is reduced in energy and has a longer wavelength. Raman spectra consist of multiple peaks and bands that may produce detailed tissue characterization. However, this Raman signal is very weak, and near-infrared light is typically used for excitation and sophisticated detection instruments, and signal processing computers are required. Raman spectroscopy has recently been applied to the detection of Barrett's associated dysplasia with promising results [57, 58].

Panjehpour et al. studied laser-induced auto-fluorescence, using a wavelength of 410 nm to distinguish normal esophageal mucosa from dysplastic and malignant tissue, with high accuracy [59]. Using a different spectral analysis technique, Von-Dinh et al. was also able to detect esophageal carcinoma with a high-degree of reliability [60]. The same group of investigators found laser-induced auto-fluorescence spectroscopy to be sensitive for the detection of diffuse high-grade dysplasia (HGD) in Barrett's esophagus and adenocarcinoma. However, only 28% of the specimens with low-grade dysplasia (LGD) and focal HGD were classified as abnormal by this technique [61]. Mayinger et al. used a filtered ultraviolet blue light source and showed specific differences in the emitted auto-fluorescence spectra of esophageal carcinoma with normal mucosa [62]. In another study, Bourg-Heckly et al. demonstrated the ability of light-induced auto-fluorescence to identify HGD in Barrett's esophagus and early cancer, and reported a sensitivity and specificity of 86 and 95%, respectively [63]. Curiously, this technique could not distinguish non-dysplastic Barrett's mucosa and squamous

mucosa. Some authors used exogenous fluorophores to enhance the spectroscopic characteristics of dysplastic and neoplastic tissues. Stael von Holstein et al. demonstrated the feasibility of laser-induced fluorescence measurements, using the photosensitizer porfimer sodium (Photofrin; Axcan, Mont St. Hilaire, Quebec, Canada), to distinguish normal and malignant tissue in an in vitro study of esophagectomy specimens [64]. Brand et al. performed a similar study, using the oral photosensitizer 5-aminolevulinic acid (5-ALA), that found a sensitivity of 77% and specificity of 71% [65]. Ortner et al. combined time-resolved fluorescence spectroscopy and topical application of 5-ALA to enhance the spectroscopic characteristics of dysplastic Barrett's esophagus [53]. Light-scattering spectroscopy and tri-modal spectroscopy are novel techniques and few data are available. Perelman et al. described the use of light-scattering spectroscopy (LSS) to determine the size distribution of epithelial cell nuclei in vitro and in vivo, and Wallace et al. reported a prospective validation study of LSS to identify dysplasia in a cohort of patients with Barrett's esophagus [54–56]. The sensitivity and specificity of LSS for detecting dysplasia (either LGD or HGD) were 90 and 90%, respectively, with all HGD and 87% of LGD sites correctly classified. In a tandem study, Georgakoudi et al. found the combination of laser-induced auto-fluorescence, reflectance and LSS, used together, referred to as tri-modal spectroscopy, resulted in improved sensitivity and specificity for the distinction of high-grade dysplasia versus non-high-grade dysplasia in Barrett's esophagus (100 and 100%), and dysplastic versus non-dysplastic Barrett's esophagus (93 and 100%) [51]. Despite the relatively promising results reported in many of these feasibility studies, continued improvement in these detection and signal processing devices will be required to justify the time and expense associated with the large clinical trials, which ultimately will be required for assessment, validation, regulatory approval, and commercial production. Furthermore, each of these spectroscopy techniques is limited to a small point of tissue, similar in size to a biopsy. Thus, they cannot survey large areas of tissue such as Barrett's, and will need to be combined with broad field, "red-flag" techniques.

OPTICAL COHERENCE TOMOGRAPHY (OCT)

OCT uses short coherence length broadband light for micrometer-sized cross-sectional imaging of the gut mucosa, making it similar to an endoscopic ultrasound, except using light instead of sound [66]. First used in 1997, time domain OCT systems had limited image speed and sensitivity [67]. Recently, the development of Fourier domain OCT has provided much greater imaging speed, sensitivity, and potential to perform

three-dimensional imaging in real-time. The limited development of the image detection devices (scanning probes) has made clinical application cumbersome and impractical, thus far [68, 69].

CONCLUSIONS AND THE FUTURE OF IMAGING FOR BARRETT'S ESOPHAGUS

This chapter has reviewed recent developments in endoscopy-based imaging for the detection of Barrett's disease, as well as dysplasia and neoplasia in patients with Barrett's esophagus. Presently, some of these technologies have already achieved regulatory approval, commercial availability, establishment of clinical utility, and practical application (albeit in academic referral endoscopy centers). Important examples include high-resolution white light endoscopy (HRE) and narrow band imaging (NBI). Validation studies are on-going for use of the endoscopic tri-modal imaging system that combines wide-field detection capabilities of HRE and auto-fluorescence imaging (AFI), with improved sensitivity (and reduced numbers of false positive results) with NBI. Regulatory approval for the use of the combination systems has already been granted in Europe and approval in America is expected in the near term.

The use of endomicroscopy and spectroscopy techniques, especially endoscopic laser confocal microscopy, are being aggressively studied as the most clinically advanced spectroscopic method of "optical biopsy" currently available in commercial systems. Longer term, the future of imaging for Barrett's disease likely rests with the development of molecular targeting with dysplasia-targeted probes (such as monoclonal antibodies) that have been conjugated to dyes or nanoparticles (such as quantum dots or Q dots). These sensitive and specific devices will serve as diagnostic molecular beacons, as well as a delivery system for therapeutic agents [47]. Several important issues are unresolved, including regulatory approval, demonstration of clinical utility, securing additional reimbursement for the required procedure time, and imaging equipment, as well clarifying the medical and liability issues associated with the interpretation and storage of these images.

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Argon Plasma Coagulation in Barrett's Esophagus: The Most Widely Available Technique

Stephen E. Attwood, MD, FRCSI and Suvadip Chatterjee, MB, MRCP

CONTENTS

Summary

Argon plasma coagulation (APC) is the most widely available technique for ablation of Barrett's esophagus. When the argon plasma is applied, thermal injury to the epithelium results. The depth of injury is the function of the voltage, the gas flow, and the pressure applied to the probe. A series of 32 patients with high-grade dysplasia were treated with APC with 34 months of follow-up. Dysplasia

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reversed in 78% of patients and cancer prevented in 87%. APC has been used as a primary form of therapy for early invasive cancer, as adjunct to other therapy such as endoscopic mucosal resection.

Key Words: Argon plasma coagulation, High-grade dysplasia, Esophageal, Adenocarcinoma

INTRODUCTION

Argon beam plasma coagulation (ABPC) consists of a high-frequency monopolar probe that delivers electrical energy through an ionized plasma of argon gas to the target tissue causing tissue surface coagulation [1]. The technology of plasma coagulation using argon relies on the physical principle that argon gas (like other gases) can be charged with electrons and the gas particles can carry that charge through the air and release the charge at the point of contact with a conducting surface (see Fig. 1). As a consequence, the resulting flow of electricity has some special and useful properties for use in medical applications. ABPC can be used in open surgery [2] laparoscopic surgery and at flexible endoscopy [3, 4]. For each application there is a dedicated applicator, and for endoscopy this is a flexible tube (carrying the argon gas) with a ceramic tip (for charging the gas molecules with electrons). The fundamental difference between ordinary electrical current and that which flows from argon plasma is the way in which the electrons travel. In a copper-conducting wire electrons flow from one metal atom to another at the speed of light and the amount of electricity that can be transmitted is huge. In a gas plasma the amount of electricity that can be transmitted is limited by the number of gas particles that are traveling across the gap between application and tissue surface, with one electron being delivered for each gas particle. The transfer of electricity can be increased by increasing the gas flow or by increasing the charge up to a point where 100% of the gas molecules are charged. In endoscopic practice argon is delivered between 2 and 6 l/min and the charge ranges from 20 to 80 W of energy [5–7]. As with all electrosurgical techniques an electrical plate is required on the patient to complete the electrical circuit. The application is contact free – with the probe carrying the argon being placed 1–3 mm off the surface of the tissue to be ablated (see Figs. 2 and 3).

An interesting effect of the limited electrical charge carried is the effect of tissue resistance. Once the surface of the tissue has been charred and dries it becomes resistant to the flow of current. The argon gas molecule then holds its electron until it finds a new area of conducting tissue – usually the tissue adjacent to the first area of ablation. The effect then of prolonged application is to widen the surface area of

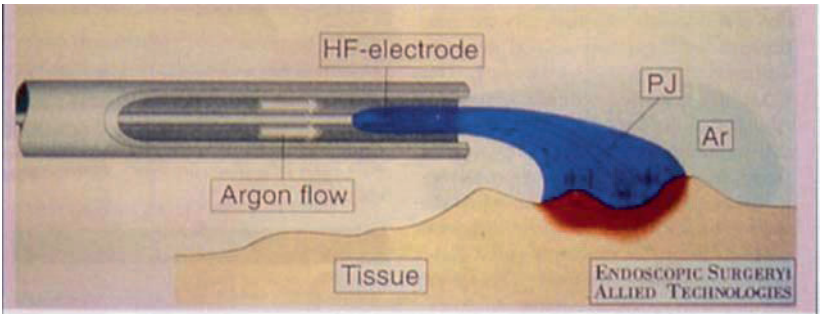

Fig. 1. Physics of the argon beam plasma coagulator.

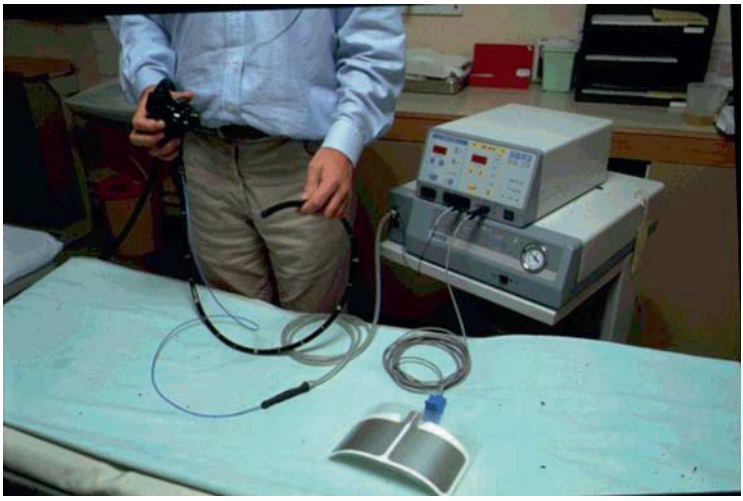

Fig. 2. The endoscopic technology for applying ABPC includes a standard endoscope, a delivery tube for the argon, a diathermy machine with pump, and completion of the electrical circuit with an electrical plate.

injury or ablation, and not to deepen it. The initial depth depends on the current (which depends on the gas flow and wattage) but not the time of application. The longer the application the wider the surface area of injury and this makes argon plasma beams useful for wide surface area ablation as would be required for Barrett's esophagus. When applied in Barrett's esophagus, ABPC generates a white coagulum and is best applied using the technique of endoscope withdrawal while applying the argon which results in longitudinal strips of ablation [8]. (see Fig. 4)

Some workers consider the depth of injury to be less predictable than alternative modalities of ablation. Ackroyd et al. looked at the depth of

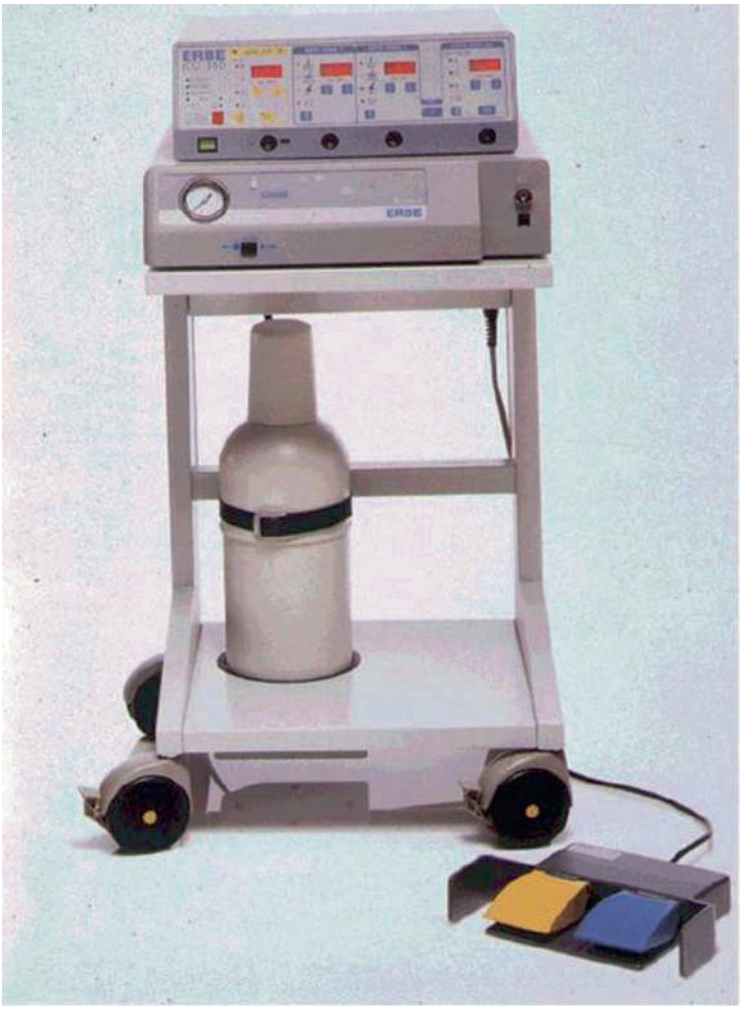

Fig. 3. ERBE diathermy with argon gas delivery system.

injury and considered the depth of injury to be 75 mm in their hands [9]. Deeper tissue ablations can be achieved using higher degrees of wattage, and using forced current or the new APC-2 development. The amount of pressure applied to the ABPC probe by the endoscopist can also affect the depth of injury. The problem with insufficient depth in the circumstance of Barrett's ablation has been the concern about the remnant glands that might grow underneath the new squamous lining that grows in place of the ablated Barrett's. In our center all patients grew a macroscopically normal-looking squamous mucosa after 3–6 weeks

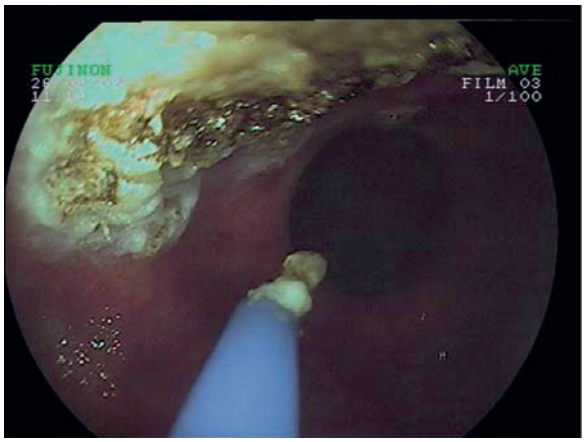

Fig. 4. Appearance of ablated mucosa after ABPC.

and areas of endoscopic gaps could easily be filled in by repeat treatments. On microscopy the squamous epithelium looked normal except for the presence of scattered buried glands of intestinal metaplasia seen in a significant proportion (30%) of the patients. Whether these glands represent a risk for cancer is very difficult to assess and this has not occurred in our series. The progression to cancer after argon beam ablation has been reported [10] where a focus of adenocarcinoma has grown underneath the surface squamous epithelium.

In clinical circumstances where deeper tissue debulking is required – as with tumors of the esophagus or stomach requiring debulking to allow the passage of food, or in the case of stents blocked by ingrowths of tumor, or tumor growing below or above the margins of stent then the electrical properties of the tissue can be manipulated by wetting the surface after each ablation using a saline wash and this allows a repeat application of devitalizing current which will penetrate deeper into the tissue. Argon is easy to use in this situation up to 1-cm deep to the original surface and is therefore an effective way of dealing with some circumstances of obstructing upper gastro-intestinal malignancy. In practice stents are more effective in first-line treatment of dysphagia palliation rather than using the argon beam de novo.

The reduced risk of deep injury makes the complication of stricture very rare, (compared to some other technologies such as PDT) and perforation is also very rare. The technology is relatively easy to apply and there are no special precautions above those usually applied for any electrosurgical technique. No special laser eye protection is needed. The availability of argon is wide and the gas relatively cheap. The appli-

cation is usually performed with a sedated patient to allow prolonged endoscopic operating times relative to a simple diagnostic endoscopy but there is no absolute need for sedation or anesthesia because the patient is not usually aware of the ablating burn (Table 1).

Table 1
The advantages of the physical properties of argon beam plasma coagulation

- Requires no special operator precautions (in contrast to laser)
- Useful after EMR to stop bleeding from the underlying submucosa as well as dealing with the surface epithelium adjacent to the excised mucosal specimen
- Deep injury to muscle layers does not occur and strictures very uncommon
- Widely available in operating rooms and endoscopy rooms as it is used for other purposes
- Relatively cheap to set up

The application of argon beam achieves a number of other surgical aims. It is useful for tissue devitalization as in Barrett's epithelium, gastric antral vascular ectasia (GAVE) syndrome, and postpolypectomy therapy. It is also useful for hemostasis of peptic ulcer bleeding [11], angiodysplasia, radiation proctitis, and bleeding after polypectomy.

Sensation of argon ablation: Argon beam ablation is remarkably comfortable from the patient's perspective. Eickhoff et al. have described the lack of direct pain effect with argon in their prospective assessment of the pain sensation in 152 applications [12]. The only exception is in the distal anal canal where skin sensors do pick up pain from argon application. The esophagus does not transmit pain sensation during argon therapy. Indirectly the distension of the stomach (or the colon) creates abdominal tension, pain on breathing, and tachycardia but this is minimized by venting the argon gas – achieved either by a naso-gastric tube placed to vent the gas, or by using a double lumen endoscope and sucking out the gas immediately after filling the organ with argon. If a single channel scope is used the operator must remove the applicator probe from the working channel of the scope to allow the suction the release the accumulated gas. Some patients belch the gas spontaneously but it is more comfortable to releasing it for the patient (using a double lumen scope and suction) before this stage to ensure their comfort. Occasionally, retrosternal pain has occurred after Barrett's ablation [13–15] and this posttreatment discomfort responds to simple analgesics, supplementing the acid suppression with proton

pump inhibitors (PPI) which is essential in patients having ablation of Barrett's esophagus.

There have been occasional reports of Neuromuscular Stimulation (NMS) with argon gas and this was seen in 10% of patients by Eikhoff et al. [12], usually mild in nature but occasionally manifesting as a feeling of tingling or electrical shock as the muscle involved contracts involuntarily. As a result of the minimal effect on comfort we have used argon with simple midazolam sedation which usually allows a patient to remain relaxed for up to 15 or 20 min of application. For wider surface areas of Barrett's epithelium this allows time to deal with up to 5 cm of esophageal length at one sitting (Table 2).

Table 2
Potential complications of argon beam plasma coagulation

1.	Subcutaneous emphysema
2.	Neuromuscular Stimulation
3.	Vagal symptoms
4.	Stricture
5.	Bleeding
6.	Fever
7.	Fistula
8.	Perforation

Complications of ABPC include strictures, fever, bleeding, or even more rarely perforation, with one death reported in the literature. Perforation and strictures were associated early during the pilot studies and at the beginning of the learning curve. Strictures were also associated with higher powers of ABPC settings and needed balloon dilatations. Blood transfusion was needed only in one setting due to delayed detachment of a scar tissue. One study reported the presence of pleural effusions and fever which might be related to micro-perforations [14, 16].

TREATMENT OF BARRETT'S ESOPHAGUS WITH ARGON PLASMA COAGULATION

The clinical value of using argon beam ablation was initially assessed in a pilot study of patients with Barrett's esophagus. In 1997, we published a pilot study on the restoration of the normal squamous lining in Barrett's esophagus by ABPC [17]. This study aimed to establish the feasibility of ABPC, in conjunction with control of gastro-esophageal

reflux, to restore a squamous lining. Thirty patients (18 men and 12 women), median age 59 years were recruited. The median length of the Barrett's segment was 5 cm (range 3–17 cm). Control of gastro-esophageal reflux was achieved with antireflux surgery in 5 patients, proton pump inhibitors at standard dose in 20 patients and double dose in 5 patients. A total of 88 ABPC procedures were performed. Twenty-seven patients completed treatment with ABPC. One had to discontinue treatment due to excess co-morbidities (rheumatoid arthritis, chronic respiratory disease). All patients had a reduction in the length of columnar mucosa to <3 cm. Sixteen patients did not have any evidence of macroscopic intestinal metaplasia, nine had a 1-cm segment and two patients who originally had 10- and 17-cm segments had only 2-cm segments. When reflux was controlled adequately a reduction in length of 2–3 cm per treatment session was achieved. All 27 patients who had been followed up for a median of 7 months had histological confirmation of replacement of the columnar lining by squamous epithelium. No underlying intestinal metaplasia was seen in 70% of the patients. In 30% of the patients, squamous epithelium was seen to overlie persistent intestinal type glands. The two patients with high-grade dysplasia (HGD) had histologically confirmed replacement with normal squamous lining with no recurrence of Barrett's either microscopically or macroscopically after 1-year follow-up. Neither of these patients had underlying glandular epithelium beneath the squamous epithelium.

The medium-term follow-up of this pilot study looked at the outcomes after a median of just over 3 years [18]. Fifty-five patients with ablated long-segment BE (more than 3 cm) were followed up for a mean of 38 months. Patients with HGD and low-grade dysplasia (LGD) were included. All patients with dysplasia underwent thorough endoscopic biopsy before ablation to exclude invasive adenocarcinoma and the diagnosis of HGD was confirmed by a second pathologist. Nine patients had LGD, nine others had HGD, and the remainder had metaplasia only. Twelve patients had reflux control by antireflux surgery and the remaining patients had maintenance PPI therapy. No adenocarcinomas developed in any of the patients following ablation. No patient with initial benign metaplasia progressed to dysplasia. All patients with initial dysplasia who completed treatment with ablation therapy had regression of the dysplasia with no subsequent recurrence.

The mean length of the Barrett's epithelium in this series before ablation was 6 cm. Barrett's epithelium was ablated to within 1 cm of the GE junction in all but four patients (mean reduction in length of Barrett's was 5 cm). The mean number of treatment sessions required was three. Sixteen (30%) of the 53 patients have had areas of intestinal metaplasia

detected beneath the neosquamous epithelium on routine histological examination of the biopsies taken form the ablated epithelium.

Two patients had esophageal perforation. Both patients had mediastinal emphysema and chest pain associated with a tachycardia immediately after ABPC treatment. The first underwent drainage via a thoracotomy but died from respiratory failure shortly afterwards. This patient had chronic obstructive airways disease and severe respiratory failure before the procedure, had high-grade dysplasia and would not have been fit for esophagectomy. The second one was treated conservatively with parenteral nutrition and kept nil-by-mouth for 5 days and made an uneventful recovery. The latter patient showed a regrowth of squamous mucosa to within 1 cm of the gastro-esophageal junction. One further patient required readmission to hospital with chest pain following the initial treatment. From these studies we concluded that ABPC was an effective method of ablating wide areas of Barrett's epithelium, with a long-lasting effect at restoring a new squamous lining that persisted as long as effective antireflux therapy was administered. The studies were too small to identify a benefit in relation to cancer prevention.

TREATMENT OF HIGH-GRADE DYSPLASIA IN BARRETT'S WITH ARGON PLASMA COAGULATION

The potential value of ABPC in preventing cancer is easier to measure in a group where the risk of acquiring cancer is much higher than in benign Barrett's. Patients with high-grade dysplasia are either likely to have invasive cancer in up to 50% (if nodularity is present) or develop invasive cancer at a cumulative rate of 10% per annum. This is an ideal group to assess if ABPC confers clinical benefit, especially in patients who are unfit for esophagectomy, or who do not want to submit themselves to this major surgery until invasive cancer has been diagnosed. The study of Van Laethem [10] examined 10 patients (7 men and 3 women) with HGD or in situ adenocarcinoma associated with BE with a mean segment length 5.8 $\pm$ 2.7 cm (range 3–12) who were unfit for surgery because of general contraindications or age ($n = 8$) or had clearly refused surgical intervention ($n = 2$) in the period between 1996 and 1999.

Complete eradication of HGD and in situ adenocarcinoma was achieved in 8 out of the 10 patients after a mean of 3.3 $\pm$ 1.5 sessions of ABPC. EUS staging in all patients categorized all patients as stage T0N0. One stricture with significant dysphagia occurred after two sessions of ABPC and required balloon dilatation. At endoscopy there were neither visible lesions nor residual Barrett's islands. Complete

histologically confirmed neosquamous re-epethelization was, however, observed in 5/10 patients (50%) only because of residual metaplastic but not dysplastic glands under the new squamous layer. HGD or tumor-in situ areas were completely eradicated in 8/10 patients (80%). One patient with initial HGD showed only partial regression of his lesion, with HGD persisting even 30 months after ABPC treatment; EUS and CT Chest did not reveal any invasive neoplasia. No additional therapy was proposed and the patient was thought to have stable disease. One patient showed a regression from HGD to LGD but a local recurrence consisting of invasive carcinoma was observed after only 3 months of endotherapy, suggesting that the initial staging was probably underestimated. Surgery was again rejected because of this patient's general condition. Additional therapy consisted of PDT but without successful ablation of the neoplastic lesion and the patient died 2 years later from neoplastic disease.

This study demonstrated that ABPC was effective in patients with HGD and superficial adenocarcinoma only in the absence of recognized mucosal lesions i.e., mucosal thickening or nodules, in the absence of abnormalities detected under EUS and in the absence of invasion of muscularis mucosae on biopsy.

The largest series of HGD treated by ABPC comes from Lewis et al. [19] Thirty-two patients with a histological diagnosis of HGD over a 7-year period. All patients underwent ABPC with an ERBE "Beamer 2" electro-surgery unit set at a 2 l/min gas flow and 70 W output. Repeat endoscopies with further ablative therapies were performed at 4- to 8-week intervals. Completion of treatment was regarded when ablation of the total area of HGD was achieved with no histological evidence of HGD on subsequent biopsy. All patients were taking acid suppression using proton pump inhibitors and were followed up with regular gastroscopies at 3, 6, and 12 months postprocedure.

After a mean follow-up period of 34 months (range 3–78 months) with eight patients at 5 years; HGD was seen to resolve in 25 patients (78%) and 22 of these had complete regression of dysplasia to neosquamous esophageal mucosa. Two persisted with HGD and one with LGD after 1 year of follow-up following commencement of treatment. Four patients (13%) progressed on to developing adenocarcinoma in a total follow-up time of 92 patient years. One patient died of an unrelated cause, while the other three continued ABPC treatment to their cancer, one of which had no residual lesion on follow-up endoscopy and biopsy. Three patients went on to subsequent esophageal resection of persistent HGD with good survival. No patients died of esophageal cancer. (see Fig. 5)

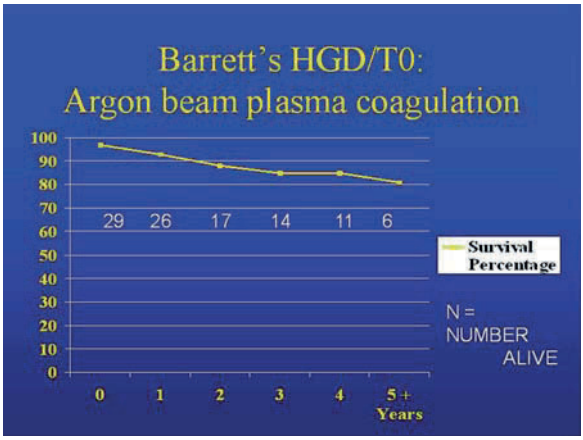

Fig. 5. Kaplan Meyer survival curve after argon beam ablation of patients with high-grade dysplasia in Barrett's esophagus.

The total number of ABPC procedures in this group was 105, with a median of two treatments per patient (range 1–13). Normal diet was restored at 24 h in all patients without dysphagia or odynophagia. No other patients required re-admission, opiate analgesia, or overnight stay. The follow-up data was analyzed and a Kaplan Meyer survival estimate calculated with 95% confidence interval (CI). A further survival curve was created and compared to the standard UK population of comparable age. The Kaplan Meyer survival curve showed that the survival of patients was comparable to the standard United Kingdom population of a similar age over the long term. As a result of this study we consider that ABPC is a safe an effective treatment for HGD in BE (Fig. 4).

A similar series of patients was treated by Ell et al. who described a series of 120 patients in whom the treatment offered initial was endoscopic mucosal resection (EMR) for early cancer or HGD, complemented by argon beam coagulation [20]. Ell discovered cancer progression in 14% of the patients after a mean follow-up of 12 months, compared to 13% after a mean period of 34-month follow-up in the study by Lewis et al. [19]. The morbidity was the same. This demonstrates that in comparison to EMR, ABPC is a realistic procedure that should be considered in patients with HGD who are of questionable fitness for surgery. The main advantage of EMR initially is the ability to examine the pathology in detail. If the patient is fit for surgical resection then this is a useful strategy. If not then simple ablation may be easier and more cost-effective.

TREATMENT OF CANCER IN BARRETT'S WITH ARGON PLASMA COAGULATION

ABPC therapy has significant value in the palliative treatment of invasive adenocarcinoma in patients unfit for resection [21]. ABPC was used in 16 patients with localized tumors who were deemed unfit for surgical resection and achieved a cure in a majority of these, who would otherwise have been left to have progressive cancer without specific therapy. ABPC was also used in the palliation of 18 patients with advanced esophago-gastric cancers for bleeding, obstruction and to prevent obstruction and as well as another 14 patients with dysphagia due to stent overgrowth. Data from these patients were collected prospectively. A total of 110 sessions of ABPC were performed for esophageal and gastric cancer. All 16 patients with early localized cancers were alive, and four at the end of a follow-up period of 21 months were disease free. Four patients, three gastric and one esophageal, had no endoscopic recurrence after the first treatment at 20, 24, 29, and 42 months, respectively. In these patients no histological evidence of tumor recurrence was obtained even after aggressive searching. Seven patients who had biopsy proven residual or recurrent disease after the first ABPC treatment required two to five treatments. Despite these persistent or recurrent tumors, all of them have remained asymptomatic. Three patients with localized carcinoma arising in Barrett's mucosa received more than five treatments. These patients were asymptomatic at 26, 30 and 32 months respectively since the start of treatment. Eighteen patients with advanced cancer underwent a median of one treatment and had a median survival of 5 months after treatment initiation. Eight patients with esophageal cancer had minimal initial dysphagia; local tumor control meant that they did not require stent insertion till late in their disease. In one of these patients with dysphagia and a short stricture ABPC was successful. Luminal patency was not restored in the other two cases and stenting was required shortly after the procedure. Complete control of bleeding was obtained in three of five bleeding gastric cancers, with partial response in the other two, both of whom died within 6 weeks. Two patients with impending gastric outlet obstruction were managed successfully by endoscopic ablation/coagulation and did not obstruct. In 13 of the 14 patients with esophageal stents, ABPC treatment was successful in controlling over- and undergrowth as well as tumor ingrowth through the stent wall. In all these patients, stent patency was restored during the first treatment. Three patients required a second treatment, and one patient required insertion of a second stent. ABPC contributed to the management of 10% of patients with esophago-gastric malignancy managed

in our unit. The reason for such a small proportion of patients to be treated by ABPC is that palliative surgery is the treatment of choice for advanced gastric cancers and stenting is used for dysphagia in advanced esophageal cancer and palliative chemotherapy is an option in a small group of them.

Early cancers in the unfit were the most encouraging to treat in this study since we avoided a major resection and achieved an apparent "cure" in 4 of 14 patients, while the rest of the group remains asymptomatic. Photodynamic therapy [22] and EMR [23] have also been described in the management of early esophago-gastric malignancy, with encouraging initial results for both modalities. However, photodynamic therapy is associated with stricture formation in up to one-third of patients, severe stricture is seen in approximately 10% and photosensitivity occurred for up to 1 month after the procedure. Variable results were obtained with ABPC in patients with advanced cancer. It was useful adjunct in all stented patients with dysphagia due to tumor ingrowth/overgrowth. ABPC also controlled bleeding from tumor, as measured by the requirement for further transfusion in three of five cases; it also controlled it partially in a further two cases. Like Robertson et al. [24] we have found ABPC effective in restoring the esophageal lumen in patients with obstructed stents, although laser therapy has also shown to be effective [25]. Even though occasionally it took 30 min to ablate the diffuse infiltration of the tumor through the wall of the stent, we were able to perform all of the procedures under sedation.

COMPARISONS OF ARGON PLASMA COAGULATION WITH OTHER ABLATIVE TECHNOLOGIES

Argon Versus Multipolar Electro Coagulation (MPEC)

MPEC probes deliver thermal energy through the operator channel of the endoscope and is readily available and inexpensive. It requires multiple treatment sessions to achieve success and seems to be associated with a higher frequency of dysphagia after Barrett's ablation. Kovacs et al. reported an 80% reversal of BE in 27 patients treated via MPEC on PPI; however, 4 had remaining islands with the appearance of BE [26]. Forty-one percent of patients on this study experienced dysphagia, odynophagia, or chest pain lasting up to 4 days. In addition, the success of ablation decreased significantly once the length of BE exceeded 4 cm, such that only 25% had eradication at this length or longer.

Dulai et al. [27] compared argon plasma coagulation with multipolar electrocoagulation for ablation of BE [27]. The selected 52 patients

were randomized. The mean length of Barrett's esophagus was 3.1 cm in the MPEC group versus 4.0 cm in the APC group ($p = 0.03$). The mean number of treatment sessions required for endoscopic ablation was 2.9 for MPEC versus 3.8 for APC ($p = 0.04$) in an intention-to-treat analysis ($p = 0.249$, after adjustment for the difference in length of Barrett's esophagus). The proportion of patients in which ablation was endoscopically achieved proximal to the gastro-esophageal junction was 88% for the MPEC group versus 81% for the APC group ($p = 0.68$) and histologically achieved in 81% for MPEC versus 65% for APC ($p = 0.21$). The mean time required for the first treatment session was 6 min with MPEC versus 10 min with APC ($p = 0.01$) in per protocol analysis. There was no serious adverse event, but transient moderate to severe upper-GI symptoms occurred after MPEC in 8% versus 13% after APC ($p = 0.64$). The study concluded that there were no statistically significant differences between ablation of Barrett's esophagus with pantoprazole and MPEC and endoscopic and histologic ablation with pantoprazole and APC.

Argon Versus Laser

Various lasers have been used in gastroenterology for mucosal ablation, including the neodymium (Nd):yttrium-aluminum-garnet (YAG) laser, the potassium titanyl phosphate (KTP) laser, the KTP:YAG laser, and the argon laser. The ablative depth of injury depends on the type of laser and is about 3–4 mm with the Nd:YAG laser [28, 29]. In 1999, Gossner et al. treated 10 patients with BE, of which 4 had HGD. This group described a "complete response" in all patients, with a mean follow-up of 10.6 months. Subsquamous SIM (specialized intraepithelial neoplasia) was reported in 20% although no other complications were documented. The longest outcome after Barrett's ablation comes from the laser ablations of Salo, in Finland who has demonstrated a long-lasting effect of ablation in restoring a squamous lining to the lower esophagus of patient with Barrett's esophagus [30, 31]. The esophageal stricture rate is higher than with MPEC [32] and thus significantly higher than with argon. The special precautions required for laser, the higher stricture rate and the learning curve for application make laser an unlikely long-term modality for the future ablation of Barrett's esopahgus.

Argon Versus Photodynamic Therapy

The administration of a chemical photosensitizer gives PDT its effectiveness while at the same time causing sufficient side effect to make PDT unlikely to be the surviving technology of choice for ablation

of Barrett's. The accumulation of protoporphyrin in the stroma causes significant stricturing effect in the submucosal layers after laser light application [33]. The only approved photosensitizer in North America, Europe, and Japan is porfimer sodium (Photofrin® [Axcan Pharma Inc, Birmingham, AL]). Photofrin® is given intravenously, results in deep injury and is associated with significant morbidity [34]. The drug remains in the skin for up to 2 months and can result in severe sunburn if standard sunlight precautions are not observed. Alternative topical chemical sensitizers such as 5-aminolevulinic acid, m-tetra (hydroxyphenyl) chlorine and benzoporphyrin derivative monoacid ring. A result in more-superficial injury and because of their lack of deep penetration are unlikely to be effective against high-grade dysplasia [35].

Overholt et al. [22] have published extensively regarding their experience of using PDT in 103 patients, most of whom had HGD. The mean follow-up in this group is over 4 years. Of the 65 patients with HGD, 78% had their HGD eliminated. On the basis of an intention-to-treat analysis, 54% had no residual BE. This is very similar in percentage terms to the outcome of the 50 patients treated with argon beam by Lewis et al. [19]. The overall stricture rate for patients treated with PDT was 30%, but for those who required more than one PDT treatment it was 50%. Other side effects reported with PDT include chest pain, dysphagia, odynophagia, pleural effusions, and atrial fibrillation [22]. Subsquamous, nondysplastic SIM occurred in 4.9% of patients, but more importantly 3 patients (4.6%) developed subsquamous adenocarcinoma. The occurrence of subsquamous SIM is reported in virtually all studies using PDT: in detailed pathology studies the prevalence is reported to be as high as 51.5% [36].

Argon Versus Endoscopic Mucosal Resection or Mucosectomy

It is most likely that the use of argon in the future will be to complement the use of endoscopic muosal resection rather than compete with it. Endoscopic mucosal resection (EMR) or more correctly Endoscopic Resection (ER), removes mucosa and submucosa by resecting through the middle or deeper part of the submucosa. Unlike the other ablative techniques, a tissue specimen is obtained that can be evaluated for staging and histology. Ell et al. prospectively evaluated the role of EMR in 64 patients with BE: 61 with early cancer and 3 with HGD. The patients were divided into two groups. Group A had lesions $\leq$2 cm or macroscopic type I, IIA, IIB, IIC lesions $\leq$1 cm; well-differentiated or moderately differentiated adenocarcinoma or HGD; and lesions limited to the mucosa. Group B had lesions $>$2 cm limited to the

mucosa and/or macroscopically type III lesions; poorly differentiated adenocarcinoma; or infiltration of the submucosa. All patients were treated with an intravenous PPI infusion for 48 h. Complete local remission was achieved in 97% of the patients in group A and in 59% of those in group B. Recurrent metachronous carcinomas occurred in 17% of patients in group A and 14% of patients in group B during a mean follow-up of 12 months [20].

Seewald et al. described ablation of BE in 12 patients after circumferential EMR. Five patients had multifocal lesions and seven had none. The median number of EMR sessions was 2.5 with an average number of 5 snare resections per EMR session. During a 9 month follow-up there was no recurrence of BE or malignancy; however, minor bleeding occurred during 4 of the 31 EMR sessions, and 2 of the 12 patients developed strictures that required dilation [37]. The use of ABPC is comparable to EMR in relation to the number of treatment sessions, patient outcomes, and recovery but is easier to perform and has a shorter learning curve.

Argon Versus Radiofrequency Ablation (RFA)

There is little comparative study between the argon and the new balloon-based, bipolar radiofrequency ablation (Stellartech Research Coagulation System, manufactured for BARRx, Inc, Sunnyvale, CA). Radiofrequency ablation requires the use of sizing balloons to determine the inner diameter of the targeted portion of the esophagus. This is followed by placement of a balloon-based electrode with a 3-cm-long treatment area that incorporates tightly spaced, bipolar electrodes that alternate in polarity. The electrode is then attached to a radiofrequency generator and a preselected amount of energy is delivered in less than 1 s at 350 W [35]. In a recent study settings of 10 or 12 J/cm^2 at 260 or 350 W, respectively, were used, achieving full-thickness ablation of epithelium without direct injury to the submucosa.

Pouw et al. studied the effect of RFA on BE with early neoplasia [38]. Patients who had BE $\leq$ 12 cm with early neoplasia were included in this study. Visible lesions were endoscopically resected. A balloon-based catheter was used for circumferential ablation and an endoscope-based catheter for focal ablation. Ablation was repeated every 2 months until the entire Barrett epithelium was endoscopically and histologically eradicated. Forty-four patients were included (35 men, median age 68 years, median BE 7 cm). Thirty-one patients first underwent endoscopic resection [early cancer ($n = 16$), high-grade dysplasia ($n = 12$), low-grade dysplasia ($n = 3$)]. The worst histology remaining after resection was high-grade ($n = 32$), low-grade ($n = 10$), or no ($n = 2$) dysplasia.

After ablation, complete histological eradication of all dysplasia and intestinal metaplasia was achieved in 43 patients (98%). Complications following ablation were mucosal laceration at resection site ($n = 3$) and transient dysphagia ($n = 4$). After 21 months of follow-up (interquartile range 10–27), no dysplasia had recurred. The study concluded that RFA, with or without prior endoscopic resection for visible abnormalities, is effective and safe in eradicating BE and associated neoplasia [38]. It appears from the above results that RFA is likely to be successful in ablating Barrett's but it requires dedicated technology and many centers may already have argon beam technology available in their endoscopy suites and further studies including randomized controlled trials will be needed to allow us to use such specialized instruments and technology, just for the purpose of Barrett's ablation.

Antireflux Therapy as Adjunct to Ablative Therapy

It is now universally agreed that GERD is the strongest risk factor for development of BE and in any patient with Barrett's or adenocarcinoma of the esophagus treatment with full-dose proton pump inhibitor is important to complement the ABPC and facilitate healing by minimizing acid reflux. In our experience there are a few patients who having avoided resection for HGD in their 40s or 50s then requested anti reflux surgery for their reflux control and this has been successful in selected cases. PPI therapy in conjunction with ABPC is the most effective method of restoring a squamous lining. Although acid suppression effectively controls symptoms of GERD and can also lead to the appearance of squamous islands within columnar-lined epithelium, it does not cause regression of the overall length of BE [39]. Sharma and co-workers have similarly demonstrated that despite the increase in number of squamous islands there was no overall change in length of the BE over an average of 5.7 years follow-up [40]. Sampliner et al. have shown convincingly that treatment with high-dose proton pump inhibitors does not markedly decrease Barrett's metaplasia [41].

The Problem of Buried Barret's Glands Underneath the Neosquamous Lining

The occurrence of subsquamous SIM postablation occurs with all modalities. It occurs in 20–30% of argon-treated Barrett's esophagus [42, 43]. The significance of this finding may not be as great as first considered. The genetic structure of the buried glands and the neosquamous mucosa is a stable phenotype not linked with markers of potential malignancy [43]. The development of intramucosal adenocarcinoma arising under neosquamous epithelium, however, has been reported

despite apparent macroscopic and microscopic clearance [10, 44] but these are isolated cases, and analysis of survival curves, particularly in the treatment of high-grade dysplasia, shows excellent results in cancer prevention [19].

CONCLUSION

The Place of ABPC Ablation in Benign Barrett's Esopahgus

ABPC is of unproven value for nondysplastic Barrett's and in low-grade dysplasia. The concerns raised about buried glands and the persistent risk of cancer also discourage many therapeutic endoscopists from adopting argon in this situation. It is possible that the radiofrequency Halo device may have a safety profile that makes ablation in nondysplastic Barrett's worth considering.

The Place of ABPC Ablation in High-Grade Dysplasia

The very low invasive cancer development after treatment of high-grade dysplasia with argon encourages its use to avoid esophagectomy, especially in the unfit. The combination of EMR (to carefully check for evidence of invasive cancer) and argon seems the safest and most effective way of managing HGD with the best quality of life and long-term outcome. Good-quality reflux control is essential to deal with the underlying driving force of malignant change in the esophagus.

The Place of ABPC Ablation of Barrett's in Malignancy

The place of ablation of Barrett's esopahgus in advanced malignancy relates only to the palliative treatment of the tumor and thus as an adjunct to stenting (unblocking or dealing with growth above or below the margins of a stent) or dealing with bleeding in a palliative setting.

The lessons learned from the introduction and development of argon ablation of Barrett's have informed and assisted the wider development of ablation technologies. This will support assessments of new technologies, particularly that of the radiofrequency device currently under clinical trials. Meanwhile, units that have argon available may find it as a useful adjunct to EMR and an option in the treatment of HGD or early cancer in patients unfit for surgical resection or those who wish to avoid the detrimental effects of esophagectomy on their quality of life.

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Radiofrequency Ablation for Eradication of Barrett's Esophagus: A Description of the Endoscopic Technique, Its Clinical Results, and Future Prospects

Roos E. Pouw, MD and Jacques J.G.H.M. Bergman, MD, PhD

CONTENTS

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Summary

Stepwise circumferential and focal radiofrequency ablation using the HALO system is a novel and promising ablative modality for Barrett's esophagus. Primary circumferential ablation is performed using a balloon-based bipolar electrode, while secondary treatment of residual Barrett's epithelium is performed using an endoscope-mounted bipolar electrode on an articulated platform. Recent studies suggest that this ablation technique is highly effective in removing Barrett's mucosa and its associated dysplasia without the known drawbacks of photodynamic therapy or argon plasma coagulation such as esophageal stenosis and subsquamous foci of columnar epithelium (*a.k.a.* "buried Barrett"). In this review chapter we will explain the technical background of radiofrequency ablation using the HALO system, give a summary of its current status, and speculate on possible future applications.

Key Words: Radiofrequency ablation, Ablation balloon, Focal ablation

INTRODUCTION

Given the morbidity and mortality that may be associated with esophagectomy, less-invasive endoscopic treatment modalities have emerged to treat high-grade dysplasia (HGD) and intramucosal cancer (IMC) in Barrett's esophagus (BE). Endoscopic resection (ER) of focal lesions allows for histological correlation enabling optimal patient selection [1]. Patients with submucosal invading lesions should be referred for surgery because they have a 15–30% risk of positive local lymph nodes whereas this risk is minimal in patients with IMC [2, 3]. ER, however, only removes a focal area from the BE keeping the patient at risk of metachronous lesions during follow-up [4]. To prevent this, ER can be combined with ablative therapy, such as photodynamic therapy (PDT) or argon plasma coagulation (APC), to remove residual (dysplastic) Barrett's mucosa [5–9]. PDT and APC, however, have significant shortcomings. First, they often do not result in complete ablation of the whole BE [5–9]. Second, studies have shown that oncogenetic alterations, as present in BE prior to ablation, can still be found in areas of residual BE and these may be associated with recurrence of neoplasia [10]. Third, foci of intestinal metaplasia (IM) may be hidden underneath the neosquamous mucosa after treatment (*a.k.a.* "buried Barrett") and some fear that these areas may progress to cancer without being detected endoscopically due to their "hidden" nature [11, 12]. Lastly, PDT and APC are associated with complications of which esophageal stenosis is the most relevant [5–9]. Stepwise

circumferential and focal radiofrequency ablation (RFA) using the HALO system is a relatively new endoscopic treatment modality for BE [13–15]. Recent studies suggest that this ablation technique is highly effective in removing Barrett's mucosa and associated dysplasia without the aforementioned drawbacks of other ablation techniques [16–21]. In this review we will explain the technical background of RFA, give a summary of its current status, and speculate on possible future applications.

TECHNICAL BACKGROUND

In the United States, the HALO ablation systems are marketed and distributed by BÂRRX Medical Inc., Sunnyvale, CA. In Europe, the systems are marketed by local distributors. Outside of the US and Europe, the systems are not yet commercially available. The HALO system comprises two distinct ablation systems: the HALO^{360} system for primary circumferential RFA and the HALO^{90} system for secondary focal RFA of BE. The HALO^{360} system includes an energy generator, ablation catheters, and sizing balloons. The HALO^{360} energy generator delivers radiofrequency (RF) energy to the electrode and has an integrated pressure:volume system to inflate the catheters and to measure the inner esophageal diameter.

The sizing catheter used for measuring the inner esophageal diameter prior to circumferential ablation consists of a 165-cm-long shaft with 1-cm markings and a clear, 4-cm-long non-compliant balloon at its distal end, with a central lumen for guide-wire passage. Upon activation via a footswitch, the sizing balloon is inflated to 4 psi (0.28 atm) by the HALO^{360} generator. Based on the baseline balloon volume:geometry and the volume needed to inflate the balloon to 4 psi, the mean esophageal inner diameter is calculated for the entire length of the 4-cm-long balloon.

The HALO^{360+} ablation catheter consists of a 165-cm-long shaft with a balloon at its distal end that holds a 3-cm-long bi-polar electrode on its outer surface. The electrode contains 60 electrode rings that alternate in polarity and completely encircle the balloon. The HALO^{360+} ablation balloon is available in five outer diameters (22, 25, 28, 31, and 34 mm) and the catheter is introduced over a guide-wire. Via a footswitch, the ablation catheter is inflated to 7 psi (0.48 atm) and upon activation RF energy is delivered to the electrode. Extensive dosimetry studies in the porcine esophagus and human esophagus prior to esophagectomy have shown that for circumferential ablation two applications of RF energy at 10 or 12 J/cm^2 and 40 W/cm^2 are the most effective regimens to ablate the full thickness of the epithelium, without injuring the submucosa [13–15].

Focal RFA of BE may be conducted with the HALO^{90} system that consists of an endoscope-mounted ablation catheter and an energy generator similar to the HALO^{360} generator, but without the pressure:volume system. The electrode array of the HALO^{90} catheter, which is identical to the HALO^{360+} electrode, is mounted on an articulated platform allowing the electrode to move front-to-back and left-to-right, ensuring optimal tissue contact. With a flexible strap the electrode can be fitted on the distal end of any endoscope with a diameter ranging from 8.6 to 12.8 mm, without impairing endoscopic view or function. The electrode is 20.62 mm long and 13.21 mm wide, with an active electrode surface of 20 $\times$ 13 mm^2, allowing for selective focal ablation. Currently, a "double $\times$ double" 15 J/cm^2 and 40 W/cm^2 or a 3 $\times$ 12 J/cm^2 ablation regimen is advised to reach effective eradication of IM.

THE HALO^{360} AND HALO^{90} ABLATION PROCEDURES

Stepwise circumferential and focal ablation of a BE starts with a circumferential ablation procedure using the HALO^{360} system, which comprises the following steps (Fig. 1):

(1) *Recording esophageal landmarks*: After spraying the esophageal wall with acetylcysteine (1%) and flushing it with plain water to remove excessive mucus, the top of the gastric folds and the maximum proximal extent of the BE (including isles) are recorded for reference during the sizing and ablation procedure. Then a stiff guide-wire (e.g., Amplatz extra stiff 0.035″, Cook, Denmark, Europe) or metal wire is introduced and the endoscope is removed.

(2) *Sizing esophageal inner diameter*: The sizing catheter is connected to the HALO^{360} generator, calibrated, and introduced over the guidewire. The sizing procedure is a "blind" procedure using the 1-cm scale on the catheter shaft for reference. For the first measurement the catheter is placed 5 cm above the maximum proximal extent of the BE. The distal end of the balloon is then located 1 cm above the most proximal extent of any Barrett's mucosa. The measurement cycle is started by pressing the footswitch; the sizing balloon inflates and the esophageal inner diameter is automatically calculated. This action is repeated for every centimeter of the targeted portion of the esophagus, advancing the balloon distally with 1-cm linear increments, until an increase in measured diameter indicates the transition to the hiatal hernia or stomach.

(3) *Selecting the appropriate HALO^{360+} ablation catheter*: Based on the esophageal inner diameter measurements an appropriate HALO^{360+} ablation catheter is selected. The outer diameter of the ablation balloon

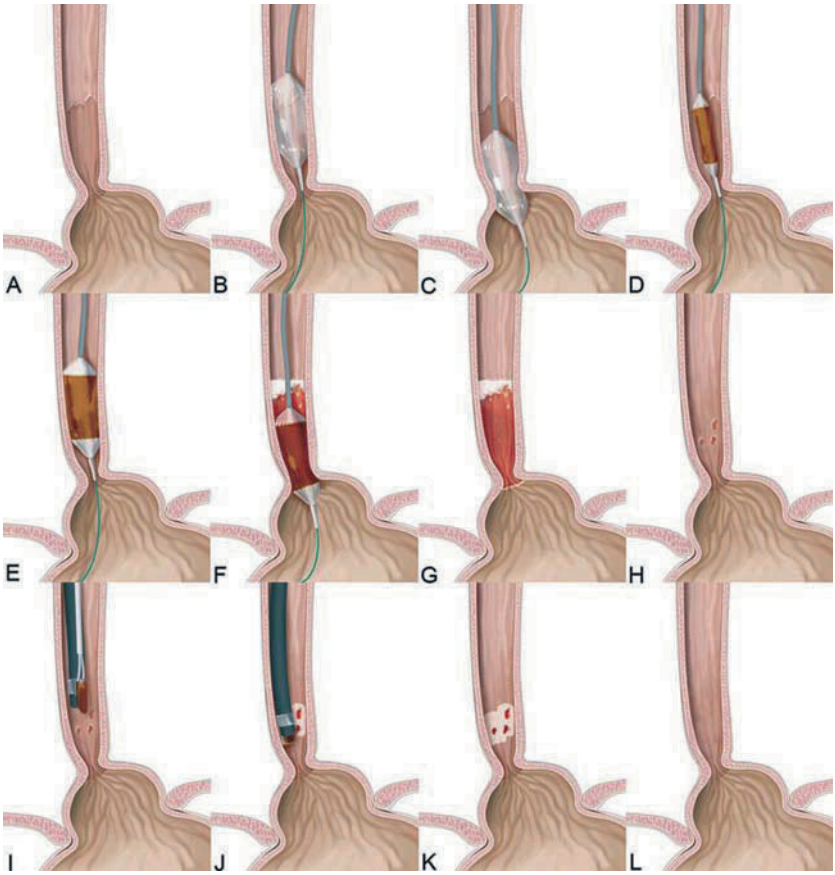

Fig. 1. A schematic illustration of primary circumferential and secondary focal radiofrequency ablation (RFA) of a Barrett's esophagus. **A:** Pre-treatment image of a Barrett's segment. **B and C:** The esophageal diameter is measured at 1-cm intervals with a sizing balloon placed over a guide-wire. **D:** Introduction of the RFA balloon catheter with the appropriate diameter over the guide-wire. **E:** The inflated RFA balloon positioned 1 cm above the top of the Barrett's segment. **F:** The RFA balloon repositioned for ablation of the second zone after ablation of the first zone with an overlap of 1 cm with the first ablation zone. **G:** Image of the treated Barrett's segment immediately after the RFA ablation with visible necrosis of the superficial mucosa. **H:** Image of the healed distal esophagus 3 months after RFA treatment with regeneration with neosquamous mucosa and three small isles with residual Barrett's mucosa. **I:** Introduction of the endoscope with the HALO^{90} cap for focal ablation placed at the tip. **J:** Ablation of the third isle of Barrett's mucosa. The necrosis caused by ablation of the first two isles visible. **K:** Image of the distal esophagus immediately after ablation of the three residual isles of Barrett's mucosa. **L:** Image of the healed distal esophagus, showing complete regeneration with neosquamous mucosa. Reproduced with the permission of www.barrett.nl.

should be smaller than the smallest measured diameter. In patients who underwent prior ER the ablation catheter should be selected conservatively, keeping in mind that the sizing balloon calculates a mean inner diameter over a length of 4 cm, which might result in an overestimation of the esophageal inner diameter at the site of the ER scar [21].

(4) *First circumferential ablation pass*: The HALO^{360+} catheter is introduced over the guide-wire followed by the endoscope that is introduced alongside the ablation catheter. Under endoscopic visualization the proximal margin of the electrode is placed 1 cm above the maximum proximal extent of the BE. The balloon is inflated, the esophagus is deflated to optimize tissue contact, and via a footswitch the electrode is then activated. Energy delivery typically lasts less than 1.5 s after which the balloon is automatically deflated. Moving from proximally to distally the balloon is repositioned, allowing a small overlap with the previous ablation zone of 5–10 mm. Ablation is repeated until the entire BE has received one application of RF energy (Fig. 2).

(5) *Cleaning procedure in between ablation cycles*: After the first ablation pass, the guide-wire, ablation catheter, and endoscope are removed.

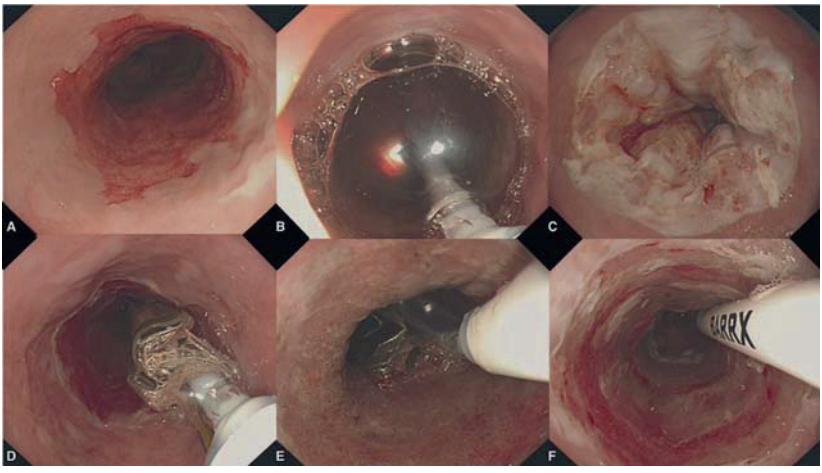

Fig. 2. Endoscopic images of a primary circumferential ablation using the HALO^{360} system. **A:** C5M6 Barrett's esophagus with high-grade dysplasia. **B:** The HALO^{360+} catheter is introduced and inflated at the upper end of the Barrett's segment. **C:** After the first application of energy the whitish coagulum resulting from the ablation shows after the catheter is deflated and advanced distally. **D:** After ablation of the whole Barrett's segment and cleaning of the electrode and ablation zone, the catheter is reintroduced for a second ablation pass. **E:** The second ablation pass results in a tan-colored ablation zone. **F:** Treatment effect after two circumferential ablation passes. Reproduced with the permission of www.endosurgery.eu.

Outside the patient the catheter is inflated to clean the electrode surface from coagulum with a wet gauze. A soft distal attachment cap (e.g., Model MB-046, Olympus, Tokyo, Japan) is fitted on the tip of the endoscope, and the soft extending rim of the cap can be used to slough off the coagulum from the ablation zone. After most of the coagulum has been removed with the cap, forceful spraying of plain water through a spraying catheter using a high-pressure pistol (e.g., Alliance^{TM}, Boston Scientific, Limerick, Ireland, UK) can be used to "blast" off residual coagulum (Fig. 2). Although the extensive cleaning procedure requires extra procedure time, it has been proven to increase the efficacy of the first ablation session from 90% surface regression to 95% [18, 19, 22].

(6) *Second ablation pass*: After the cleaning procedure, the entire BE is ablated again using the same energy settings (Fig. 2).

A circumferential ablation treatment using the HALO^{360} system takes approximately 40–60 min, depending on the length of the BE.

Six to eight weeks after the first circumferential ablation treatment, patients are re-scheduled. In case of residual circumferential BE > 2 cm and/or multiple isles or tongues, patients are treated with a second circumferential ablation. In case of an irregular Z-line, small tongues, circumferential extent <2 cm, or diffuse isles, patients are treated with secondary focal ablation using the HALO^{90} system, following the steps below (Fig. 1):

(1) *Introduction of the HALO^{90} catheter*: The HALO^{90} electrode is fitted on the tip of the endoscope and positioned at the 12 o'clock position in the endoscopic video image. The HALO^{90} device is introduced under visual control. When the laryngeal cavity is visualized the tip of the endoscope is deflected slightly downward allowing the leading edge of the catheter to be passed behind the arytenoids. The patient is asked to swallow and the endoscope is gently advanced. In about 8% of cases introducing the HALO^{90} catheter may prove difficult. In those cases a Zenker diverticulum should be excluded, and introduction of the device should never be forced. Sometimes we use a biopsy forceps or the spraying catheter as a guide to enter into the proximal esophagus. In difficult cases a CRE-balloon may be used to open the upper esophageal sphincter by manually inflating the balloon to a low pressure and to move the endoscope and HALO^{90} device in along with the balloon.

(2) *First ablation pass*: Residual Barrett's epithelium is positioned at the 12 o'clock position in the endoscopic video image. The electrode is brought into close contact with the mucosa, deflected upward, and activated via a footswitch. While keeping the electrode into place it is immediately activated again, resulting in a "double" application of

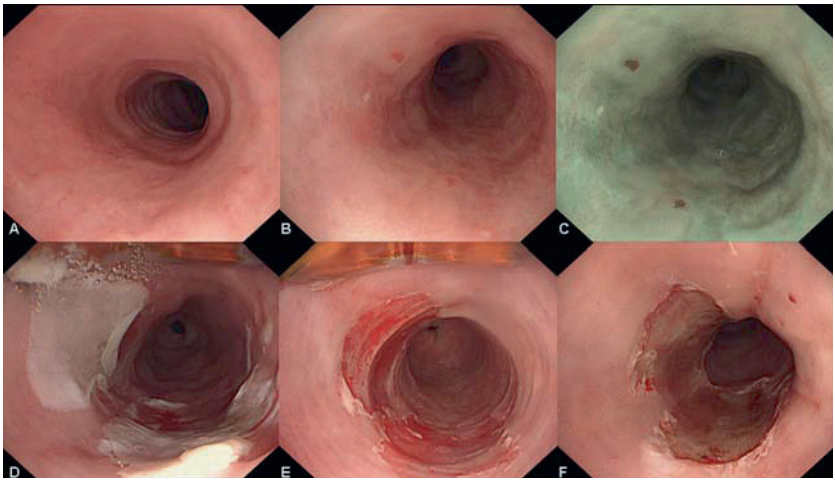

Fig. 3. Endoscopic images of a focal ablation procedure using the HALO^{90} system. **A:** Antegrade view of an initial C6M7 Barrett's esophagus after one circumferential and one focal ablation session. **B:** Upon detailed endoscopic inspection with high-resolution white light endoscopy 2 min isles with residual isles of Barrett's mucosa are identified. **C:** Corresponding image with narrow band imaging. **D:** Ablation effect immediately after ablation with the HALO^{90} system; the distal end of the catheter is visible at the 12 o'clock position in the endoscopic field. **E:** Endoscopic appearance after the first ablation pass (2×15 J/cm^2) and cleaning of the ablation zones. **F:** After the second ablation pass (double $\times$ double 15 J/cm^2) the ablation zones have a tan-colored appearance. Reproduced with the permission of www.endosurgery.eu.

energy (Fig. 3). Since the HALO^{90} electrode is already introduced, ablation of the entire Z-line is recommended, even if no clear tongues are observed, to ensure eradication of IM at the gastroesophageal junction (Fig. 4).

(3) *Cleaning procedure*: After all residual BE has been ablated, the coagulum is carefully pushed off the esophageal wall with the leading edge of the electrode, followed by cleaning of the electrode surface outside the patient and cleaning of the ablation zone with a spraying catheter and pressure pistol as described above (Fig. 3).

(4) *Second ablation pass*: Using the ablation zones from the first ablation pass for orientation, all ablated areas are treated with a double application of energy again (Fig. 3).

Ablation can be repeated every 6–8 weeks, until all BE has been eradicated visually, and then confirmed histologically. Most patients will need one circumferential ablation session and one to two focal ablation sessions to eradicate all dysplasia and IM. We advise a maximum

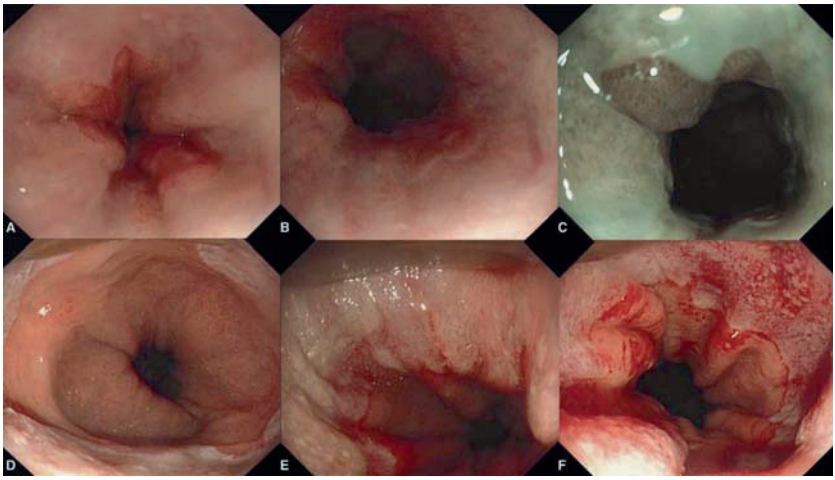

Fig. 4. Endoscopic appearance of targeted ablation of the entire circumference at the top of the gastric folds, using the HALO^{90} system. **A and B:** High-resolution white light inspection of the neosquamocolumnar junction after primary circumferential ablation. Differentiating Barrett's mucosa from cardia mucosa is, however, difficult. **C:** Corresponding image with narrow band imaging. **D:** To ensure eradication of all intestinal metaplasia at the top of the gastric folds, the entire circumference is ablated using the HALO^{90} system. After the first ablation pass (2×15 J/cm^2) whitish coagulum can be seen. **E and F:** After cleaning of the ablation zone and electrode surface, the entire neosquamocolumnar junction is ablated a second time (double $\times$ double 15 J/cm^2). Reproduced with the permission of www.endosurgery.eu.

number of two circumferential and three focal ablation sessions, which should be sufficient in most patients.

POST-TREATMENT CARE

After RFA proper anti-suppressant therapy is very important, not only to minimize patient discomfort, but also to allow the esophagus to heal optimally and regenerate with squamous epithelium. Next to high-dose proton pump inhibitors as maintenance medication, provisional addition of extra acid suppressants after each treatment is advisable. We prescribe all patients esomeprazole 40 mg BID, supplemented with ranitidine 300 mg hs noctem, and sucralfate suspension (200 mg/ml) 5 ml QID for 2 weeks after each ablation session [18, 19]. After RFA, patients are advised to adhere to a liquid diet for 24 h that they may gradually expand to a soft and normal diet at their own discretion. Patients may experience symptoms of chest discomfort, sore throat, difficulty or pain with swallowing and/or nausea, which usually improve

each day. Proposed analgesic measurements are suppository analgesics, e.g., acetaminophen 400 mg max. QID, if necessary supplemented with voltaren 50 mg max. BID. Other proposed analgesic regimens are antacid/lidocaine slurry, liquid acetaminophen with or without codeine, and anti-emetic medication. Some patients may present with severe chest pain and fever; observation and conservative management with an optimal anti-secretory and analgetic regimen usually suffices in these cases.

FOLLOW-UP REGIMEN

Two months after the last treatment the absence of residual Barrett's epithelium is examined by endoscopic inspection. The use of high-resolution endoscopes with Lugol's staining (2%) or preferably NBI is important to detect even small areas of residual IM (Fig. 3). A strict biopsy protocol should be applied with four quadrant biopsies immediately distal (<5 mm) to the neosquamocolumnar junction and every 1–2 cm of the neosquamous epithelium (Fig. 5). Since no

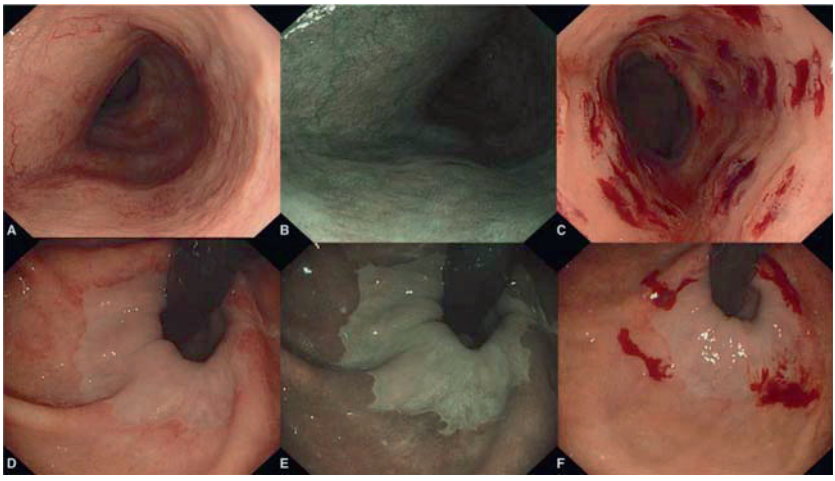

Fig. 5. Follow-up endoscopy with biopsies after eradication of a long segment Barrett's esophagus with radiofrequency ablation. **A:** High-resolution white light image of an initial C9M10 Barrett's segment, completely regenerated with neosquamous epithelium after successful treatment with radiofrequency ablation. **B:** Corresponding narrow-band imaging view. **C:** Four quadrant biopsies are obtained for every 1–2 cm over the entire length of the initial Barrett's segment. **D:** A normal appearing neosquamocolumnar junction. **E:** Corresponding narrow-band imaging view. **F:** To histologically confirm the absence of intestinal metaplasia, four quadrant biopsies are obtained 5 mm distal to the neosquamocolumnar junction. Reproduced with the permission of www.endosurgery.eu.

long-term follow-up data after RFA are available thus far it is recommended to schedule patients for follow-up endoscopy 2 and 6 months after the last treatment and then annually.

OVERVIEW OF CLINICAL TRIALS

After initial dosimetry studies in the porcine esophagus and human esophagus prior to esophagectomy [13–15], a number of prospective clinical studies were initiated to evaluate the safety and efficacy of RFA in the whole spectrum of BE patients: non-dysplastic BE [16, 17], LGD [18, 19], HGD [19–21], and IMC [20, 21].

In the AIM trial reported by Sharma et al., 102 patients with non-dysplastic BE were included and treated with RFA. The first phase of the study (AIM-I) was a dosimetry phase ($n = 32$) to evaluate the dose–response and safety of circumferential ablation by one application of RF energy ranging from 6 to 12 J/cm^2. There were no dose-related adverse events, and for the second phase of the trial (AIM-II), the effectiveness phase ($n = 70$), two applications of 10 J/cm^2 were delivered for circumferential ablation [16]. In the AIM-II trial, complete eradication of IM at 12 months was achieved in 48/70 subjects (70%), using only the HALO^{360} system for circumferential ablation [16]. The HALO^{90} device for focal ablation became available halfway during the first human trials. Fleischer et al. described the use of the HALO^{90} device for additional ablation in patients from the AIM-II trial with residual BE. At 30 months follow-up, this resulted in complete clearance of IM in 97% of patients by intention to treat analysis [17]. None of the patients from the AIM trial presented with esophageal stenosis, and no buried Barrett's glands were found in any of the >4,000 neosquamous biopsies obtained during follow-up [16, 17].

In a prospective trial by Sharma et al. that included 10 patients with confirmed LGD, RFA resulted in 100% clearance of dysplasia and 90% clearance of IM at 2-year follow-up, again without any esophageal strictures or buried Barrett's glands [18].

For ablation of BE in patients with LGD or HGD, the strongest evidence that RFA reduces the risk of malignant progression comes from the randomized sham-controlled trial by Shaheen et al. that was conducted in 19 US centers. Although it has not been completely published yet, the 1-year interim results of this high-profile quality study provide convincing evidence that RFA is effective in eradicating IM and dysplasia in patients with LGD and with flat HGD. By intention to treat analysis, a total of 101 patients with HGD ($n = 43$) and LGD ($n = 58$) were included and randomized to RFA treatment or sham (2:1). At 12 months, 85% of patients treated with RFA had clearance of dysplasia

(sham: 24%, $p < 0.001$), and 77% had clearance of IM (sham: 0%, $p < 0.001$). In the sham arm, 18.9% of patients had progression of dysplasia: 3/19 from LGD to HGD and 4/18 from HGD to EC. In the RFA arm 4.7% of patients had progression of dysplasia: 2/39 from LGD to HGD and 1/25 from HGD to EC. Five patients presented with an esophageal stricture (6%), all resolved with a mean of two endoscopic dilatations. There were no related deaths or perforations [19].

Gondrie et al. reported on a total of 23 patients with HGD and/or IMC, of which 13 underwent ER of IMC and visible lesions prior to RFA. After a median of 1.5 circumferential and 2.6 focal ablation sessions, and additional "escape" ER in two patients, complete eradication of all dysplasia and IM was achieved in all patients (100%). There were no adverse events or buried glandular mucosa in any of the 839 biopsies obtained during follow-up. Only one patient presented with dysphagia that resolved after one endoscopic dilatation. This patient already had a relative stenosis resulting from widespread ER prior to RFA, which may have become symptomatic after a treatment session in which circumferential ablation and ER of a nodule were combined [20, 21]. An important observation from the studies by Gondrie et al. is the possibility to resect areas of Barrett's mucosa that persist after multiple RFA sessions with the ligate-and-cut technique, without the need for submucosal lifting [20, 21]. This is a significant advantage compared to other endoscopic ablation techniques that typically result in submucosal scarring, which makes escape treatment with ER complicated.

In a report by Hernandez et al., 7/10 patients with non-dysplastic BE ($n = 7$), LGD ($n = 2$), and HGD ($n = 1$) reached complete clearance of IM with RFA. During 12 months follow-up, 247 biopsies were taken from the neosquamous epithelium, of which 1 biopsy showed subsquamous IM ("buried Barrett") [24]. This biopsy, however, was obtained just proximal to the gastric folds in a patient who had only been treated with one circumferential (HALO^{360}) ablation. According to the report, the "buried Barrett" was "treated" with repeat ablation. However, since it is difficult to differentiate Barrett's mucosa from cardia mucosa endoscopically, it can be argued that the patient had not been sufficiently treated with the single ablation session, and that the biopsy showed sampling and sectioning artifact of residual IM at the top of the gastric folds, leading to the "buried Barrett" finding.

Gondrie et al. demonstrated that stepwise circumferential and focal ablation of BE with HGD results in restoration of normal appearing neosquamous mucosa without any of the oncogenetic abnormalities as present before treatment, using fluorescence in situ hybridization analyses of brush cytology specimens obtained from the BE prior to ablation and from the neosquamous epithelium after RFA [25]. These findings

were confirmed by Finkelstein et al., suggesting that the neosquamous tissue holds no residual malignant potential.

Compared to the 0–56% stricture rate associated with other endoscopic ablation techniques [5–9], the minimal rate of esophageal stenosis reported in the trials discussed above is remarkable. A study by Beaumont et al., comparing measurements of esophageal inner diameter, motility, and compliance before RFA treatment and 2 months after the last ablation session, showed no significant differences, grounding the observation that RFA does not impair the functional integrity of the esophagus [26].

POSITION OF RFA FOR BARRETT ERADICATION

RFA After ER of Visible Lesions Containing IMC or HGD

Patients with visible abnormalities in a BE containing IMC or HGD may be treated with RFA, but only after ER of the IMC or visible lesion (Fig. 6). First, ER provides a relatively large tissue specimen that allows

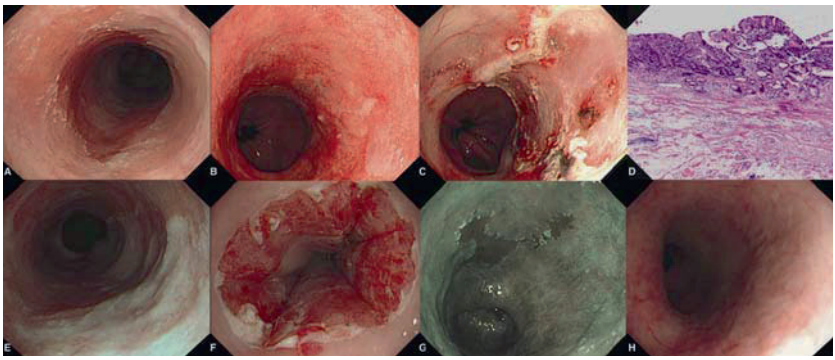

Fig. 6. Endoscopic and histological images of a C6M10 Barrett's esophagus with early cancer treated with a combination of endoscopic resection and radiofrequency ablation using the HALO system. **A:** Antegrade view on a C6M10 Barrett's esophagus. **B:** A lesion suspicious for early cancer at the 2–4 o'clock position. **C:** View on the resection wound after endoscopic resection of the lesion in two pieces. **D:** Histopathological evaluation of the specimens showed a radically resected adenocarcinoma infiltrating in the muscularis mucosae (T1m3). **E:** Same area 6 weeks after the endoscopic resection. The wound has healed completely with scarring. **F:** Ablation effect after primary circumferential ablation using the HALO^{360} system (2×12 J/cm^2). **G:** Residual isle of Barrett's mucosa remaining 6 weeks after prior circumferential ablation. **H:** After additional focal ablation of residual isles of Barrett's mucosa, complete removal of the whole Barrett's segment was reached. Reproduced with the permission of www.endosurgery.eu.

for optimal histopathological staging of a lesion, enabling selection of patients with intramucosal cancer and a low risk of lymph node involvement, for endoscopic treatment [1, 20, 21]. Patients with submucosal invading cancer and a significant higher risk of lymph node metastasis should be referred for surgical resection. Second, RFA should be performed on an endoscopically flat mucosa to ensure that the uniform ablation depth, as uniquely effected by the HALO system, truly reaches as deep as the muscularis mucosae.

RFA for Flat HGD

Barrett patients with HGD seem to be ideal candidates for RFA, since eradication of their dysplastic BE may prevent development of IMC. Proper selection of these patients is, however, of the utmost importance. Patients should have no visible lesions: these require endoscopic resection for optimal staging and treatment. We have also required absence of cancer in biopsies (4Q/1–2 cm) obtained during at least two high-resolution work-up endoscopies within 2 months prior to RFA and no studies have yet evaluated the use of RFA for flat IMC.

RFA for LGD

The natural course of LGD in BE is a controversial issue. Recent publications, however, have shown that after a consensus diagnosis of LGD, patients are indeed at an increased risk of malignant degeneration, suggesting that eradication of all BE at risk would prevent development of cancer [27]. Compared to the standard management of these patients, frequent endoscopic surveillance, RFA is, however, more invasive and should at this stage only be performed in clinical trials after confirmed diagnosis of LGD.

RFA for Non-dysplastic BE

The risk of progression to cancer in patients with non-dysplastic BE is small. Although different types of research aimed at objective risk-stratification of non-dysplastic BE have shown promising results, no objective markers are yet available to identify patients with an increased risk of developing cancer. Albeit RFA seems a very promising ablation modality for BE, there are still some unclear issues that need to be studied further in clinical trials, and long-term follow-up data should be awaited, before RFA is routinely used for the treatment of non-dysplastic BE.

DIRECTIONS FOR FUTURE RESEARCH

First, since the HALO^{90} technology only became available halfway during the first human trials the optimal energy settings to eradicate dysplasia and IM have not been completely unraveled. Currently, different energy settings and ablation regimens are applied for focal ablation, e.g., "double × double" 15 J/cm^2 and 3 × 12 J/cm^2 ablation. Furthermore, very small residual isles (<2 mm) may just as well be targeted with APC, which may be quicker, cheaper, and equally effective for this indication as ablation with the HALO^{90} system. But further clinical studies are required to decide on the optimal application and indication for the HALO^{90} system.

Second, though RFA may appear to be the new "super weapon" for BE ablation, it has to be stressed that ER remains the cornerstone of endoscopic treatment as was discussed above. Combining ER of visible lesions with RFA of residual BE, therefore, seems to be the ideal treatment modality for patients with early BE neoplasia. Thus far, however, there is only limited data on the combination of ER with RFA. In an evaluation by Pouw et al. circumferential RFA seemed safe in case no prior ER was performed. However, mucosal lacerations were observed in patients who had prior ER > 33% of the circumference and > 2.5 cm in length and who underwent ablation with a catheter that exceeded the smallest measured inner esophageal diameter. The few cases of esophageal stenosis after RFA all occurred in patients with ER > 50% of the circumference and >2 cm in length [22]. Based on these observations, it is advisable to limit the extent of ER to <50% of the circumference and <2 cm in length and to conservatively select the ablation catheter (e.g., if the smallest measured diameter is 30 mm, a 28-mm balloon would be appropriate in case of no prior ER; prior ER, however, warrants the selection of a 25-mm balloon). It is expected that ongoing clinical studies will provide more information to optimize this promising combination of ER with RFA.

Third, ablation of the gastroesophageal (GE) junction should be discussed for RFA using the HALO system. The often tortuous course of the distal esophagus and widening into a hiatal hernia may make it difficult to bring the electrode of the HALO^{360+} catheter into good circumferential contact with the mucosa at the GE junction. This may result in insufficient ablation of the BE at this level and given the difficulty to endoscopically differentiate Barrett's mucosa from gastric mucosa, a rim of untreated BE may persist at the top of the gastric folds. To prevent this, we advise to ablate the full circumference of the GE junction using the focal HALO^{90} device. Histological confirmation is, however, mandatory to ensure complete clearance of IM. For this end, biopsies

must be obtained immediately distal (< 5 mm) to the neosquamocolumnar junction. Despite this approach, however, Gondrie et al. reported the finding of focal IM in a single biopsy at this level that was not re-confirmed during multiple follow-up endoscopies in five patients [20, 21]. The clinical relevance of this finding remains unclear. One may argue that these patients, with an initial diagnosis of HGD or IMC, are still not completely cured from their underlying disease. IM of the cardia, however, is found in up to 25% of normal subjects and in those cases it is not considered a premalignant condition [28]. Furthermore, given the patchy nature of this finding, targeted additional treatment is difficult and not required because patients with an initial diagnosis of HGD/IMC will remain under endoscopic follow-up anyway. Long-term follow-up data, however, may provide relevant information on the natural history of this finding.

Fourth, we would like to address the issue of "buried Barrett's glands" after ablation. The clinical relevance of "buried Barrett" is still uncertain, but of concern is the possibility of occult malignant progression of the buried glands, as has been suggested by incidental reports of adenocarcinoma arising underneath neosquamous epithelium after ablation therapy [11, 12]. Others believe that the malignant potential of the buried glands is negligible, since their covered nature protects them from the harmful influence of the gastroesophageal refluxate [29, 30]. Thus far, no truly buried Barrett has been detected in patients that had complete eradication of all IM after RFA. Since this finding is in disconcordance with the rate of subsquamous IM (0–53%) found after other ablative techniques [5–8], some argue that the biopsies do not sample the neosquamous epithelium deep enough to reliably evaluate the presence of buried Barrett's glands. Ongoing studies evaluating sampling depth and presence of buried glands in biopsies and ER specimens from neosquamous epithelium after RFA should enlighten this issue.

In this respect, the artifacts that may lead to a wrongful diagnosis of buried Barrett should also be addressed. Biopsies from neosquamous epithelium near the neosquamocolumnar junction may lead to sampling of the transition from neosquamous to columnar epithelium. This may lead to a histological finding of glandular mucosa underneath the neosquamous epithelium, which may mistakenly be interpreted as buried Barrett. The same holds when a biopsy is taken from presumably neosquamous epithelium, while there is in fact a small isle of IM that was not detected endoscopically. Tangential sampling of the isle and tangential sectioning of the biopsy may then also result in an erroneous finding of buried Barrett. A diagnosis of buried Barrett's glands should, therefore, only be made if the endoscopist is positive that there were

no BE isles after detailed inspection with NBI and if the biopsies are not obtained at the level of the neosquamocolumnar junction, as was the case in the above-mentioned case report of a single patient, single biopsy "buried gland" [24].

Fifth, now that RFA has been proven safe and effective and seems to result in normal appearing neosquamous epithelium without any pre-existing oncogenetic alterations and buried Barrett's glands, an important question that remains is from where the neosquamous epithelium originates. Different hypotheses have arisen over the last years, involving outgrowth from existing pools of squamous cell progenitors, repopulation from adjacent areas with squamous epithelium, or multipotent progenitor cells [31–33]. To fully understand the process of squamous repopulation after ablation further studies are required, since more insight in the source of the neosquamous epithelium may enlighten if replacing Barrett's epithelium with neosquamous epithelium by RFA indeed reduces the risk of developing cancer.

Lastly, it is questionable if every endoscopist should be trained in RFA. Although this novel ablation technique is relatively easy to apply, RFA is just one aspect in the whole spectrum of endoscopic management of BE patients. Selection of patients with a proper indication for RFA involves thorough endoscopic work-up, the possibility to safely perform ER, and accurate histological evaluation of tissue specimens for the presence of risk factors for lymph node metastasis. We think that RFA should, therefore, be centralized in centers with multidisciplinary expertise in this field. To realize this, adequate training courses (e.g., www.endosurgery.eu), aimed at the whole spectrum of endoscopic management, are mandatory to maintain the status of endoscopic treatment as a valid and safe alternative to surgical treatment in the management of early Barrett's neoplasia [34–36].

SUMMARY

Current data suggest that RFA may indeed meet the criteria of the "ideal ablation technique" for total Barrett eradication. RFA has been proven to be highly effective in eradicating IM and its associated dysplasia; the regenerating neosquamous epithelium is free of the pre-existing oncogenetic alterations, has a low complication rate, preserves the esophageal functional integrity, and is relatively easy to apply. There are, however, still some hazy issues concerning the presence of buried Barrett's glands following RFA, the optimal use of the HALO^{90} catheter, the optimal combination of ER with RFA, and the long-term treatment effect. For patients with IMC and HGD, RFA appears to be

a less-invasive and valid alternative to PDT, APC, and esophagectomy, be it after thorough endoscopic work-up and ER of IMC and visible lesions. For patients with LGD or non-dysplastic BE, however, further clinical studies and long-term follow-up data should be awaited before RFA is routinely used for BE eradication.

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Decision Making in Ablation: Disease, Patients, and Institutional Factors

Gary W. Falk, MD, MS

CONTENTS

Summary

Decision making in endoscopic ablation therapy involves assessment of the disease, the patient, and institutional factors. A lesion in the Barrett's esophagus can be classified as "low risk" if the diameter is less than 2 cm, if it is well or moderately differentiated, and if it is limited to the mucosa. The patient's life expectancy, comorbidity, adherence to endoscopy, and attitude toward cancer risk all have to be considered. Finally, the local expertise in histologic assessment, staging, and surgery needs to be taken into account in an extensive discussion of therapeutic options with the patient.

Key Words: Esophageal adenocarcinoma, Dysplasia, Esophagectomy, Barrett's esophagus

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INTRODUCTION

The decision to perform endoscopic therapy in patients with Barrett's esophagus is complex. Many factors enter into the decision-making process including characteristics of the lesion in question, patient characteristics, and institutional factors including expertise in pathology, surgery, and interventional endoscopy (Table 1). Given the dismal survival of advanced esophageal adenocarcinoma, it is essential to consider each of these variables in order to develop the best approach for each patient. This chapter will review the various factors that enter into the "equation" in tailoring the right treatment for the right patient with intraepithelial neoplasia defined as either high-grade dysplasia or intramucosal carcinoma.

Table 1
Management of high-grade dysplasia/superficial cancer: variables to consider

- Patient
  - Age
  - Comorbidities
  - Compliance with endoscopic surveillance
  - Cancer fears
- Lesion
  - Length
  - Nodularity
  - Dysplasia
    - Grade
    - Extent
- Local expertise
  - Pathologist
  - Surgeon
  - Endoscopist

THE PATIENT

A variety of patient-related factors enter into decision making for ablation. These include age and hence life expectancy, comorbidities, compliance with and tolerance of rigorous endoscopic follow-up, and risk factors for the subsequent development of adenocarcinoma. It is also essential to remember that regardless of the endoscopic approach to

ablation, the conditions that led to the development of Barrett's esophagus and esophageal cancer are still present in a given patient after any endoscopic treatment approach. A careful discussion of pros and cons of endoscopic versus surgical approaches is warranted for each patient recognizing the maxim that "one size does not fit all."

Patient Perception of Cancer Risk

It is currently unknown how perception of cancer risk enters into the patient's decision making for surgical versus endoscopic approaches to dysplasia and early cancer. Intuitively, one would believe that in a patient who is cancer "phobic," surgery would be the preferred approach whereas for those less concerned about the development of cancer, an endoscopic approach would be more appealing. Unfortunately, we do not know how these perceptions enter into a patient's decision-making process. We do know that choice of treatment may be influenced by whether the initial evaluation is performed by a gastroenterologist or a surgeon [1]. We also know that patient perception of cancer risk in Barrett's esophagus surveillance programs is not accurate. Shaheen et al. found that 68% of such patients overestimated their 1-year risk of cancer and 38% overestimated their lifetime risk [2]. On the other hand, work from the Netherlands found just the opposite: 69% of patient underestimated their risk of developing adenocarcinoma [3]. As such it appears that patients really do not have a good estimate of their own cancer risk.

Compliance with Endoscopic Follow-Up Protocols

Any decision to approach intraepithelial neoplasia endoscopically requires compliance by both the patient and the physician with rigorous and meticulous endoscopic follow-up. For example, the Wiesbaden group protocol for follow-up after endoscopic mucosal resection of intraepithelial neoplasia involves follow-up endoscopy at 1, 2, 3, 6, 9, and 12 months after treatment, then at 6-month intervals up to 5 years, and annual endoscopy thereafter [4]. In the setting of simple endoscopic surveillance without endoscopic therapy for high-grade dysplasia, the Hines group employs a careful "hunt" for cancer over the first 12 months consisting of endoscopic examinations with intensive biopsy sampling every 3 months followed by surveillance at 6-month intervals for the second year if no high-grade dysplasia is found, followed by annual intervals thereafter [5]. However, if high-grade dysplasia is found again, the entire "hunt" sequence is resumed. Thus, inability to comply with a rigorous endoscopic follow-up protocol is a contraindication to endoscopic approaches to intraepithelial neoplasia.

Preoperative Risk Assessment

Many patients with intraepithelial neoplasia are elderly with multiple comorbidities. As such, careful preoperative risk assessment may help identify individuals who are poor operative candidates thereby making the choice for endoscopic ablation much simpler. A variety of studies have identified factors that may predict complications and mortality from esophagectomy. Rice et al. found that preoperative factors that predicted for an ideal outcome in patients with superficial carcinoma included $FEV_1 > 2$ l, surveillance detected lesions, a preoperative diagnosis of high-grade dysplasia and a planned transhiatal approach [6]. Steyerberg et al. found that for patients with both superficial and deeper stages of esophageal cancer who underwent surgery, the following were predictors of surgical mortality: increasing age, comorbidities (cardiac, pulmonary, renal, hepatic, and diabetes), preoperative chemoradiotherapy, and low hospital volume [7]. Finally, Lagarde et al. have developed a nomogram that predicts the severity of complications after esophagectomy in patients undergoing esophagectomy [8]. Multivariate predictors of complications include the following factors: increasing age, history of cerebrovascular accident/transient ischemic attack or myocardial infarction, lower FEV1, EKG changes such as Q waves or ST-T changes, and more extensive surgery, i.e., a transthoracic rather than trashiatal approach. Thus, it appears that careful patient selection will identify a group of patients for whom surgery is a high-risk option making the decision for endoscopic ablation much more simple.

Risk Factors for the Development of Cancer

A variety of epidemiologic factors have been identified that either increase or decrease the risk for the development of esophageal adenocarcinoma. Given the fact that the conditions that led to the development of both Barrett's esophagus and esophageal adenocarcinoma are likely to persist after any endoscopic intervention, it is important to recognize these factors. However, it remains unclear if modifying these risk factors will modify the course of a given individual's disease after endoscopic intervention. Among the well-accepted risk factors for the development of esophageal adenocarcinoma are increasing age [9, 10], male gender [10], Caucasian ethnicity [11], obesity, especially male pattern central obesity [12–14], and smoking [15, 16].

Protective factors include aspirin and NSAID ingestion [17, 18] and a diet high in fruits and vegetables [19]. Factors of uncertain significance include family history [20], infection with *Helicobacter pylori* [21, 22], alcohol consumption [23, 24], antireflux therapy be it surgical or pharmacologic [25–27], and dietary supplements [28].

THE LESION

A variety of factors in the Barrett's segment influence the approach to ablation. These include grade of dysplasia, presence and appearance of any focal lesions, and length of the Barrett's segment.

Grade of Dysplasia

Currently, dysplasia remains the only factor useful for identifying patients at increased risk for the development of esophageal adenocarcinoma in clinical practice. As such, any decision about endoscopic ablation must weigh the risk of developing cancer prior to embarking on an endoscopic intervention. It is estimated that the risk of developing cancer in Barrett's esophagus patients without dysplasia is approximately 0.5–0.7% annually [29, 30]. It is also important to remember that epidemiologic data suggest that despite the alarming increase in the incidence of esophageal adenocarcinoma in the western world, the vast majority of patients with Barrett's esophagus still will never develop cancer and will die of causes besides cancer [30, 31]. Despite the ready availability of a variety of different ablation techniques, it is difficult to justify a decision to embark on ablation for patients without dysplasia for the following reasons: (1) cancer risk for a given patient is low; (2) the need for surveillance is not changed; (3) all of the techniques involves considerable financial cost; and (4) adverse events still occur.

Low-grade dysplasia is recognized adjacent to and distant from Barrett's esophagus-associated adenocarcinoma in resection specimens and typically occupies a far greater surface area of the involved esophagus than does high-grade dysplasia or cancer [32, 33]. The natural history of low-grade dysplasia is highly variable: some patients clearly progress on to develop high-grade dysplasia or adenocarcinoma, whereas "regression" is seen in the majority of these individuals. However, "regression" in many cases could be related to diagnostic accuracy and/or sampling error. Interobserver variability, even among expert GI pathologists in the interpretation of low-grade dysplasia, is especially problematic [34]. The inability to reproducibly diagnose low-grade dysplasia may explain the highly variable natural history of this lesion. Taken together, studies to date suggest that low-grade dysplasia results in an intermediate risk for the development of adenocarcinoma [35]. The role of ablation therapy for this level of dysplasia remains under investigation

On the other hand, high-grade dysplasia in Barrett's esophagus is a well-recognized risk factor for the development of adenocarcinoma [36–38]. Unsuspected carcinoma has been detected at esophagectomy in approximately 40% of patients with high-grade dysplasia in older series [39]. However, recent studies suggest that use of endoscopic

mucosal resection in conjunction with a rigorous biopsy protocol prior to esophagectomy can decrease the finding of unsuspected carcinoma to 12.8% [40]. The natural history of high-grade dysplasia has been evaluated in several cohort studies. Buttar et al. found that cancer developed in 38 and 56% of individuals at 1 and 3 years with diffuse high-grade dysplasia and 7 and 14% of individuals with focal high-grade dysplasia [36]. Reid et al. encountered cancer in 59% of patients at 5 years [37]. On the other hand, Schnell et al., in a study of 79 patients, found cancer in 5% during the first year of surveillance and in 16% of the remaining patients followed for a mean of 7 years (20% of the total group developed cancer) [38]. Others have reported regression of high-grade dysplasia over time as well [38, 41]. A recent meta-analysis found that the incidence of adenocarcinoma in patients with high-grade dysplasia was approximately 6.58% annually [42]. Mucosal abnormalities in patients with multifocal high-grade dysplasia may also be a risk factor for adenocarcinoma [43, 44]. Thus, high-grade dysplasia remains a worrisome lesion, although progression to carcinoma may take many years and is not inevitable.

Macroscopic and Microscopic Features of the Lesion

As described above, mucosal nodularity in patients with high-grade dysplasia is associated with an increased risk of adenocarcinoma. The Paris classification of superficial neoplastic lesions (Fig. 1) was initially developed to help predict the extent of invasion into the submucosa of gastric cancer and as such, the choice between endoscopic versus surgical approaches [45]. It has subsequently been adopted for esophageal lesions as well. Furthermore, deep invasion can be suspected by the presence of the "non-lifting" sign whereby a lesion fails to lift after injection of saline into the submucosa. Work by the Wiesbaden group has defined low-risk lesions amenable to endoscopic approaches as having the following characteristics: lesion diameter < 2 cm and macroscopically Paris type I (polypoid), IIa (flat and slightly elevated), or IIb

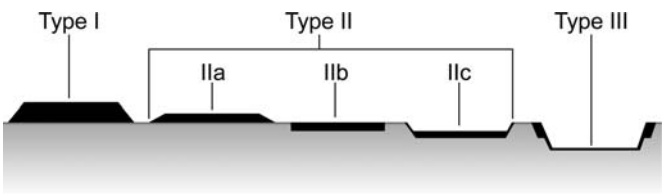

Fig. 1. Paris classification of the endoscopic appearance of superficial neoplastic lesions of the digestive tract mucosa.

(flat and level); IIc (flat depressed $<$ 10 mm); well or moderately differentiated histologic grade; lesions limited to the mucosa proven by histology of the resected specimens; and absence of either blood vessel or lymphatic invasion [4].

Peters et al. further refined our understanding of the Paris classification by examining the endoscopic features that predicted favorable pathologic characteristics [46]. They found that histologic grade 1 lesions were associated with submucosal cancer in only 6% of cases, whereas submucosal cancer was encountered in 44% of grade 2 lesions and 50% of grade 3 lesions. The endoscopic lesions most predictive of submucosal cancer were Paris type 0-I and 0-IIc. All other Paris type lesions were associated with submucosal cancer in $\leq$ 10% of cases.

In summary, mucosal nodularity and multifocal high-grade dysplasia are associated with an increased risk of cancer at the time of esophagectomy or progression to cancer over time. Paris Type 0-I and 0-IIc lesions are especially worrisome for submucosal cancer at the time of endoscopic mucosal resection and patients with grade 2 or 3 differentiation, lesions $>$ 2 cm, and evidence for lymphatic or vascular invasion on endoscopic mucosal resection are poor candidates for continued endoscopic ablative therapies.

Tumor Depth

Early invasive cancer may be classified as intramucosal when neoplastic cells penetrate through the basement membrane to the lamina propria or muscularis mucosa and submucosal when neoplastic cells infiltrate into the submucosa [47]. The prognosis for these two lesions is very different because the risk of lymph node metastasis is approximately 0–7% for intramucosal cancer but increases to 5–50% for submucosal cancer [48–51]. Given the fact that lymph node metastases are a clear prognostic factor for decreased survival, tumor depth is perhaps one of the most significant factors in decision making for the approach to superficial neoplasia [6].

There is emerging controversy on how to best handle submucosal disease. A recent surgical study evaluated the outcome of submucosal cancers by classifying invasion as limited to the upper third (sm1), middle third (sm2), and lower third of the submucosa (sm3) and found that lymph node metastases were found in 0/25 sm1 lesions in contrast to 6/23 sm2 lesions and 12/18 sm3 lesions [48]. The outcome for patients with sm1 disease was no different than that for patients with intramucosal carcinoma. This has led some to now extend indications of endoscopic mucosal resection to low-risk submucosal cancer characterized by the following criteria: sm1 invasion, absence of infiltration

into lymphatics or veins, and histology characterized by well or moderate grades of differentiation [52]. However, a different surgical series found lymph node metastases in 22% of sm1, 0% of sm2, and 78% of sm3 adenocarcinomas [51]. As such, the concept of treating submucosal cancer with endoscopic mucosal resection is evolving but remains highly controversial.

Segment Length

Esophageal cancer develops in both short and long segments of Barrett's esophagus. Studies to date have yielded mixed results for length as a risk factor, in part because of the low incidence of progression to cancer in cohort studies. Observational studies suggest that the prevalence of cancer and dysplasia is higher in longer lengths of Barrett's epithelium [53–57]. A prospective cohort study by Rudolph et al. of the Seattle Barrett's esophagus project found that segment length was not related to subsequent risk of cancer [58]. However, when patients with high-grade dysplasia at index endoscopy were excluded, a nonsignificant trend for risk of cancer was noted. Weston et al. found that a segment length of $\geq$ 6 cm was associated with an increased risk for developing high-grade dysplasia or adenocarcinoma [56]. Others have also found an increased risk of subsequent development of dysplasia or carcinoma with increased length of Barrett's epithelium [57, 59]. However, a recent meta-analysis found only a trend for decreased cancer risk for short segment Barrett's esophagus [60]. Taken together, these data suggest that the relationship between segment length and cancer risk is uncertain. However, the longer the Barrett's segment length, the higher the probability of sampling error with endoscopic surveillance. Other decisions regarding endoscopic ablation based on segment length include the threshold for performing focal versus circumferential endoscopic mucosal resection and thermal ablation alone or in combination with endoscopic mucosal resection.

LOCAL EXPERTISE

The Pathologist

Pathology expertise is critical in decision making for patients with intraepithelial neoplasia. It is well recognized that pathologic interpretation of Barrett's esophagus specimens is problematic in the community as well as in academic centers. Alikhan et al. found that only 30% of a group of community pathologists correctly identified high-grade dysplasia, and intestinal metaplasia negative for dysplasia was identified as invasive carcinoma by 5% of the pathologists [61]. Pathologic

interpretation is also problematic for expert gastrointestinal pathologists, where interobserver reproducibility is substantial at the ends of the spectrum of Barrett's esophagus, namely negative for dysplasia and high-grade dysplasia/carcinoma but not especially good for low-grade dysplasia or indefinite for dysplasia [34].

However, there are also problems with interobserver agreement among pathologists in distinguishing high-grade dysplasia from intramucosal cancer, even when using esophagectomy specimens [47]. Recently, the Cleveland Clinic group also found poor interobserver agreement among a group of seven gastrointestinal pathologists in distinguishing high-grade dysplasia from either intramucosal or submucosal carcinoma in preresection biopsy specimens [62]. These findings point out some of the problems in pathologic interpretation: experience of the pathologist, quality of the slides, size of the specimens, and the difficulties for all pathologists in interpreting dysplasia [63]. In an effort to improve pathologic interpretation, current practice guidelines now recommend endoscopic mucosal resection of any nodularity in the Barrett's segment prior to making final treatment decisions [64, 65]. Recent data support just such an approach. Mino-Kenudson et al. found that the interobserver agreement for Barrett's esophagus-associated neoplasia on endoscopic mucosal resection specimens was higher than that for mucosal biopsies [63]. This was especially the case for intramucosal cancer and submucosal cancer.

The Surgeon

Esophagectomy has long been viewed as the preferred approach to high-grade dysplasia, given the common findings of unsuspected cancers at the time of surgery as described above However, the prevalence of unsuspected carcinoma may be overestimated in these studies because of the lack of systematic preoperative biopsy protocols and failure to adequately sample mucosal abnormalities, which are known to be associated with the identification of carcinoma, at the time of preoperative endoscopy [66]. Data from Prasad et al. suggest that use of endoscopic mucosal resection in conjunction with a rigorous biopsy protocol prior to esophagectomy can decrease the finding of unsuspected carcinoma to 12.8% [40]. Furthermore, recent work from the University Chicago group suggests that submucosal cancer, a clinically more worrisome lesion due to increased propensity to lymph node metastases, is found in only 13% of patients undergoing surgery for a preoperative diagnosis of high-grade dysplasia [67]. This finding was more common in individuals with mucosal lesions than those with no visible lesions. Aggressive surgical intervention for patients with high-grade dysplasia

patients has also been criticized on the basis of data indicating that progression to cancer is not inevitable in these patients [36–38, 68, 69].

Surgery has a number of advantages as a treatment strategy for high-grade dysplasia: potential for cure of superficial adenocarcinoma, removal of remaining at-risk mucosa, elimination of the need for further surveillance, and removal of diagnostic uncertainty (Table 2) [70]. However, esophagectomy is a technically demanding operation and outcome is clearly related to surgical volumes, with a mortality rate of 18.8% for an annual surgical volume less than 2 compared to 9.2% for a volume greater than 6 [71]. Similar results are seen for hospital volumes: mortality decreases as volume of procedures increases [72, 73]. Data such as these are typically cited when pointing out the disadvantages of an aggressive surgical approach to high-grade dysplasia. However, emerging data from selected tertiary care centers suggest that surgery can now be performed with a mortality of $<1\%$ in patients with high-grade dysplasia and consistently $< 5\%$ for patients with intramucosal carcinoma [6, 70, 74–79]. These excellent outcomes are most likely related to careful patient selection in high volume centers with the infrastructure and clinical care pathways of preoperative assessment, patient selection, procedure selection, intraoperative management, and postoperative care to optimize patient outcome [80]. For example, minimization of intraoperative fluids and blood loss, early aggressive pain medication, typically by patient-directed analgesia, early extubation, and mobilization are all important factors in improving the outcome

Table 2
Surgery of high-grade dysplasia and superficial adenocarcinoma: advantages and disadvantages

Advantages
• Removes cancer
• Removes remaining mucosa at risk
• Diagnostic certainty
• Low mortality in expert hands
• Long-term quality of life excellent
Disadvantages
• Technically demanding
• Early morbidity
• High mortality in nonexpert hands
• Many patients poor operative candidates

of this operation [80]. Potential patient predictors of poor surgical outcomes have been identified and described above in the section on patient factors.

There is considerable early morbidity associated with the operation, accompanied by a lengthy recovery time, along with the potential for long-term residual symptoms including nausea, diarrhea, dysphagia, bloating, and weight loss [74–76, 81–84]. Despite this, quality of life in these patients is surprisingly good and approaches that of patients of similar age at the end of 1 year [74–76, 81, 82]. Thus, when performed by skilled surgeons with adequate volume and careful patient selection, this operation can be done safely. Minimally invasive techniques are now available as well, which appear to be safe, with outcomes comparable to open surgical approaches [85, 86].

The Endoscopist

Endoscopic skills important in clinical decision making for ablation include expertise and equipment for imaging and endoscopic ablation along with a commitment to careful and meticulous follow-up of these patients. Endoscopic management options, all of which have pros and cons, include continued surveillance or endoscopic intervention using one or combinations of the technologies described below.

Continued Surveillance

Given the limitations of surgical intervention for patients with high-grade dysplasia, continued endoscopic surveillance is a potential management strategy for Barrett's esophagus patients with high-grade dysplasia [64, 87, 88]. In particular, the "Seattle" biopsy protocol, consisting of four-quadrant biopsies at 1-cm intervals with large capacity forceps in conjunction with aggressive sampling of any mucosal abnormality, has been advocated as a technique to reliably detect carcinoma preoperatively in patients with high-grade dysplasia [66]. This approach would avoid potentially unnecessary "prophylactic" surgery and the inherent risks involved. The basis for this approach has come from studies by the Seattle group and others [38, 66, 89]. Levine et al. found that a rigorous biopsy protocol consisting of four-quadrant jumbo biopsies at intervals ≤ 2 cm combined with multiple biopsies from areas in the Barrett's segment from which high-grade dysplasia had been found previously in conjunction with additional biopsies of any mucosal abnormality could accurately predict the presence or absence of intramucosal or submucosal cancer in 93% of the 28 patients undergoing esophagectomy [89]. Subsequently, they found that a 2-cm protocol would miss 50% of cancers that were detected by the 1-cm protocol if there were

no visible mucosal lesions and that 29% of cancers would be missed by the 2-cm protocol when there were visible mucosal lesions [66]. Other studies have also shown that detection of early cancer and dysplasia is clearly enhanced by systematic as opposed to random biopsy protocols [90, 91].

Despite the fact that this type of intensive protocol results in more material for histological examination, this approach also has a number of limitations. First, only a very small percentage of the mucosa is sampled and as such, there is always a risk for sampling error [33, 92]. Second, there are problems with interobserver agreement among pathologists in distinguishing high-grade dysplasia from intramucosal cancer, even when using esophagectomy specimens, as described above [34, 47, 62]. Lastly, intensive surveillance protocols are time consuming, expensive, and require compliance from both patients and physicians, with a risk of losing patients to follow-up. Thus, continued surveillance has the advantage of keeping the esophagus in situ, but the disadvantages of high frequency continued endoscopy and the potential for sampling error accompanied by ongoing diagnostic uncertainty. Current American Gastroenterological Association guidelines recommend that if continued surveillance is opted for as a strategy for managing high-grade dysplasia after confirmation by an expert pathologist, that surveillance characterized by at least eight biopsies every 2 cm be carried out at 3-month intervals for 2 years followed by 6-month intervals thereafter [65].

Endoscopic Therapy

A variety of endoscopic approaches have developed in recent years in an attempt to find the right balance that results in a high probability of curing cancer while decreasing the risks associated with esophagectomy. The key advantages of each of the endoscopic techniques are that the esophagus remains in situ and the risks of surgery are avoided. Recent data with these techniques are encouraging, demonstrating low morbidity and mortality and excellent 5-year survival [4, 40, 93, 94]. However, each of these techniques has disadvantages as well, including the need for continued meticulous surveillance, the potential for "at-risk" mucosa remaining behind after therapy, and diagnostic uncertainty. As demonstrated by the Wiesbaden group for endoscopic mucosal resection, Prasad et al. for photodynamic therapy after endoscopic mucosal resection, and Shaheen et al. for radiofrequency ablation, cancer may still develop in a small subset of these patients after endoscopic therapy [40, 94, 95]. The emerging concept of endoscopic

mucosal resection of visible lesions combined with either circumferential endoscopic mucosal resection or thermal injury treatment of the remaining at-risk mucosa is now taking hold. This is based on the high metachronous cancer rate found by the Wiesbaden group in the at-risk mucosa, with its persistent molecular abnormalities, remaining behind after endoscopic mucosal resection. Summarized below is a brief discussion of pros and cons of ablation techniques.

Thermal Ablation Techniques

Randomized controlled trials have now been conducted to compare a variety of thermal ablation techniques to each other. These clinical trials have highlighted the difficulty in obtaining complete endoscopic and histologic ablation with argon plasma coagulation, multipolar electrocoagulation, and photodynamic therapy with 5-aminolevulinic acid [96–98]. Studies of thermal ablation routinely found incomplete macroscopic regression of the Barrett's segment and buried intestinal metaplasia beneath the neosquamous epithelium, which not surprisingly, led to reports of subsquamous cancers developing in patients with previously nondysplastic Barrett's epithelium [99–101]. Furthermore, persistent genetic abnormalities were noted after photodynamic therapy, despite down-staging histology from high-grade dysplasia to lesser abnormalities and the subsequent redevelopment of high-grade dysplasia [102]. Others have also demonstrated persistent molecular abnormalities after ablative therapy in residual dysplastic and nondysplastic epithelium [103–105].

As such, it appears that many techniques evaluated to date have fallen by the wayside or will do so shortly. These include multipolar electrocoagulation, the heater probe, argonplasma coagulation, laser, and in all likelihood photodynamic therapy in its current iterations. The reasons that these techniques likely have no long-term future include difficulty in obtaining uniform ablation, cost, side effects, and persistent endoscopically evident or microscopic columnar epithelium after therapy. Current thermal techniques still in play include radiofrequency ablation and cryotherapy. The only conceivable place at present for techniques such as multipolar electrocoagulation and argon plasma coagulation is for small islands and areas of residual Barrett's esophagus after treatment with another more effective modality. All thermal techniques have one other critical flaw: complete pathologic confirmation of the index lesion can never be obtained leaving both the physician and patient uncertain as to the results of the treatment. Pros and cons of thermal ablation techniques are summarized in Table 3.

Table 3
Thermal and photodynamic therapy: advantages and disadvantages

Advantages

- Low mortality
- Low morbidity
- Esophagus remains in situ
- Comparable survival to esophagectomy
- Decreased progression of high-grade dysplasia to cancer

Disadvantages

- At-risk mucosa remains behind
- Continued cancer risk
- Lack of tissue confirmation
  - Diagnostic uncertainty at entry and follow-up
- Need for ongoing meticulous surveillance
- Underlying subsquamous intestinal metaplasia
- Lifelong antireflux measures
- Persistent molecular abnormalities in unablated mucosa
- Photodynamic therapy
  - Capital costs
  - Photosensitivity
  - Strictures
- Radiofrequency ablation and cryotherapy
  - Limited short- and long-term data
- Uncertain quality of life

Photodynamic Therapy

A randomized controlled study has evaluated photodynamic therapy with porfimer sodium compared to a strategy of continued surveillance for patients with high-grade dysplasia [69]. At 2 years, complete ablation of high-grade dysplasia occurred in 77% of the photodynamic therapy group compared to 39% of patients in the surveillance group with progression to cancer in 13 and 28% respectively. Importantly, complete elimination of intestinal metaplasia occurred in only 52% of the photodynamic therapy group and 7% of the surveillance group and complications were common: strictures occurred in 36% and photosensitivity in 69%. At 5 years, the probability of complete ablation of high-grade dysplasia after photodynamic therapy was only 48% and progression to cancer occurred in 15% [106]. While superior

to the control arm, these results demonstrated some of the problems with this technique including continued risk of cancer, ongoing need for surveillance, along with the cost and morbidity of this procedure. Work from the Mayo Clinic found that patients with high-grade dysplasia treated with photodynamic therapy had long-term survival comparable to patients treated with esophagectomy and low rates of cancer-associated death [40]. Photodynamic therapy has the advantages of leaving the esophagus in situ, evidence from randomized controlled trials that it is superior to continued surveillance and evidence form cohort studies that survival is comparable to esophagectomy. Disadvantages include the considerable capital expense of the equipment required, high rate of strictures, prolonged photosensitivity and thus implications for quality of life, lack of tissue confirmation, and problems in attaining complete ablation of intestinal metaplasia.

Radiofrequency Ablation

Studies to date have evaluated radiofrequency ablation of nondysplastic Barrett's epithelium as well as low-grade and high-grade dysplasia. For high-grade dysplasia, patients with either no nodularity or nodularity removed by endoscopic mucosal resection, a registry study of the 360° radiofrequency ablation device demonstrated complete elimination of high-grade dysplasia in 90.2% of individuals at a median follow-up of 12 months but complete elimination of intestinal metaplasia in only 54% of individuals [107]. The more recent randomized sham control study of radiofrequency ablation for high-grade dysplasia demonstrated complete resolution of high-grade dysplasia in 81% of the treatment group compared to 19% of the sham group using a combination of the circumferential and focal probes at 1-year follow-up [95]. Importantly, progression to cancer occurred in 2.4% of the treatment group compared to 19% of the sham group. Complete elimination of intestinal metaplasia occurred in 77% of the treatment group compared to 2% of the sham group. Adverse events were encountered in 3 of 298 treatments including bleeding and chest pain whereas 6% developed strictures which were easily dilated.

Taken together with other data on radiofrequency ablation, we now know that a combination of circumferential and focal probes provide the optimal results, that this technique can be safely combined with endoscopic mucosal resection and that buried intestinal metaplasia appears to be rare. We also know that this method does not completely eliminate cancer risk or progression of low-grade dysplasia to high-grade dysplasia. As with other ablative techniques other than endoscopic mucosal resection, radiofrequency ablation does not allow tissue confirmation of efficacy leaving a measure of uncertainty for each patient. Published

results of radiofrequency ablation come primarily from centers of excellence and as such, we do not know about safety and efficacy when disseminated outside of expert centers. Only a limited number of patients have been studied to date and we do not know about long-term results beyond 2.5 years.

Cryotherapy

Cryotherapy remains under study as an ablative technique, be it as a stand-alone approach or in combination with endoscopic mucosal resection. There are two current techniques: carbon dioxide and liquid nitrogen. However, very limited data are available as to its efficacy in Barrett's esophagus. Johnston et al. studied 11 patients with complete endoscopic and histologic reversal in 7 of the 11 patients at 6 months [108]. A preliminary report of cryotherapy in a small group of patients with high-grade dysplasia and cancer demonstrated that the technique had potential and a randomized sham-controlled study is now underway [109]. The concern with this technique, besides lack of published data, is uneven application inherent in spraying of the cryogen rather than direct balloon-based application to isolated segments of the esophagus. Cryotherapy is currently best limited to clinical trials given the lack of published data to date.

Endoscopic Mucosal Resection

Endoscopic mucosal resection is a therapeutic option for patients with either high-grade dysplasia or intramucosal carcinoma in the setting of appropriate risk stratification. As described above, endoscopic mucosal resection permits accurate histological staging of neoplasia arising in Barrett's epithelium when compared to esophageal resection specimens. Negative margins on endoscopic mucosal resection specimens correlate well with absence of residual disease at the time of surgery but submucosal involvement is associated both with residual disease at the time of surgery and lymph node metastases [110]. As emphasized by the Wiesbaden group, endoscopic mucosal resection with curative intent should only be attempted for low-risk lesions. The issue of submucosal cancer limited to the superficial layer is an evolving area of debate as described above.

The pioneering work of the Wiesbaden group with endoscopic mucosal resection in a total of 100 patients resulted in compete local remission in 99 after a mean of 1.47 endoscopic mucosal resections with no strictures and the only minor bleeding in 11 patients [4]. However, there were 11 metachronous lesions in 11 patients for a recurrence rate of 11%, characterized by local recurrence in 6 and disease at a different location in 5. There were two deaths in the series: one

patient with CREST died from pneumonia and one patient died from carcinoma of the oral cavity. The 5-year life table survival of these patients was 98%. However, it is important to emphasize some key methodological aspects of the Wiesbaden group's work. Prior to entry into the study, patients with confirmed adenocarcinoma were meticulously staged with the following techniques: high resolution white light endoscopy, methylene blue chromoendoscopy, biopsies of all macroscopically visible lesions as well as unstained areas on chromoendoscopy, four-quadrant biopsies every 1–2 cm of the Barrett's segment, and endoscopic ultrasonography. All patients with proven adenocarcinoma underwent chest radiography, CT of the abdomen and chest, and ultrasound of the abdomen. Of note, there was no standard approach to residual Barrett's epithelium although 49 patients underwent thermal ablation with either argon plasma coagulation for short segment Barrett's esophagus or aminolevulinic acid photodynamic therapy for long segment Barrett's esophagus. Follow-up examinations were rigorous and involved four-quadrant biopsies as well as biopsies of any visual lesions at 1, 2, 3, 6, 9, and 12 months followed by every 6 months for 5 years along with EUS and CT scans at every other visit. Residual or metachronous disease, defined as high-grade epithelial neoplasia or early cancer after complete local remission was treated by endoscopic mucosal resection. While the work by Ell et al. makes a very strong case for the safety of endoscopic mucosal resection in superficial adenocarcinoma of the esophagus meeting low-risk criteria, their work reminds us of the problem of at-risk mucosa that remains behind after therapy, as recurrent or metachronous lesions were found in 11% of patients. There is a cost of this at-risk mucosa: continued high frequency endoscopic surveillance, costs encumbered by frequent endoscopy and biopsy, patient concerns regarding diagnostic uncertainty, and quality of life issues related to frequent endoscopy.

Studies to date suggest that circumferential endoscopic mucosal resection results in complete remission of intraepithelial neoplasia and Barrett's epithelium in 75–100% of patients [111–115]. Complication rates vary but early bleeding, the occasional perforation, and late strictures remain issues (Table 4).

Thus endoscopic mucosal resection has the advantage of leaving the esophagus in situ, tissue confirmation of disease as well as evidence from cohort studies regarding excellent long-term survival. Disadvantages include need for continued and high frequency meticulous surveillance as well as at-risk mucosa remaining behind. The role of circumferential endoscopic mucosal resection is currently under study but is still hampered by high stricture rates.

Table 4
Endoscopic mucosal resection advantages and disadvantages

Advantages
• Can remove cancer
• Pathologic staging available on resected specimen
• Low mortality
• Low morbidity
• Esophagus remains in situ
Disadvantages
• >10% metachronous lesions when used as stand-alone technique
• At-risk mucosa remains behind
• Diagnostic uncertainty during follow-up
• Technically demanding for circumferential technique
• Need for ongoing meticulous surveillance
• Uncertain quality of life

Combination Therapy

Recent studies now indicate that complete ablation of Barrett's esophagus with endoscopic mucosal resection in combination with radiofrequency ablation is feasible. The Amsterdam group described the technique of circumferential and focal ablation radiofrequency ablation in a small number of Barrett's patients with residual dysplasia after endoscopic mucosal resection of visible lesions [116, 117]. Gondrie et al. found complete absence of Barrett's epithelium, dysplasia, cancer, and buried intestinal metaplasia in all patients studied at a median follow-up of 14 months. Others have described excellent long-term results with combinations of EMR and photodynamic therapy as well [40, 94].

Comparisons to Surgical Therapy

While there are no randomized controlled trials that have compared endoscopic to surgical approaches for the management of high-grade dysplasia and superficial carcinoma, a number of observational studies now suggest that long-term survival of the two techniques is comparable [40, 93, 118]. Studies extending over 5 years are now available on endoscopic mucosal resection, photodynamic therapy, and a combination of the two demonstrating comparable long-term survival to esophageal surgery for high-grade dysplasia or superficial carcinoma and low rates of cancer-associated death [40]. A recent population-based study of patients with early esophageal cancer found

comparable long-term survival for patients managed with endoscopic therapy compared to those treated with surgical resection [118]. However, while the 5-year survival is comparable between the two treatment modalities, cancer develops during follow-up of endoscopically treated patients in approximately 6% [40, 93].

Unresolved Issues in Endoscopic Therapy

There are many unresolved issues in ablation therapy. Assuming equal endoscopic skills, it remains important to know which endoscopic therapy should be applied to a given patient. Should endoscopic mucosal resection be limited to focal lesions only? What is the length threshold for circumferential endoscopic mucosal resection? Who should get thermal techniques and what parameters should be used to determine which patient should get which combination techniques?

What factors predict if a patient will respond to a given therapy? Possible variables include segment length, hiatal hernia size, adequacy of acid suppression, and biomarkers. To date, one study has evaluated biomarkers to predict response to photodynamic therapy. Prasad et al. found that p16 loss, detected by fluorescence in situ hybridization of cytology specimens obtained prior to photodynamic therapy for high-grade dysplasia or intramucosal carcinoma predicted a lesser response to photodynamic therapy [119]. While not ready for prime time, future studies will need to carefully examine biomarkers or other patient factors that predict response. A recent multivariate analysis by Pech et al., based on the long-term results of the Wiesbaden group's approach to patients with intraepithelial neoplasia with endoscopic mucosal resection with or without photodynamic therapy, identified the following as risk factors for disease recurrence after ablation therapy: long-segment Barrett's esophagus, multifocal neoplasia, piecemeal resection, and no ablative therapy of the residual Barrett's segment after a complete response by EMR [94].

While early data are promising with radiofrequency ablation, it is difficult to conceive of any technique reliably eliminating all subsquamous intestinal metaplasia. Biomarker abnormalities persist in this subsquamous epithelium and we still do not know what degree of subsquamous columnar epithelium, if any, can be tolerated after ablation. Recent studies in a small number of patients with buried intestinal metaplasia after photodynamic therapy found that buried Barrett's epithelium had reduced crypt proliferation and near normal DNA content compared to pretreatment Barrett's epithelium, raising the question of the neoplastic potential of the buried Barrett's epithelium [120]. Furthermore, better techniques of detecting buried columnar epithelium are needed.

Confocal endomicroscopy is one such technique under study. Molecular imaging advances would also be helpful.

Several reports suggest that the cardia behaves in unexpected and potentially undesirable ways after ablation therapy. Nodules with high-grade dysplasia or cancer may develop months to years after therapy [121, 122]. The reason for this is unknown. While squamous epithelium may develop below the gastroesophageal junction after ablation, it is unclear what the natural history of that metaplastic mucosa is [123]. Not only can problems develop at the cardia but techniques such as radiofrequency ablation are difficult to apply to the cardia, even with the focal probe, due to positioning and the anatomic alterations in the setting of a large hiatal hernia.

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Multipolar Electrocoagulation (MPEC): An Early, Widely Available Technique

V. Raman Muthusamy, MD
and Prateek Sharma, MD

CONTENTS

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Summary

Multipolar electrocoagulation (MPEC) ablation is a simple-to-use, familiar, widely available, inexpensive, and safe option for the endoscopic treatment of Barrett's epithelium. While its use has primarily been tested in non-dysplastic Barrett's epithelium, it may also be of value in non-nodular low-grade and high-grade dysplasia. It can achieve endoscopic and histologic ablation in at least 70–80% of the treated patients, with successful ablation typically achieved within three to four ablation procedures. Head-to-head comparisons with other thermal ablative techniques such as APC show the two techniques to be similar, although a non-statistically significant trend to improved efficacy was seen favoring MPEC. Successful acid suppression appears to be helpful in achieving effective ablation with this technique. Future studies comparing this technique with alternative ablation modalities, assessing its durability and the need for continued surveillance in successfully ablated patients, and evaluating whether ablation reduces the risk of subsequently developing adenocarcinoma are needed. Given these uncertainties, its use at present may best be limited to ablating residual short/limited areas of non-nodular Barrett's esophagus with high-grade dysplasia or early cancer.

Key Words: Barrett's esophagus, Endoscopic ablation, Multipolar electrocoagulation

INTRODUCTION

Previous studies have shown that neither acid suppression nor surgical fundoplication has been effective in reversing Barrett's esophagus to normal squamous epithelium [1, 2]. While photodynamic and laser therapy were the initially used methods of endoscopic palliation, MPEC was among the first modalities used to re-establish native Barrett's epithelium because it provided an inexpensive, widely available, and technically straightforward alternative to the aforementioned therapies. This chapter will detail the technique of MPEC ablation, its advantages and limitations, review the existing literature using this method, and discuss remaining areas of uncertainty regarding its use in Barrett's ablation.

MPEC EQUIPMENT AND TECHNIQUE

The technique for MPEC ablation is outlined in Fig. 1. Unlike the protocol for some ablation techniques, MPEC ablation does not require the use of acetic acid or other mucolytics to disrupt the mucus layer

1. Use acid suppression (Goal: pH<4 for <4.2% of time) with confirmation by pH testing
2. Prior to the initial ablation, consider endoscopic "tattoo" placement just proximal to the squamocolumnar junction to identify treatment landmarks at future ablation sessions
3. Use of 10 F probe through a therapeutic endoscope
4. Use of energy setting of 15–20 watts
5. Place probe at the gastroesophageal junction over Barrett's epithelium and obtain good tissue contact (direct or tangential)
6. Ablate until white coagulum appears
7. Pull endoscope proximally with probe in contact with mucosa until reaching the native squamocolumnar junction. Continue treatment circumferentially until the Barrett's segment is completely ablated
8. Work proximally until the top of the squamocolumnar junction is reached
9. Repeat treatment at 4–8 week intervals until endoscopic and histologic ablation achieved

Fig. 1. Suggested stepwise ablation technique for MPEC ablation of Barrett's esophagus.

overlying the epithelium prior to ablation. The MPEC probe delivers thermal energy to the targeted esophageal mucosa by the completion of an electrical circuit between two or more electrodes on the probe tip. The maximum temperature achieved is 100°C [3]. The electrical generator should be set to deliver between 15 and 20 W of energy. Theoretically, the depth of tissue injury is limited by the fact that electrical transmission is terminated once the mucosa is desiccated from MPEC therapy, resulting in no further tissue injury. The probes that deliver the energy through the endoscope come in 7 F and 10 F sizes (Gold Probe; Microvasive Endoscopy, Boston Scientific Corp., Natick, MA). No data are available about difference in performance characteristics between the two probe sizes, but it would appear that the larger probe size would enable coverage of a greater surface area per coagulation, leading to a probable reduction in procedure time. Similarly, either the tip or the side of the probe may be used for ablation, although tangential application of the probe would treat a larger surface area. Contact time should be just long enough to create a white coagulum. An example of the application of this MPEC ablation technique is shown in Fig. 2. Published studies have utilized both a proximal-to-distal and distal-to-proximal ablation technique, although the latter appears to be favored [4–6]. In addition, while initial studies utilized hemi-circumferential treatment of a 2–3 cm length of Barrett's epithelium per ablation session, more recent studies

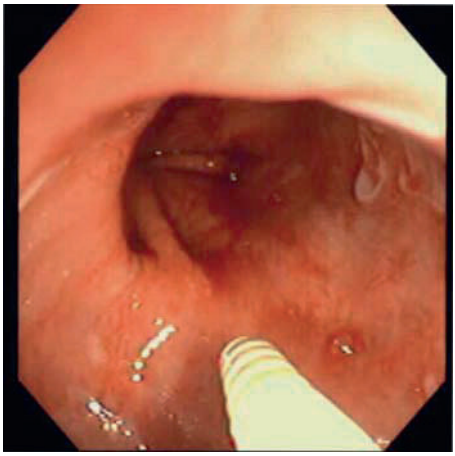

Fig. 2. Endoscopic image showing MPEC ablation of Barrett's epithelium.

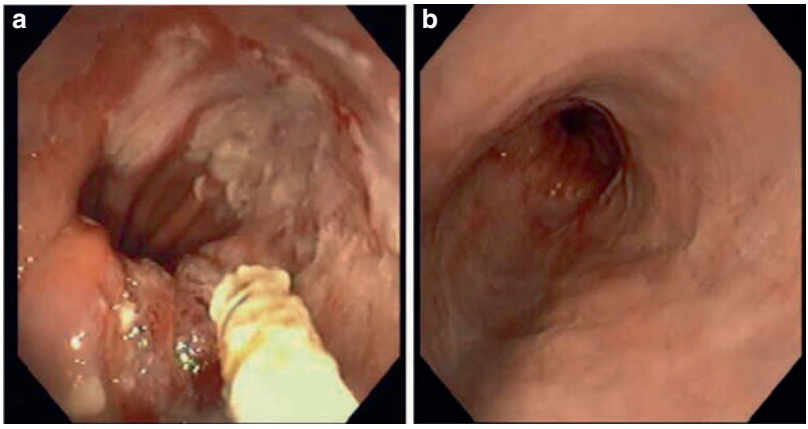

Fig. 3. (**A**) Endoscopic appearance of Barrett's esophagus immediately post-MPEC ablation. (**B**) Follow-up endoscopy showing endoscopic reversion to squamous epithelium, which was also confirmed histologically.

have shown that circumferential ablation of the entire length of Barrett's epithelium can be performed without an increase in stricture risk [4–7]. After treatment, acid suppression should be continued and follow-up endoscopy and ablation should be performed after 4–8 weeks. However, one study has shown that follow-up ablation at even 1-week intervals is feasible [4]. Figure 3 demonstrates the endoscopic appearance of a treated Barrett's segment immediately after and at the completion of MPEC ablation therapy session.

ADVANTAGES OF MPEC TECHNIQUE

MPEC ablation has numerous advantages. It does not require an additional drug or treatment agent such as a photosensitizer or liquid nitrogen. The technique is familiar to most gastroenterologists and allows for the use of the tip or side of the electrode to achieve ablation. Additionally, the required energy source is readily available in most endoscopy units due to the widespread use of MPEC in achieving endoscopic hemostasis. It also does not require expensive or fragile disposable treatment catheters, as seen with radiofrequency ablation or photodynamic therapy (PDT).

Another previously mentioned advantage of MPEC ablation is that after tissue desiccation occurs with treatment, further energy transfer and subsequent tissue injury is halted. This mechanism has been proposed to account for the low stricture rate associated with MPEC. Stricture formation is typically associated with injury to the submucosal layer encompassing more than half the circumference of the esophagus. The average thickness of Barrett's epithelium has been reported as 0.5 mm, with a mucosal thickness of 1.5 mm and distal esophageal wall thickness of approximately 4 mm [8]. However, the depth of ablation achieved by MPEC may vary from 1.7 to 4.8 mm and is dependent on a variety of factors that include the energy (watt) setting, degree of pressure applied to the mucosa, and the duration of ablation [9]. Thus, despite the safety features associated with thermocoagulation, injury to the submucosa and muscularis propria may occur if proper technique is not followed. The use of the appropriate energy setting, modest probe pressure on the mucosa, and stopping therapy upon the creation of a white coagulum seem likely to avoid deep tissue injury.

LIMITATIONS OF MPEC TECHNIQUE

One of the primary limitations of this technique involves the small size of the treatment electrode, even when a 10 F probe is used, and the need for tissue contact to achieve ablation. This makes treating large areas of Barrett's epithelium tedious and cumbersome. However, a study comparing this device to a non-contact technique, argon plasma coagulation (APC), showed MPEC ablation procedure times to be equivalent to APC when adjusted for the length of Barrett's epithelium treated [5]. Another limitation may be the depth of ablation achieved with standard MPEC technique which may not be sufficient to achieve eradication of nodular high-grade dysplasia or early adenocarcinoma [10, 11]. Finally, given the multiple variables (tip or side ablation, amount of tissue contact and apposition) that can be present with MPEC ablation, some

inequity in the administration of energy may occur over the treated region. This may lead to variability in depth of injury produced, which in turn may lead to residual intestinal metaplasia and the presence of buried glands under new squamous epithelium.

RESULTS OF MPEC FOR THE ABLATION OF BARRETT'S EPITHELIUM

The initial use of MPEC for ablation of Barrett's epithelium was described in 10 patients with non-dysplastic Barrett's esophagus averaging a mean length of 4.4 (range 2–9) cm [7]. Patients had one half of the metaplastic circumference treated with MPEC therapy while the other half served as a control. Anti-secretory therapy with a mean dose of 56 mg of omeprazole was utilized, and 9 of 10 patients underwent 24 pH testing prior to ablation to document acid suppression. MPEC ablation was performed at 4–6 week intervals until endoscopic evidence of re-epithelialization was noted. Subsequently, large capacity forceps were used to confirm histologic reversion to squamous epithelium. All 10 patients achieved endoscopic and histologic elimination of Barrett's epithelium with MPEC, despite inadequate acid suppression (i.e., time intra-esophageal pH <4: $>4\%$) in 2 patients. A mean of 2.5 (range 2–4) MPEC sessions were needed. After a period of 6 months, 9 patients agreed to treatment of the non-ablated hemi-circumference using a similar ablation and biopsy protocol. Five of the nine patients had achieved complete ablation of Barrett's epithelium at the time of publication, with the remaining four patients with ongoing MPEC therapy. At a mean of 12 (range 10–18) months follow-up, none of the 10 patients who had successful ablation of the initially treated metaplastic hemi-circumference had evidence of endoscopic or histologic reversion to Barrett's epithelium.

A second single-center study similarly examined patients with greater than 2 cm of non-dysplastic Barrett's esophagus [4]. All patients were treated twice-daily with proton-pump inhibitors and underwent esophageal motility and pH testing prior to ablation and at 9 and 18 weeks post-ablation. Patients received weekly MPEC in 2–3 cm sections in a hemi-circumferential fashion and were offered ablation of the other half at 9 weeks. Twenty-seven patients with a mean Barrett's esophagus length of 3.4 (range 2–10) cm were enrolled in the study. Successful ablation was achieved in 81% (22/27) of patients, despite 10 patients registering an abnormal post-ablation pH study. Additionally, MPEC efficacy appeared to be more affected by the length of the treated Barrett's segment rather than successful acid suppression, with complete Barrett's eradication in 21 of 23 (91%) patients with ≤ 4 cm of

Barrett's esophagus but only in 1 of 4 (25%) patients with $>$ 4 cm of Barrett's esophagus.

Montes and colleagues studied 14 patients with a mean of 4.8 (range 3–7) cm of non-dysplastic Barrett's esophagus who had previously been treated with laparascopic anti-reflux surgery [12]. All patients were free of reflux symptoms and off anti-secretory medications. Monthly MPEC treatments were done in a hemi-circumferential fashion over 2–3 cm per treatment. Ablation was successful, confirmed by endoscopy and histology, in all cases; a mean of 3.7 (range 3–7) treatment sessions were required. During a mean follow-up period of 21.6 (range 18–30) months, all patients remained symptom free off medications and showed no endoscopic or histologic evidence of Barrett's recurrence.

A larger, multi-center trial evaluated 58 patients with 2–6 cm of non-dysplastic Barrett's who received up to six MPEC ablation treatments at 4–6 week intervals while on acid suppression [13]. The mean length of Barrett's esophagus was 3.4 cm with 62% having at least 3 cm of Barrett's esophagus. Unlike previous trials, the ablation protocol at each of the three sites aimed for circumferential treatment of the entire segment of Barrett's esophagus at each session. Endoscopic evaluation included the absence of columnar appearing epithelium at endoscopy and chromoendoscopy using Lugol's staining and histology was obtained via large capacity biopsies in a four-quadrant fashion every 2 cm in the region of the treated Barrett's epithelium. Endoscopic ablation was successful in 85% of patients, while histology confirmed ablation in 78% of patients. The mean number of treatment sessions necessary to achieve complete ablation was 3.5 (range 1–6). Interestingly, the number of treatment sessions needed to completely ablate $<$ 3 cm segments was not different than that needed to ablate $\geq$ 3 cm segments. However, information regarding the percentage of ablation failures in each of these groups was not presented.

COMPARATIVE TRIALS OF MPEC TO OTHER ABLATIVE MODALITIES

As the aforementioned data for MPEC ablation was accumulating, other ablative techniques were also being utilized to treat and reverse Barrett's esophagus. More recently, there has been interest in trials comparing ablative modalities to each other with regard to success rates, treatment duration, complications, and durability. To date, there have been two published studies comparing MPEC ablation to other modalities [5, 6]. Both were randomized controlled trials where MPEC was compared with argon plasma coagulation (APC) for the eradication of Barrett's esophagus (non-dysplastic and low-grade dysplasia).

The first study by Dulai et al. compared 52 patients with 2–7 cm of Barrett's esophagus who were randomized to either MPEC or APC ablation [5]. The only measured difference between the groups was the mean length of the Barrett's segment (3.1 cm for MPEC compared to 4.0 cm for APC). Acid suppression with twice-daily PPI therapy was utilized, and one patient with low-grade dysplasia was enrolled in the MPEC arm of the study. Two patients dropped out from each group due to intervening medical illness or loss to follow-up. Although the primary outcome variable, the mean number of sessions needed to achieve ablation, was significantly reduced for MPEC compared to APC (3.0 vs. 3.9, $p = 0.05$), this may have been affected by the significantly different lengths of the pre-ablation Barrett's segment between the groups. In addition, there was a significant 3–4 min reduction in procedure time in favor of MPEC ablation when compared to the APC technique. However, by intention to treat analysis, there was no significant difference between the two modalities in endoscopic and histologic ablation rates. MPEC achieved endoscopic and histologic ablation in 88 and 81% of patients, respectively. This was not significantly different from the APC group (81 and 65%, respectively). Of note, the mean length of Barrett's esophagus was longer (6.0 cm vs. 3.3 cm, $p < 0.01$) in patients with failed ablation. No serious adverse events occurred with either technique.

Similar efficacy results were also seen in a second randomized comparison between these two modalities by Sharma et al. [6]. This study consisted of 35 patients (19 APC, 16 MPEC) with 2–6 cm of Barrett's epithelium treated with twice-daily PPI therapy. Ablation of the entire Barrett's segment was performed at 4–8 week intervals, with a maximum of six ablations. Of note, patients in this study were followed for a minimum of 2 years. Complete endoscopic and histologic reversal was seen in 69% (24/35) of patients; MPEC 75% and APC 63%. There was no difference between the groups in the number of treatment sessions needed to achieve ablation, and no factors were identified that predicted response to ablation therapy. No major complications were noted; however, one APC-treated patient developed a mild stricture that resolved with a single dilation. A meta-analysis of these two trials again showed no significant difference between the two techniques, with MPEC achieving successful ablation in 78.6% and APC in 64.4% of the treated patients [14]. The odds ratio of successful MPEC ablation compared to APC was 2.01 (95% C.I. 0.77–5.23, $p = 0.15$). A summary of all published papers utilizing MPEC for Barrett's ablation is presented in Table 1.

Table 1
Summary of published manuscripts utilizing MPEC for ablation of Barrett's esophagus

Study author	*Year*	*N*	*Barrett's length (mean or median)*	*Acid suppressions*	*% Ablated (endoscopic and histologic)*	*Mean # of treatment sessions*	*Major complications*	*Follow-up (months)*
Sampliner et al. [7]	1996	10	4.4	Omeprazole 20 mg BID	100	2.5	None	12
Kovacs et al. [4]	1999	27	3.4	Lansoprazole 30 mg BID	82	2.5	None	4.5
Montes et al. [12]	1999	14	4.8	Fundoplication; no PPI	100	3.7	None	21.6
Sampliner et al. [13]	2001	58	3.4	Omeprazole 40 mg BID	78	3.5	None	6
Dulai et al. [5]	2005	26	3.1	Pantoprazole 40 mg BID	81	2.9	None	0
Sharma et al. [6]	2006	16	3.0	Rabeprazole 20 mg BID	75	4	None	24

COMPLICATIONS AND PRECAUTIONS FOR PERFORMING MPEC ABLATION

Major complications with MPEC ablation have been rare. No cases of perforation have been reported. Hospitalization for chest pain has been reported in only a single patient [13]. Gastrointestinal bleeding has been reported from an esophageal ulcer in a single patient 2 weeks after MPEC therapy. The patient was hospitalized, but did not require transfusion [7]. Another patient had coffee-ground emesis shortly after ablation, but without a change in hemodynamics or hematocrit, the patient did not require admission [13]. The development of strictures has been reported in 2/151 (1.3%) patients treated in the aforementioned six studies on MPEC ablation. Both patients had a previous history of strictures that had been dilated prior to beginning ablation therapy, and the post-ablation strictures resolved with 1 and 3 dilations, respectively. This low rate of stricture development compared to other modalities such as PDT is likely due to limitation of deep tissue injury by tissue desiccation from MPEC-delivered energy that results in preventing further electrical and energy transmission when proper technique is used. Minor complications such as dysphagia, odynophagia, chest pain, nausea, heartburn, and fever have been reported to occur in 7–43% of cases, but these symptoms have been short-lived (typically under 2 weeks in duration) and self-limited [7, 13]. In addition, no esophageal motility abnormalities have been observed in patients post-ablation [4].

CONCERN OVER SUBSQUAMOUS INTESTINAL METAPLASIA (SSIM) AND DURABILITY

A major concern regarding endoscopic therapy is the identification of SSIM on endoscopic surveillance biopsies post-ablation. The presence of SSIM, particularly when there is no endoscopic evidence of columnar lining, is worrisome for the development of subsquamous neoplasia that may escape detection via surveillance biopsies. The initial study of MPEC ablation reported 2 of 10 patients with SSIM, which resolved with additional MPEC therapy [7]. A larger, multi-center reported 4 of 58 patients with endoscopically normal-appearing mucosa to have intestinal metaplasia on biopsy; 3 with SSIM (5%) [13]. Although Dulai and colleagues had nearly three quarters of patients with residual intestinal metaplasia after ablation showing SSIM, all these patients had endoscopic evidence of columnar-lined esophagus [5]. Several studies have not reported this issue, but this may be due to a failure to use jumbo biopsy forceps during surveillance biopsies [4].

A study utilizing EUS as a possible means of identifying response to ablation therapy showed that of 25 patients undergoing ablation therapy, the mean EUS wall thickness was unchanged in 6 patients with residual intestinal metaplasia [8]. In contrast, the 19 patients with successful ablation (endoscopic and histologic) had a statistically significant reduction in mean wall thickness from 4.1 to 3.6 mm ($p < 0.01$). Only 1 of 11 patients with a reduction in wall thickness by EUS had residual intestinal metaplasia. The authors concluded that the reduction in wall thickness was a reassuring sign that squamous hyperproliferation or extensive subsquamous intestinal metaplasia were not present. However, the gold standard for exclusion of SSIM is the evaluation of esophagectomy specimens. To date, only a single report of one patient with previous MPEC ablation undergoing esophagectomy is available. The examined specimen showed no intestinal metaplasia under the neosquamous epithelium [15].

In addition to the concern over buried glands, the durability of the achieved ablation is uncertain. The original publications of MPEC ablation had follow-up durations of 0–24 months. A longer follow-up study that included patients from the original reported study of MPEC ablation showed the technique to be durable [16]. This study included 11 patients (4 with low-grade dysplasia) with a mean Barrett's length of 4.4 cm who had successful ablation. All patients had endoscopic reversal maintained at a mean of 36 (range 19–53) months follow-up, but 3 of 11 (27%) had persistent SSIM. All patients with low-grade dysplasia had no histologic evidence of intestinal metaplasia at follow-up. Another study evaluating efficacy and durability described six patients with intramucosal cancer who underwent a combination of laser and MPEC ablation because they either refused surgery or were not surgical candidates [17]. The results showed that at a mean follow-up of 3.4 years, two patients had total resolution of intestinal metaplasia, two had residual non-dysplastic intestinal metaplasia, one had low-grade dysplasia, and one patient with immunosuppression due to solid organ transplantation developed cancer. Despite these data, longer term studies regarding these critical issues are still lacking.

NEED FOR pH CONTROL

The need for adequate acid suppression, defined as a pH < 4 for $< 4.2\%$ of the time on esophageal pH monitoring, has been suggested as necessary for re-epithelialization. This goal, however, may be difficult to achieve [18]. A study of 25 patients (length 2–6 cm) being evaluated for MPEC ablation therapy showed that 16% had abnormal pH studies on twice-daily PPI and an additional 8% had abnormal

supine acid exposure [19]. Acid suppression showed an arithmetic trend towards worsening with age, but not with increasing Barrett's length. Interestingly, normalization of esophageal acid exposure appears to be neither a necessary prerequisite nor a guarantee of successful ablation. In a study of 20 patients undergoing MPEC ablation, 3 patients did not achieve normalization of esophageal pH on twice-daily PPI, but all of them achieved successful endoscopic and histologic ablation [20]. In contrast, 5 of 17 (29.4%) patients with normal pH studies failed ablation after six treatment sessions. In addition, a second study showed that while abnormal pH studies were more common in patients with failed ablation, nearly half (10/22) of the successfully ablated patients had abnormal pH studies [4]. In summary, based on the current studies, it is unclear if pH normalization is critical for the development of neosquamous epithelium or if it is of primary importance for the prevention of recurrent Barrett's esophagus. At present, it does appear that acid suppression is most likely necessary to achieve ablation, but the exact level of acid suppression needed appears uncertain.

ADDITIONAL UNRESOLVED ISSUES

Several additional areas of uncertainty persist regarding endoscopic ablation using MPEC and other modalities. One potential advantage of ablation of non-dysplastic BE is a reduction in cost via the elimination of the need for post-ablation endoscopic surveillance in successfully ablated patients. However, the long-term durability of this technique is unknown, with little existing follow-up data extending beyond 2 years post-ablation. This question will need to be answered before we can modify existing endoscopic surveillance guidelines and will be crucial in determining whether ablation is cost-effective. Probably the most critical question is whether endoscopic ablation can reduce the risk of developing esophageal adenocarcinoma. Such data is currently lacking and will likely require follow-up of a 5–10 years or more before meaningful results are obtained. The performance of such a study appears daunting, however, as one estimate suggested that 4,000 non-dysplastic Barrett's patients would need to be followed for at least 5 years to detect a difference between medical and ablation therapies [5]. Little data also exist regarding the normalization of biomarkers in the neosquamous epithelium achieved by MPEC ablation. However, one small study showed normalization of three biologic parameters felt to serve as intermediate markers for the risk of progression to esophageal adenocarcinoma: proliferation (Ki67), polyamine biosynthesis (ornithine decarboxylase levels), and p53 mutation [21]. Also, there is uncertainty regarding which patients would most benefit from endoscopic ablation therapy. At this time, only patients with HGD and/or early

cancer are appropriate candidates. For non-dysplastic BE, identification of biomarkers that accurately predict increased risk of progression of Barrett's esophagus to adenocarcinoma would aid in appropriate patient selection for ablation procedures. For MPEC, a potential concern is the applicability of this technique to patients with dysplastic Barrett's epithelium, as with the exception of four patients with low-grade dysplasia, all the patients in the six studies in Table 1 had non-dysplastic Barrett's esophagus. While it appears likely that similar results with MPEC can be obtained in low-grade dysplasia and non-nodular high-grade dysplasia due to their similar epithelial thicknesses, these assumptions require validation. MPEC may be best suited for the treatment of flat, non-nodular HGD of shorter lengths or for treatment of residual BE in longer lengths that have been treated with photodynamic therapy, radiofrequency ablation, or cryoablation.

SUMMARY

Multipolar electrocoagulation (MPEC) ablation is a simple-to-use, familiar, widely available, inexpensive, and safe option for the endoscopic treatment of Barrett's epithelium. While its use has primarily been tested in non-dysplastic Barrett's epithelium, it may also be of value in non-nodular low-grade and high-grade dysplasia. It can achieve endoscopic and histologic ablation in at least 70–80% of the treated patients (results very similar to other techniques such as APC and radiofrequency ablation), with successful ablation typically achieved within 3–4 ablation procedures. Head-to-head comparisons with other thermal ablative techniques such as APC show the two techniques to be similar, although a non-statistically significant trend to improved efficacy was seen favoring MPEC. Successful acid suppression appears to be helpful in achieving effective ablation with this technique. Future studies comparing this technique to alternative ablation modalities, assessing its durability and the need for continued surveillance in successfully ablated patients, and evaluating whether ablation reduces the risk of subsequently developing adenocarcinoma are needed. Given these uncertainties, its use at present may best be limited to ablating residual and/or short/limited areas of non-nodular Barrett's esophagus with high-grade dysplasia or early cancer.

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Endoscopic Mucosal Resection in Barrett's Esophagus: Endoscopic Surgery

Kenneth K. Wang, MD and Yutaka Tomazawa, MD

CONTENTS

Summary

Endoscopic mucosal resection is a technique to remove mucosal irregularities in Barrett's esophagus to enhance diagnosis and also to provide therapy. The Paris classification of lesions is explained. The basic principal is to lift the lesion by injecting a subepithelial bleb or banding. The polyp created is then snared and removed using a standard polypectomy technique. The various techniques to obtain the specimen, including submucosa dissection, are described. Careful

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histologic assessment of the specimen is necessary to appropriately stage the lesion and the likelihood of metastases.

Key Words: Endoscopic resection, Cap technique, Multiband device

The use of endoscopic mucosal resection in the diagnosis and treatment of neoplastic disease has been increasing because this technology fulfills all the basic tenets of open surgical cancer therapy. Surgical principles for neoplastic therapy involve being able to expose the lesion in its entirety, perform a complete resection of the neoplastic lesion with a reasonable margin, restore the continuity of the GI tract after resection, and have histological confirmation of the completeness of resection. It has been rare in the past for gastroenterologists to have this capability which represents a future direction for gastrointestinal endoscopic oncology that has become established in Asian countries.

LESION TYPES

Most mucosal lesions can be described using the Paris classification which was the result of a meeting between western endoscopists, pathologists, and surgeons to interpret Japanese classification of mucosal neoplasia. Japanese endoscopists have always performed very careful observations of mucosal lesions and have exacting descriptions. The overall consensus was to adopt a great deal of the Japanese classification system [1]. Early neoplasia (superficial) is termed a Type 0 lesions. The 0-I lesions are polypoid and can be classified as 0-Ip (pedunculated) or 0-Is (sessile). The 0-II-III lesions are non-polypoid. 0-IIa is slightly elevated, 0-IIb is flat, 0-IIc is slightly depressed, and 0-III is ulcerated. These types are all associated with more-invasive forms of cancer.

Overall, the lesions that can best be treated with endoscopic mucosal resection would be the 0-I, 0-IIa, and 0-IIb lesions [2]. The 0-IIc and 0-III lesions are much more difficult to resect and may require more attempts at mucosal resection to remove.

BASIC PRINCIPLES

Endoscopic mucosal resection basically applies to a term that involves using standard polypectomy techniques in flat mucosa to remove tissue. The terminology is a misnomer since it is important with this technique to resect into submucosal tissue that has led some practitioners to term this endoscopic resection. However, the situation has become further confused by the development of devices such as the braided snare,

monofilament snare, spiral snare, and the barbed snare, all of which are capable of removing flat mucosa, even without any lifting techniques due to their inherent tissue grasping abilities [3, 4]. Commonly, endoscopic mucosal resection techniques are thought to involve some type of mechanism to lift the mucosa rather than techniques to improve the ability of the snare to remove tissue. The initial description of mucosal resection involved overtubes that allowed the mucosa to protrude into an opening in the overtube [5–8].

The initial step for mucosal resection is lifting of the target mucosa. This is generally required as an essential step with most but not all mucosal resection techniques. The lifting part of this usually comes from pre-injection. The injection is usually made from a dilute epinephrine solution (1:200,000) that causes separation of the mucosa from the sub-mucosa. This step not only provides a potential space and a tissue plane for the resection to occur as shown in Fig. 1, but it also provides important information regarding the ability of the tissue to be separated from the muscularis propria to prevent a perforation. The injection of a dilute epinephrine solution also causes changes in the mucosa that often allows better visualization of neoplastic lesions. Some endoscopists also add a contrast agent such as indigo carmine that allows easier delineation of the base of the resection. There are several reasons why lifting may not occur. The most common is that there is adhesion of the lesion to the muscularis propria. However, recent biopsies of the lesion could produce inflammation that causes the lesion to become adhered without actual neoplastic invasion. In this case, waiting for 2–3 weeks can allow the procedure to be performed. In addition, scarring from prior ablation therapy could also cause the mucosa to become fibrotic and unable to be lifted from the submucosa. Of course, the least appealing explanation would be extension of the lesion onto the muscularis propria.

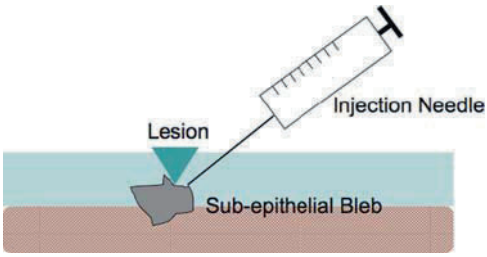

Fig. 1.

Once the tissue can be lifted, then mucosal resection techniques use a variety of mechanical means to elevate the tissue to allow their removal with a snare device. One of the most common elevation mechanisms is vacuum suction, such as with the cap technique. The mucosal resection is performed with a pre-fitted snare at the tip of the barrel. The other mechanism uses a variceal multi-band ligation device to maintain the elevated tissue. Other variations on the theme have been to lift the tissue using a biopsy forceps, have the tissue protrude within an opening in an overtube, or using an endoloop to constrict the tissue to allow removal.

All of these techniques involve trying to elevate otherwise flat tissue. The snare involved generally can be generic, although with the cap system, there has to be a crescent snare, which can seat itself around the barrel. Routine snares cannot be used with this application. The multi-band device uses a hexagonal snare, although the use of other snare types really would not be precluded.

Once the resection is performed, the tissue can be retrieved with the cap device simply by sucking the tissue into the barrel. Using the banding approach, usually multiple resections are performed and then the tissue can be retrieved using a Roth basket. The disadvantage in doing this is that it is difficult to discern which piece of tissue may be of greatest interest. This can be overcome by pre-marking the tissue of interest by injecting with a contrast solution, such as India ink, into the area prior to resection. Oftentimes, the target lesion becomes obscured with manipulation and it can be beneficial to mark the area to be resected using a cautery device such as a multipolar device to ensure the resection of the appropriate area.

CURRENT-AVAILABLE DEVICES

Commercially, the most common devices for endoscopic mucosal resection are the cap-type devices. These are constructed in either flexible or hard plastic and are available as either flat or oblique caps (see Fig. 2). The largest sized caps are usually flexible and at an oblique angle, which can take the largest size specimens. These caps can remove a specimen of about 3 cm in diameter with a soft oblique cap that is almost 2 cm in diameter. All of these caps are friction fitted to endoscopes, so the caps must be purchased for a specific endoscope type. The largest caps are designed for double-channel therapeutic endoscopes. If the cap does not fit snuggly on the tip of the endoscope, the cap can be taped to the endoscope to prevent accidental dislodgement especially when being withdrawn from the pharynx.

The cap also needs to be situated so that it is parallel to the tip of the endoscope. There is a faint line in the cap that can be used to align

Fig. 2. Hard plastic cap EMR device fitted onto the tip of a diagnostic endoscope. *Arrow* indicates *line* that can be used to make the cap parallel to the tip of the endoscope.

the cap to the end of the endoscope. If this is not done appropriately, the snare that fits into the tip of the endoscope will not fit appropriately onto the cap since it will exit the endoscope at an odd angle to the cap (see Fig. 3).

The positioning of the snare around the lip of the cap is the most difficult portion of the cap procedure. The snare must be seated flat against the lip of the cap in order for the tissue to be suctioned into the cap without dislodging the snare. This is shown in Fig. 4.

The snare must be carefully placed using suctioned mucosa to displace the snare onto the side of the cap. This is usually done whenever flat mucosa can be found that can be suctioned into the cap. Typically this is in the antrum of the stomach but this can be done in the fundus or even in the esophagus so long as the mucosa is relatively flexible and free of folds.

Once the snare is placed into position, there must be care exercised to prevent tension on the snare from dislodging the position of the snare.

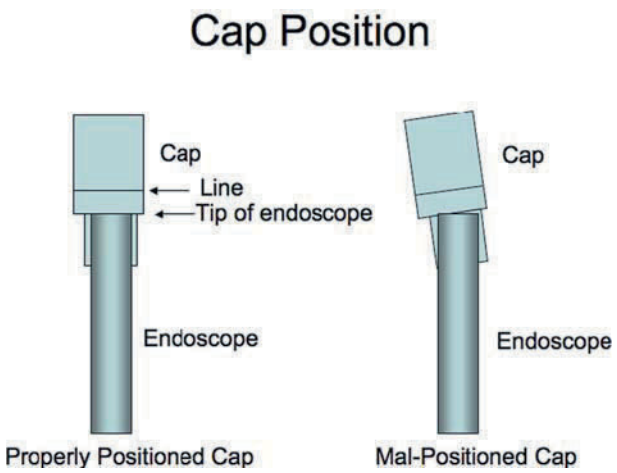

Fig. 3. A properly positioned cap allows the snare to be positioned on the lip of the cap appropriately. If the cap is angulated, this is more difficult to achieve.

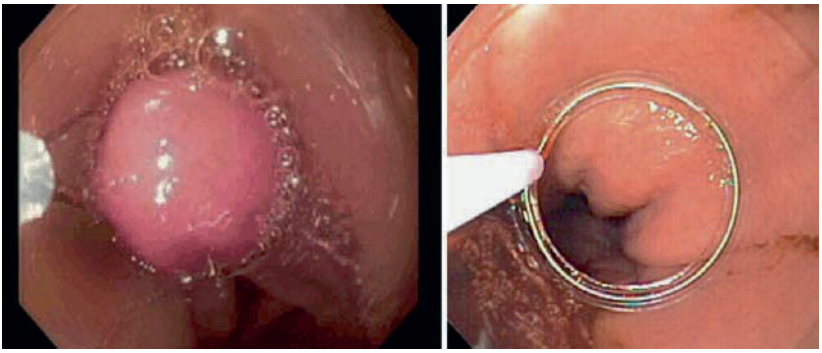

Fig. 4. This shows the snare fitted around the cap. Typically this occurs with the snare sheath 8–10 o'clock position. The snare has a point which is directed to the lip of cap allowing the snare to be positioned.

This can occur with movement of the endoscope. The assistant must stand fairly close to the endoscopist since the snare length is relatively short. Once this is positioned correctly, the target lesion can then be suctioned and the snare closed for the resection. The cap device can be used in areas that do not lift or are partially scarred but this requires extensive experience with EMR. This technique is very helpful in these situations but obviously the risk of complications can be much higher.

All of the cap techniques, as mentioned previously, depend on the use of a specialized crescent snare, which allows itself to be pre-fitted into the barrel of the cap prior to suctioning the mucosal resection. This

snare cannot be re-used and often can be bent while in the cap. The kit that is supplied comes with the injection needle, a snare, as well as a spray catheter for chromoendoscopy.

The multi-band technique is a modification of a standard variceal banding device except that the barrel of the ligating device is larger in diameter permitting a snare to fit in the biopsy channel with the control strings for the bands (see Fig. 5). The banding device is available in two sizes. One is a so-called diagnostic set that has a cap that will fit on a diagnostic endoscope, and the other is a therapeutic cap, which, in turn, fits on the tip of a therapeutic endoscope. The therapeutic banding device is usually preferred because larger tissue can be removed. In addition, various instruments can be exchanged in and out of the channel of the instrument while maintaining reasonable suction. The banding device is supplied with a cap with six pre-fitted bands, all of which are released using a control thread that is threaded through to a control knob that is mounted in the biopsy channel through the endoscope. The device is simpler to use since the tissue can be suctioned into the banding device much like a variceal ligator. The tissue should be suctioned deep within the cap to permit the bands to hold the tissue. Once the tissue is captured within the band, a hexagonal snare is used to resect the tissue. There is no real difference that has been noted between snaring tissue above or below the band. A typical variceal ligator cannot be used in this fashion since the barrel is not wide enough to permit the passage of a snare. This device is supplied with the cap, the control knobs, and the thread. No additional instrumentation is provided, except for a needle, which must be fitted to any device to supply irrigation through the cap.

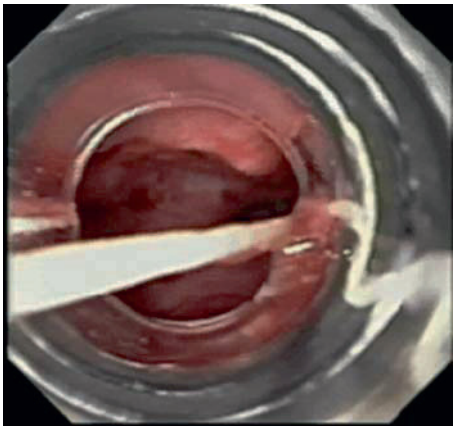

Fig. 5. The view through the banding device. Ideally, the control strings for this device should be in the 10 and 4 o'clock positions.

Multiple resections can be performed with this device and it is often necessary to resect specimens side by side. There is always a concern with this technique regarding potential suction of muscularis propria and even though the band should prevent full thickness resection, this has been reported. It is important to resect tissue completely without leaving too much of a "bridge" in between resections since these areas can contain neoplasia. Overlapping by about 20% ensures adequate removal without a great risk for perforation.

DEFINING THE LESION

A number of studies have been done to try and discern which lesions would be most amenable to endoscopic mucosal resection. Generally, it was found that flat or elevated lesions were most easily resected [2]. Ulcerated lesions are more difficult although they still can be removed. These lesions are generally not large in size; most lesions that are removed with this technique are less than 3 cm in diameter. Usually, when greater than 3 cm, there is a high likelihood that there is metastatic disease present.

Most of these lesions are flat or elevated which allows easier delineation of the resection margins. However, indigo carmine can be used as a mucosal contrast agent that is not absorbed and can highlight microscopic differences in the mucosa. It is very difficult to discern how far dysplastic lesions extend in the flat mucosa. Another method to try to determine if adequate boundaries are obtained is to perform frozen section analysis on this. We found a fairly high agreement between the frozen sections and regular histology in one of our prior studies [9].

Endoscopic ultrasound has been used to stage lesions prior to mucosal resection. This should generally be done using high frequency probes in a water-filled esophagus. Using an EUS endosocope usually is not very productive since the balloon needed for acoustical coupling tends to flatten lesions and is not very accurate for assessing depth [10].

ENDOSCOPIC MUCOSAL RESECTION AS A DIAGNOSTIC TECHNIQUE

We have previously published that by performing endoscopic mucosal resection, the preoperative diagnosis is changed in 40% of the cases [11]. Most of the time, this is a change for the worse. In other words, higher grades of dysplasia or cancer are detected. However, there are often cases where previously suspected cancers were not found to contain any cancer upon mucosal resection. This is obviously of great benefit to the patient.

EXISTING DATA

A number of studies have been published using endoscopic mucosal resection for the treatment of Barrett's esophagus. These are shown in Table 1. Endoscopic mucosal resection can definitely eliminate early cancers and areas of high-grade dysplasia with very high efficacy, at least initially. The occurrences after mucosal resection are defined by the degree of dysplasia remaining in the Barrett's mucosa. If no dysplasia is found, the incidence of recurrence is down as far at 16%. In cases where there has been dysplasia remaining, the incidence of recurrence is over 30%. This definitely implies, then, that endoscopic mucosal resection in the setting of Barrett's esophagus should probably be combined with some type of other ablative therapy if there is significant disease remaining. It is important for mucosal resection specimens to be carefully processed and a pathological description of the surgical margins obtained.

Table 1

Author	*Patients*	*EMR type*	*Success rate (%)*	*Complication (%)*
Nijhawan and Wang [12]	25	Cap, band	100	0
Buttar et al. [13]	16	Cap	94	6
May et al. [14]	70	Cap	98	10
Seewald et al. [3]	12	Snare (circumferential)	100	50
Giovanni et al. [15]	21	Snare (circumferential)	86	19
Conio et al. [16]	27	Cap	93	10
Lopes et al. [17]	41	Cap (circumferential)	76	14

PATHOLOGY

Mucosal resection specimens need to be carefully assessed histologically. Specimens need to be "breadloafed" meaning that multiple sections need to be made through an EMR. This allows the endoscopist to understand if complete resection of neoplastic lesions has occurred. In addition, careful assessment of depth of resection is essential to determine risk of metastasis [18]. We have found that submucosal invasion is

associated with metastasis in over 30% of patients. In addition, if immediate knowledge of the pathology is required, frozen section analysis of depth of invasion has been found to correlate well with permanent sections [9]. This allows the assessment of depth of invasion to be done before multiple resections are performed in large lesions.

SUMMARY

Endoscopic mucosal resection is a very common technique for removing areas of neoplastic tissue in flat mucosa. This has definitely extended the abilities of the gastroenterologists to treat people with premalignant lesions and even early cancers. It may even obviate the need for esophagectomy in a large number of these patients. Now, not only can we carefully diagnose lesions that are present, we can actually treat neoplastic lesions and monitor patients in case they reoccur. This can be done using surgical principles assessing margins of resection as well as depth of tumor principles.

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Combination – Multimodal Therapy

Oliver Pech, Hendrik Manner, and Christian Ell, MD, PhD

CONTENTS

Summary

Multimodal therapy includes a combination of endoscopic techniques with background proton pump inhibitor therapy. Endoscopic resection allows direct staging of neoplasia and removal of visible mucosal irregularities. Ablation of the residual Barrett's epithelium can be accomplished by a number of thermal techniques. The latter's ablation is important in reducing neoplastic recurrence and metachronous malignancy in any residual Barrett's epithelium.

Key Words: Endoscopic resection, Thermal ablation, Photodynamic therapy

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INTRODUCTION

As described in detail in previous chapters there is a wide variety of different treatment methods for early Barrett's neoplasia: There are different endoscopic resection techniques [endoscopic resection (ER), endoscopic submucosal dissection (ESD)], athermal [photodynamic therapy (PDT)] and thermal ablation methods [argon-plasma-coagulation (APC), multipolar electrocoagulation (MPEC), radiofrequency treatment (RFT)], and also cryoablation techniques. Endoscopic resection (ER) and photodynamic therapy (PDT) are the best-validated treatment methods in patients with high-grade intraepithelial neoplasia and mucosal Barrett's cancer and are widely used all over the world [1, 2].

In contrast to all of the mentioned ablative treatment methods, ER allows histological assessment of the resected specimen in order to assess the depth of infiltration of the tumor and freedom from neoplasia at the lateral and (more importantly) basal margins, imitating the surgical situation [3]. These significant advantages of ER are the main reason why ER should be preferred to ablative treatment methods, even PDT, whenever possible, especially keeping the low accuracy of endoscopic ultrasound (EUS) regarding local tumor staging in mind. A major advantage of PDT and radiofrequency ablation is that these methods permit the treatment of widespread mucosal abnormalities that may be present in Barrett's epithelium [1, 4, 5].

A major problem of endoscopic treatment without removal of the remaining Barrett's esophagus is the high rate of metachronous neoplasia and recurrences going up to 30% [6]. The reasons for the high rate of recurrence appear to be a percentage of undetected neoplasia in the residual Barrett's segment after treatment and, more importantly, the fact that the residual Barrett's metaplasia appears to have an increased risk of malignant transformation due to genetic abnormalities not influenced by the endoscopic treatment. One attempt to reduce the rate of recurrent malignancy after successful treatment might be the ablation of the remaining Barrett's epithelium with one of the established ablative techniques.

Taking all mentioned arguments into account, combining ER with ablative treatment modalities seems to be an attractive and effective concept to remove both neoplasia and non-dysplastic Barrett's epithelium.

STAGING

Accurate staging is mandatory before endoscopic treatment of early esophageal cancer. The most important part of the staging procedure is careful evaluation of the neoplasia and the borders of the lesion using a high-resolution endoscope, and searching for multifocal neoplasia. In addition, the macroscopic type of the lesion should be determined, as it has been shown that there is a significant correlation with infiltration depth [7, 8]. Conventional EUS and EUS with miniprobes (20 or 30 MHz) could be carried out in order to evaluate the depth of infiltration and the lymph-node status of the tumor. It has been shown that the accuracy of T staging is limited, particularly for distinguishing between the important stages T1m and T1sm. Accuracy diagnosing submucosal cancer is only ranging from 33 to 85% [9–13]. Underdiagnosis made by EUS occurred in 12.5–67% of cases, especially in patients with incipient submucosal infiltration (sm1) [9, 10]. In contrast, EUS is highly accurate differentiating T1 and T2 tumors [11]. One way of solving this dilemma is to carry out diagnostic ER when infiltration of the muscularis mucosa has been ruled out by EUS. If after diagnostic ER the resection specimen shows submucosal infiltration of the tumor, the patient still can be referred to surgical resection.

ENDOSCOPIC RESECTION AND PDT

There are several studies combining ER and PDT in patients with HGIN and mucosal Barrett's cancer (Fig.1). Nijhawan et al. treated 25 patients with suspicion for neoplastic lesions in Barrett's esophagus by ER [14]. Histopathologic evaluation of the resection specimen disclosed these lesions as being superficial Barrett's carcinoma in 13 patients and HGIN in 4 patients. The remaining 8 patients had only LGIN and non-neoplastic changes. Four patients with residual cancer

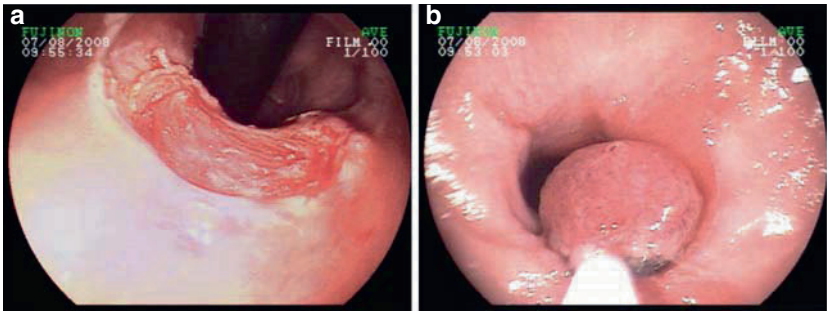

Fig. 1. a, **b** Endoscopic resection of a mucosal Barrett's cancer with a reusable ligation device.

after ER and 3 others underwent PDT with photofrin afterwards. After a mean follow-up of 14.6 months no patients have had cancer detected.

A further study published 1 year later from the same group again investigated the combined treatment in 17 patients with neoplastic Barrett's esophagus [15]. First, ER was performed in all patients followed by PDT with photofrin. Complete remission was achieved in 16 of 17 patients; complete eradication of Barrett's esophagus was observed in 53%. One patient was referred for surgery because of neoplastic features in biopsy specimen. However, the surgical specimen did not show any residual cancer. After following these patients for more than 1 year none had recurrent malignancy.

Our group recently published a large series on endoscopic treatment of early Barrett's neoplasia in 349 patients [16]. Sixty-one had HGIN and 288 presented with mucosal carcinoma. ER was performed in 279 patients, PDT with 5-aminolevulinic acid as a photosensitizer in 55 patients and both methods were combined in 13 patients for treatment of neoplastic Barrett's esophagus. Treatment was highly effective with a remission rate of 96.6%. However, during a follow-up of more than 5 years, metachronous and recurrent neoplasia was observed in 21.5% of cases. Most patients were retreated successfully and long-term complete response was achieved in 94.5%. In this series, PDT was not only used as a treatment for neoplasia but, together with APC, also for ablation of non-neoplastic Barrett's epithelium. Complete Barrett's eradication was observed in 86% of the 200 ablated patients.

Combination of the best-validated treatments has proven to be highly effective in order to remove all neoplastic changes and also remaining Barrett's esophagus. Especially ablation of the whole Barrett's epithelium seems to be important to reduce the risk of recurrence of neoplasia which was one of the major drawbacks of endoscopic therapy of early Barrett's cancer and HGIN.

ENDOSCOPIC RESECTION AND ARGON-PLASMA-COAGULATION

APC is one of the first and best-validated methods for ablation of non-neoplastic Barrett's esophagus (Fig. 2). Several trials have been shown that complete ablation can be achieved in 38–97.6% of patients [17–21]. However, one drawback of this method is the high rate of buried Barrett's epithelium under newly developed squamous epithelium in about 20% of patients [22].

Usually, APC is used for ablation of small neoplastic remnants at the margins after ER. Larger areas of neoplasia should be treated by ER rather than APC. In a recently published trial by our group, APC

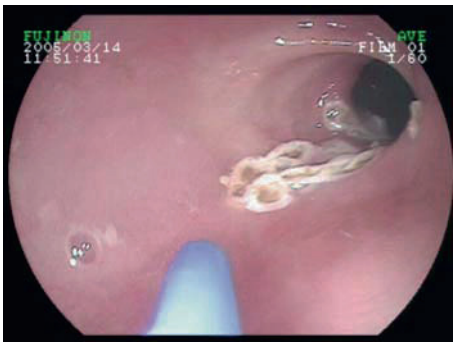

Fig. 2. Argon-plasma-coagulation for ablation of residual Barrett's mucosa after prior endoscopic resection of early neoplasia.

and PDT were used to remove the remaining non-neoplastic Barrett's epithelium after successful ER of HGIN and early mucosal Barrett's cancer in 136 and 64 patients, respectively [16]. Complete removal of Barrett's epithelium could be achieved in 86% after a mean of 3.1 sessions (range 1–12). Interestingly, metachronous HGIN and Barrett's cancer were significantly more often found in that group of patients receiving no ablative treatment after complete removal of neoplasia. Although this was a retrospective analysis, this is the first study that was able to demonstrate a positive effect of ablative treatment of the remaining non-neoplastic Barrett's epithelium in order on the reduction of the rate of metachronous neoplasia or recurrences.

ENDOSCOPIC RESECTION AND RADIOFREQUENCY ABLATION

Radiofrequency ablation is a recently introduced method for the treatment of non-neoplastic and neoplastic Barrett's esophagus (Fig. 3). In a large US multicenter trial, this method has been proven to be safe and effective for ablative treatment in patients with Barrett's esophagus [23]. However, like with all ablative methods a histological confirmation of the infiltration depth and probable infiltration of lymph vessels (L-status) of the treated mucosa is not available. When treating neoplasia, a possible problem might be the underestimation of a neoplastic lesion and the endoscopist might end up treating a submucosal carcinoma or cancer infiltrating lymph vessels harboring lymphatic spread. Therefore, all visible and detectable lesions within the Barrett's segment should be treated by endoscopic resection.

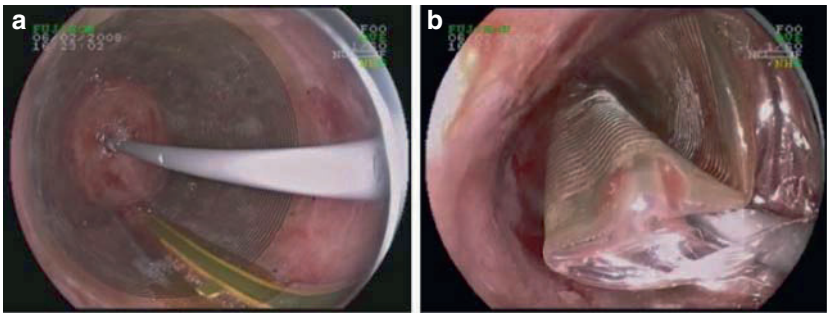

Fig. 3. **a**, **b** Radiofrequency ablation of residual long-segment Barrett's esophagus after endoscopic resection of focal mucosal carcinoma.

Two recently published studies from the Amsterdam group combined ER of visible neoplastic lesions with circumferential and focal radiofrequency ablation of the remaining Barrett's esophagus containing HGIN in 23 patients. Ablation without prior ER was performed in 10 patients with flat HGIN. Complete elimination of neoplasia and Barrett's metaplasia was possible in all of the 23 included patients and none of the 836 biopsies of the neosquamous mucosa contained subsquamous Barrett's esophagus [24, 25].

A multicenter trial with 16 centers from the United States investigated the safety and efficacy of RFT in patients with HGIN in Barrett's esophagus [26].One hundred forty-two patients were treated by circumferential RFT with the HALO system. The median Barrett length was 6 cm. An ER prior ablative treatment was permitted in this study. Strictures occurred in only one patient and no buried glands were found during follow-up. Of the 92 patients with at least one follow-up endoscopy a complete removal of HGIN was confirmed in 90.2% and of Barrett's epithelium in 54.3%.

The published data on combination of ER with RFT are very promising and RFT seems to be a safe and efficient method to remove the remaining Barrett's epithelium after ER. However, the follow-up is very limited and final conclusions cannot be drawn to date, especially regarding long-term safety in these patients with HGIN treated by RFT only.

Table 1 summarizes all major studies with multimodal treatment of early Barrett's neoplasia.

CONCLUSION

Endoscopic treatment of HGIN and mucosal Barrett's carcinoma has proven to be safe and effective, even on long-term follow-up. A combi-

Table 1
Major studies with multimodal treatment of early Barrett's neoplasia

Author	*Year*	*Patients*	*Treatment*	*Complete remission neoplasia (%)*	*Complete remission BE (%)*	*Complications*	*Follow-up (months)*	*Recurrence rate (%)*
Nijhawan and Wang [14]	2000	17 (4 HGIN, 13 MC)	11 ER, 7 ER+PDT	100	–	0%	14.6	0
Buttar et al. [15]	2001	17 (7 BE/LGIN/HGIN, 10 MC/SMC)	ER + PDT	94	53	Strictures 30%, Bleeding 6%, Phototoxicity 11.7%	13	0
May et al. [6]	2002	115 (19 HGIN, 95 MC, 11 SMC)	66 ER, 32 PDT, 9 ER+PDT, 3 APC	98	–	Minor Bleeding 7.5%. Strictures 4.5%	31	30
Behrens et al. [27]	2005	44 HGIN	14 ER, 27 PDT	97.7	–	Minor bleeding 9.3%	38	17.1

Pech et al. [28]	2005	66 (35 HGIN 31 MC)	52 PDT, 8 PDT+ER, 6 PDT+APC	98.5	–	Minor bleeding 1.5%	37	17
Gondrie et al. [24]	2008	12 (1 LGIN, 11 HGIN)	ER and RFT	100	100	–	9.5	0
Gondrie et al. [25]	2008	12 (2 LGIN, 9 HGIN)	ER and RFT	100	100	1 stricture	14	0
Ganz et al. [26]	2008	142 HGIN	ER and RFT, RFT	90.2	54.3	1 stricture	12	–
Pech et al. [16]	2008	349 (61 HGIN 288 MC)	279 ER, 55 PDT, 13 ER+PDT, 2 APC, 200 ablation of BE	96.6	86 (in ablation group)	Major (bleeding 2%) Minor 16.6%	63.6	21.5

HGIN: high-grade intraepithelial neoplasia; LGIN: low-grade intraepithelial neoplasia; MC: mucosal Barrett's cancer; SMC: submucosal Barrett's cancer; ER: endoscopic resection; PDT: photodynamic therapy; APC: argon-plasma-coagulation; RFT: radiofrequency treatment; BE: Barrett's esophagus.

nation of different methods should be used for the treatment of neoplastic lesions and non-neoplastic Barrett's esophagus: Localizable HGIN and mucosal cancer should be resected using ER either with the cap or the ligation device. Ablation of the remaining Barrett's epithelium can be performed by PDT, APC, MPEC, or RFT and has shown to significantly reduce the rate of neoplastic recurrence or metachronous malignancy. A major problem of PDT, APC, and MPEC are relevant complications – mainly stricture formation. In addition, several studies have shown that buried glands are found in a relevant proportion of patients after ablative treatment with these methods. A new ablation technique is RFT which has proven to be an effective method for Barrett's ablation with a very low complication rate. Buried Barrett's after RFT is almost never found. However, large multicenter trials with longer follow-up are needed to draw final conclusions.

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Photodynamic Therapy (PDT): The Best-Validated Technique

V. Raman Muthusamy, MD and Kenneth J. Chang, MD

CONTENTS

Summary

Photodynamic therapy (PDT) has been used in medicine to ablate and destroy unwanted tissue for nearly 50 years. Its unique mechanism of action is non-thermal and utilizes the activation of a photosensitizer by local application of a specific wavelength of light and the subsequent generation of oxygen radicals by the

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"excited" photosensitizer. These oxygen radicals create localized cellular injury and necrosis in the region of photoactivation. While a variety of photosensitizers have been studied, only porfimer sodium is approved for use in the United States. Approved gastrointestinal applications include the treatment of both squamous cell cancer and adenocarcinoma of the esophagus in non-surgical candidates for the purposes of palliation of malignant dysphagia or tumor eradication. More recently, approval for the treatment of Barrett's esophagus with high-grade dysplasia (HGD) has been granted. The technique achieves success rates of 70–100% for these indications, but residual Barrett's epithelium usually remains. Due to its status as the most-widely used ablation technique with more than 15 years of clinical data, PDT is the only method of ablation that has currently been shown to be durable, reduce the risk of cancer recurrence, and achieve outcomes similar to esophagectomy for the treatment of Barrett's with HGD. Despite its high cost and known complications (development of photosensitivity reactions and esophageal strictures in nearly a third of patients), PDT appears to meet established criteria for cost-effectiveness. While initial studies of newer ablative techniques offer promising efficacy results with the advantages of cost-reduction and decreased complications, it is uncertain if these methods are durable, reduce the risk of subsequent cancer, or achieve outcomes similar to surgical therapy. Until data regarding these issues are available, PDT remains the best-validated endoscopic treatment option to surgery for patients with Barrett's esophagus with HGD and early-stage esophageal cancer.

Key Words: Barrett's esophagus, Endoscopic ablation, Photodynamic therapy, High-grade dysplasia, Esophageal cancer

INTRODUCTION

Photodynamic therapy (PDT) has been used for the ablation of premalignant and neoplastic disease for nearly 50 years. It has been used previously for non-gastrointestinal applications in a wide variety of benign and malignant diseases. These include benign prostatic hypertrophy, macular degeneration, and the treatment of dermatologic, head and neck, breast, ovarian, pulmonary, prostatic, brain, and urologic malignancies [1]. In gastroenterology, it has been approved for use in Europe for the treatment of early gastric cancers. Other gastrointestinal applications include the palliation of unresectable cholangiocarcinoma, ablation of extensive Familial Adenomatous Polyposis (FAP)-associated colorectal and duodenal adenomas, and the eradication of

non-dysplastic Barrett's esophagus. However, with respect to gastrointestinal disease, the United States Food and Drug Administration (FDA) has only approved the use of PDT, using a single photosensitizer, for the palliative treatment of patients with completely or partially obstructing esophageal cancer and for the ablation of Barrett's esophagus with high-grade dysplasia (HGD) in patients not electing surgery [2]. This chapter will discuss the mechanism of action of PDT, review the available photosensitizers and necessary equipment, describe a recommended technique for performing PDT, and address its advantages and limitations. We will also review the existing literature with regard to efficacy and complications, identify key parameters that require further assessment, and summarize the role of PDT in relation to other ablative modalities used to treat dysplastic Barrett's esophagus and esophageal cancer.

MECHANISM OF ACTION

PDT requires a photosensitizer and a light source emitting the appropriate wavelength needed to activate the photosensitizer. The process of tissue injury, illustrated in Fig. 1, begins once the light activates the photosensitizer, causing it to enter an "excited" triplet state. In the presence of oxygen, this photoactivation leads to the generation of singlet oxygen and free radicals. These oxygen radicals cause a localized non-thermal cellular injury which evolves into cell necrosis over several days. Tissue destruction is based on direct cytotoxicity, nitric oxide-mediated microvascular thrombosis, induction of apoptosis, and induction of the T-lymphocyte-mediated immune response [3]. A variety of photosensitizers are available, each with unique depths of tissue penetration and specific wavelengths necessary to achieve photoactivation.

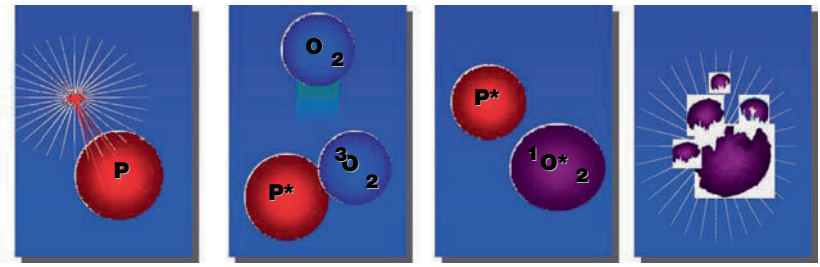

Fig. 1. Illustration of the mechanism of action of PDT.

The depth injury achieved ultimately depends on a multitude of factors including the choice of photosensitizer, the wavelength of light used, the energy dose, and the time between photosensitizer administration and photoactivation.

AVAILABLE PHOTOSENSITIZERS AND EQUIPMENT

Photosensitizers are preferentially absorbed and retained in neoplastic tissue due to their macro-molecular structure. It is this property that makes PDT an attractive ablation therapy. Photosensitizers vary in their properties based on modifications in their composition of porphyrins, chlorine, and chlorophyll. Of the three major photosensitizers used in PDT, meta-tetrahydroxyphenyl chlorin (Foscan; Biolitec AG, Jena, Germany) is the only one not available in the United States in any form [4]. It is a very powerful, intravenously administered (0.15 mg/kg) photosensitizer that requires small doses of light at 652 nm to achieve tissue injury. It has a period of cutaneous photosensitivity of only 2–3 weeks, but has been associated with a high rate of stricture formation and tissue necrosis when used to treat patients with squamous cell head and neck cancers. The elevated rate of stricture formation observed is likely due to the excess illumination used during the photoactivation phase of treatment. Foscan has had limited use in the GI tract, but has been used successfully in a handful of patients with Barrett's esophagus and HGD who previously failed treatment with 5-aminolevulinic acid (ALA; Medac Ltd., Hamburg, Germany). Precise determination of the illumination time with this technique appears critical to avoid serious complications associated with tissue necrosis.

ALA is only approved for dermatologic applications via a 20% solution (Kerastick, DUSA pharmaceuticals, Valhalla, NY) in the United States. It is a pro-drug of protoporphyrin IX (PpIX), and is converted to this photosensitizer after administration. It is activated by light at 635 nm. In Europe, ALA has been used to treat Barrett's esophagus with and without dysplasia as well as early esophageal cancers. ALA has several theoretical advantages over other photosensitizers used in the treatment of esophageal disease. It can be delivered orally and reaches peak esophageal PpIX concentrations 4–6 h after ingestion, allowing for same day dosing and photoactivation [2]. In addition, PpIX preferentially accumulates in the superficial layers of the esophageal wall. This limits the resulting depth of tissue injury to about 2 mm and reduces the high stricture rates associated with deeper tissue injury. The short half-life of ALA also markedly reduces the duration of photosensitivity risk to 1–2 days. Administration of ALA has been associated with transient (3–4 days) liver abnormalities in about one half of

treated patients as well as short-term nausea, vomiting, and hemodynamic instability.

Porfimer sodium, or Photofrin (Axcan Pharma, Birmingham, AL), is the only FDA approved photosensitizer. It is a purified form of hematoporphyrin derivative (HpD), which was used previously, and has been commercially available since 1994 [4]. It consists of a mixture of oligomers of up to eight porphyrin units that may form dimers and trimers with each other. Avoidance of this interaction requires the drug be administered immediately (or at least within 1 h) after being reconstituted from its packaged lyophilized powder. Once reconstituted, the solution should also be protected from light exposure. Porfimer sodium is dispensed in 75 mg vials and is dosed at 2 mg/kg, leading most patients to require 2–3 vials per treatment. After reconstitution, it is injected at a concentration of approximately 2.5 mg/mL, with typical injected volumes of 60–80 mL. Administration of the drug via rapid intravenous push (3–5 min) is believed to reduce cutaneous distribution and subsequent photosensitivity. Post-administration, it is believed to be cleared from most tissues within 48–72 h, but retained longer in tumors, skin, and the reticuloendothelial system. The drug is activated by light at 630 nm and delivers a tissue depth of penetration of 5–8 mm [3].

Lasers utilized for PDT include dye and diode varieties. Dye lasers utilize a laser-emitting light (usually green) at its natural frequency and wavelength to energize a dye module that produces laser light of an increased wavelength. This is done because most substances do not make the longer wavelength red laser light needed to activate photosensitizers and achieve the desired tissue penetration of up to 1 cm. Thus, the dye laser converts the naturally occurring green light into the necessary red laser wavelength (630–635 nm) [1]. Commonly used dye lasers, such as Laserscope (San Jose, CA) and Lumenis, Ltd. (formerly Coherent Lasers Medical Group, Santa Clara, CA), can achieve a large power output of up to 7 watts (W) as well as the desired wavelength. However, they are bulky, require dedicated cooling and power sources, and are not specifically indicated for use with PDT. Solid-state diode lasers such as the Diomed (Andover, MA) have several advantages. They can be operated from standard power (110 V) outlets, do not require a separate cooling source, are portable (43 lbs, 19 $\times$ 8.5 $\times$ 6 in. in size), and also less expensive [2]. In addition, the Diomed laser helps avert dosimetry errors by including a program that automates the duration and light power required for therapy based on the target organ, degree of pathology, and fiber length. The Diomed model is the only laser specifically approved for use with porfimer sodium in the United States. While diode lasers produce less power output,

the currently available Diomed laser can produce 2.0 W of energy at 630 nm, which is sufficient to achieve the goal power of 0.4 W/cm with the longest currently available diffuser fiber length (5 cm).

The goal of the light delivery device used in PDT of the esophagus is to achieve even distribution of light circumferentially, with the emitted light being in a perpendicular orientation to the long axis of the esophagus. A variety of delivery devices are available, but the FDA has approved one (Optiguide DCYL 200 series) for use with PDT [2]. These single-use fibers work with the Diomed laser and consist of a silica-core light delivery system with an outer diameter of 1.6 mm and lengths varying from 1 to 5 cm. A pointed tip is present to facilitate burying of the fiber in a nodule or tumor (interstitial PDT) during a focal treatment. Due to concerns that poor centering of the fiber would lead to unequal illumination and asymmetric treatment, leading to a possible increase in strictures and buried glands, cylindrical centering balloons (Xcell PDT Balloon, Cook Endoscopy, Winston-Salem, NC) were developed to fix the position of the fiber within the esophagus. The balloons were 81 cm long with an outer diameter of 25 mm and illumination windows that were 3, 5, and 7 mm in length [2]. These balloons were expensive (approximately $1,000/balloon) and unfortunately, did not seem to improve treatment results or reduce complications compared to a bare fiber approach, leading to their eventual removal from the market

DOSIMETRY

Determining the appropriate light dose and corresponding treatment time are the most important technical aspects of PDT. The equation Energy (Joules (J)/centimeter (cm)) = Power (W/cm) × Time (seconds) is used to estimate the necessary treatment time. Most commonly, an energy dose of 200 J/cm of cylindrical fiber length is used for Barrett's esophagus with HGD while 300 J/cm is used for the treatment of esophageal cancer [1]. For patients with HGD treated with the centering balloon, a dose of 130 J/cm was used [5]. The power is typically kept at 0.4 W to avoid unwanted thermal effects such as cauterization of blood that can reduce adequate and uniform dispersion of light from the diffuser. The total power output needed to achieve this power for a 5-cm fiber is 0.4 W/cm × 5 cm = 2.0 W. This total power is achieved by all the commonly used laser sources, including the Diomed laser that has specific FDA approval for use in photodynamic therapy. Of note, a reduction in power per unit length of esophagus will require increased treatment time to achieve the same energy exposure. Using this equation, the treatment time for Barrett's with HGD

is (200 J/cm)/(0.4 W/cm) = 500 s and that for esophageal cancer is (300 J/cm)/(0.4 W/cm) =750 s. It should be noted that the treatment does not vary based on the fiber length used as long as a constant power per unit of diffuser length is maintained, and overall treatment times per segment treatment are usually under 12.5 min.

TREATMENT PROTOCOL/TECHNIQUE

Prior to PDT ablation of HGD or early esophageal cancer, appropriate evaluation includes office consultation with review of previous histopathology and radiologic studies (CT). A pre-ablation endoscopy using the Seattle protocol of four-quadrant jumbo biopsies every 1 cm in the entire region of Barrett's esophagus and/or cancer should be performed, with additional biopsies obtained in areas of mucosal irregularities. An endoscopic ultrasound with fine needle aspiration should also be performed at the time of the pre-ablation endoscopy to assess for mural invasion of any visualized nodules and to determine the presence of malignant adenopathy. Endoscopic mucosal resection (EMR) of nodular regions should be performed to evaluate for invasive cancers. If EMR is performed, PDT should be delayed 6–8 weeks to achieve adequate mucosal healing. Surgical consultation should also be offered to interested patients.

Once the plan for PDT treatment length and dosimetry is confirmed, infusion of porfimer sodium at 2 mg/kg over 3–5 min is done, typically on a Monday. As a precautionary measure, photosensitivity precautions should be reviewed and instituted immediately post-infusion. Approximately 48 hr after infusion (Wednesday), endoscopy with photoillumination is performed. Prior to the procedure, the laser is calibrated and power output and treatment time are confirmed. During the procedure, supplemental oxygen at 2l/min via nasal cannula should be administered to achieve adequate patient oxygenation (>92% saturation) to achieve maximal tissue injury during photoactivation. Gastric pH may be measured pre-ablation to confirm acid suppression and titrate antisecretory therapy. Photoablation is usually initiated distally, with the distal end of the diffuser about 5 mm below the lower end of ablation zone. During illumination, steady air insufflation is needed to achieve esophageal distension and center the fiber in the lumen. Because of the bright laser light, visualization of the fiber location can be difficult, but this problem can be averted by using blue light available on narrow band imaging scopes [6]. Periodic interruption of procedure to confirm the proper location of the diffuser is recommended. After the initial segment is treated, unlike all other ablation modalities, the esophageal mucosa will appear unchanged. While some endoscopists prefer not to

ablate more than one segment (5 cm maximum) per session, additional segments may then be treated as long as the overlapping of treatment sections, or "double-treating," is avoided. This is recommended to minimize post-ablation strictures. Many centers have patients return for a "relook" endoscopy at 96 hr (Friday) to evaluate for untreated segments, as tissue injury is readily apparent by this time. Untreated regions or areas requiring additional energy (nodules) can be treated at this time, typically at 50–100 J/cm. However, others have found no increase in ablation efficacy with this additional treatment and have discontinued this practice [7].

After the initial ablation, patients should be given medications to minimize post-procedure side effects, which include chest pain, odynophagia, fever, nausea, and constipation. About 10% of patients will require hospitalization, typically due to dehydration [6]. Hospitalization rates may be reduced via the use of home health nurse to administer intravenous fluids and medications. In addition to the medications detailed above, acid suppression with twice-daily proton pump inhibitors appears necessary in order to achieve mucosal healing, aid in the development of neosquamous epithelium, and in preventing Barrett's recurrence.

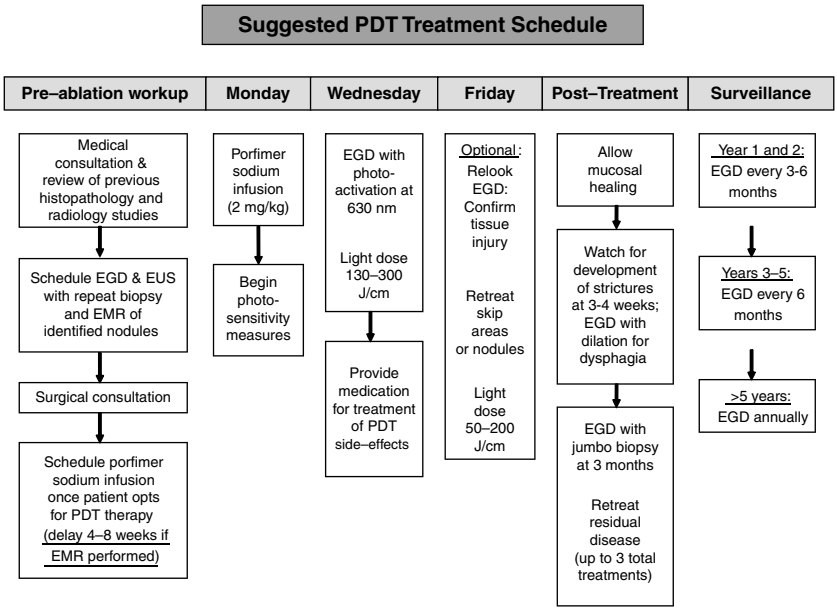

Fig. 2. A typical PDT treatment schedule.

Surveillance endoscopy and biopsy is typically done at 3 months using the Seattle protocol, and up to a total of three treatments may be performed at 3-month intervals. Once successful ablation is achieved, endoscopic surveillance usually occurs at 3 to 6-month intervals for 2 years, then at 6-month intervals until year 5 post-ablation, at which time annual surveillance is performed. Routine use of EUS for post-PDT-ablation surveillance, in the absence of mucosal abnormalities, is likely unnecessary [8]. A typical treatment schedule is illustrated in Fig. 2.

ADVANTAGES OF PDT

There are several advantages associated with PDT ablation. It achieves a significantly greater depth of penetration than other ablative techniques, with a maximum depth of tissue necrosis of greater than 5 mm [9]. This allows the potential for the eradication of early cancers, which may have a small amount of mural penetration, and for the ability to re-establish luminal patency in patients with obstructive lesions. The technique is also not technically difficult to perform, although proper identification of landmarks and confirmation of the proximal and distal treatment margins is required. Due to the need to simply pass a narrow treatment fiber into the region of the tumor or dysplastic tissue to achieve illumination, PDT uniquely allows for treatment of lesions within or below narrow esophageal strictures that are not accessible by other modalities that require passage of the stricture with an endoscope to perform ablation. Given that this is a non-contact ablation modality, it also allows for the ability to treat long segments of tissue. However, because of concerns that overlapping treatment regions may increase stricture risk, treatment of multiple contiguous segments is not recommended. Thus, some physicians have limited the extent of treatment at a single session to the maximum length of the available treatment fiber, which is currently 5 cm [6]. A final advantage is the relatively uniform depth of ablation achieved compared to other modalities when the photoactivation technique is optimized by centering the diffusion fiber in the esophagus.

LIMITATIONS OF PDT

Limitations of the technique include its high cost, frequent complications, and somewhat limited availability. While a 10–15% reduction can be achieved with bulk purchases, the list price for a 75 mg vial of porfimer sodium is between $2,000 and $2,500 [2]. Given the need to give 2 mg/kg, most patients will require two to three vials per treatment. In

addition, the recommended Diomed laser costs approximately $70,000, although it may be rented out on a per case basis. Last, the disposable light diffusion catheters cost between $470 and $650, depending on diffuser length. When it was available, the centering balloon cost up to an additional $1,000. PDT-related complications are quite frequent, with acute symptoms such as chest pain, odynophagia, nausea, vomiting, abdominal pain, fever, and pleural effusion being reported in 33–75% of patients. The formation of esophageal strictures, which can be quite difficult to resolve, occurs after PDT treatment in about a third of patients. Cutaneous phototoxicity is also frequent, occurring in about 30% of patients [2]. Due to these issues regarding cost and risk, the utilization of PDT outside of select academic and tertiary care centers has been limited. The utility of PDT is also limited by numerous contraindications. They include patients with porphyria or a known allergy to porphyrins, esophageal or gastric varices, existing broncho- or tracheoesophageal fistula, tumors eroding into major blood vessels, esophageal ulcers greater than 1 cm, and patients incapable of following photosensitivity precautions. These contraindications are primarily based on photosensitizer characteristics or potential complications that may result or be exacerbated by the relatively deep tissue injury produced by PDT.

CLINICAL TRIAL RESULTS

Although ALA is not approved for use in the United States, it has been used extensively in Europe and a brief review of this clinical trial data will be presented here. With a depth of penetration of only 2 mm, ALA has primarily been used to treat Barrett's epithelium with or without dysplasia. Results from a randomized, placebo-controlled trial in patients with LGD indicated a 98% efficacy in eliminating dysplasia, with 83% of treated patients showing an endoscopic response [10]. A median 30% decrease in the length of Barrett's esophagus was observed at 2-year follow-up. However, ALA has also been shown to effectively treat HGD and superficial T1 cancers (as staged by EUS) as well. Gossner and colleagues eliminated cancer in 77% of treated patients at a mean follow-up of 9.9-months, with all tumors <2 mm thick achieving successful ablation [11]. The same group assessed their results in a separate group of 35 HGD and 31 early adenocarcinoma patients with a median of 37 months of follow-up. The response rates for ablation of HGD and cancer were 97 and 100%, respectively [12]. A direct comparision of ALA to hematoporphyrin in patients with malignant dysphagia in advanced esophageal cancer showed a clear advantage for porphyrin-based photosensitizers, which have a three-

to fourfold increased depth of tissue penetration when compared to ALA [13, 14].

Though recent studies have primarily focused on the treatment of Barrett's esophagus and adenocarcinoma, many initial studies of PDT involved the treatment of squamous cell cancer of the esophagus (SCCE). Porfimer sodium or HpD were used in the vast of majority of these predominantly single-center studies, which ranged from in size from 4 to 37 patients [15]. Treatment efficacy for ablation of cancer in these reports ranged from 52 to 92%. Patients with advanced cancer have obtained lower response rates of 40–60%, with partial remissions achieved in 50–75% of such patients [4]. Another study of 104 patients with EUS stage T1 or T2 SCCE who were treated with PDT alone or with concomitant chemoradiation showed 87% of patients were tumor-free at 6 months [16]. The 5-year survival rate was 87%, with a 95% rate for T1 cancers by EUS. Of note, PDT with chemoradiation was not superior to PDT monotherapy.

PDT for intramucosal or early-stage esophageal adenocarcinoma has also been investigated by several groups (Table 1). Efficacy rates of 57–100% have been achieved with porfimer sodium with mean follow-up intervals of 10–51 months [15] Similar or better results have been reported with other photosensitizers [9]. There is significant variability among the studies regarding the choice of photosensitizer, treatment protocol, follow-up intervals, and definition of endpoints. What does appear critical based on these studies is the appropriate patient selection via the use of pre-ablation staging EUS [4]. Patients with stage T1 or intramucosal cancer appear to achieve the best results, with porfimer sodium being preferred over HpD due to its deeper tissue penetration.

While endoscopic placement of self-expanding metal stents is currently the preferred modality for achieving palliative relief of malignant dysphagia, two randomized studies of PDT with porfimer sodium provided data that lead to the 1995 approval of PDT for this indication in the United States. The first compared 110 patients receiving PDT with porfimer sodium to 108 patients treated with a Nd:YAG laser, the most widely used endoscopic ablative modality at that time [17]. The methods were equivalent in relieving dysphagia, but an increased frequency of complete tumor response (8.2% versus 1.9%) and reduced perforations (1% versus 7%) were seen with PDT treatment. The second study also compared these two modalities in 52 patients with obstructive esophageal tumors [18]. Again, both methods were shown to relieve dysphagia equally, but PDT was associated with improved quality of life and increased durability of dysphagia relief. While endoscopic stenting is more widely available and offers rapid relief of dysphagia,

Table 1
Large studies of PDT for the treatment of Barrett's esophagus with high-grade dysplasia or early adenocarcinoma

Study author	*Year*	*N*	*Diagnosis*	*Agent*	*Results*	*#Treatment sessions*	*Major complications*	*Follow-up (months)*
Overholt et al. [25]	1999	100	LGD(14):HGD (73); CA(13)	POR	Ablation success: 77% CA; 90% HGD; 93% LGD; 43% with no Barrett's	1.3	STR-34%; PS-4%; AF-3%	19
Panjehpour et al. [32]	2000	60	LGD(10):HGD (43); CA(7)	POR	100% CA ablation; 96% HGD ablation; 42% with no Barrett's	1.2	Str-33%	9.8

Wolfsen et al. [35]	2004	102	HGD(69):CA (33)	POR	56% complete Barrett's ablation	1	STR-20%; PS-18%; PERF-1%	18.5
Overholt et al. [5]	2005	132	HGD	POR	77% HGD ablation	2	PS-69%; STR-36%	18
Pech et al. [12]	2005	66	HGD(35)/CA (31)	ALA	Complete remission: 97% HGD/100% CA	HGD: 1.3/CA: 1.2	None; No strictures	37

AF: atrial fibrillation; ALA: 5-aminolevulinic acid; CA: cancer; HGD: high-grade dysplasia; LGD: low-grade dysplasia; PERF: perforation; POR: porfimer sodium; PS: photosensitivity; STR: stricture.

reduced costs, fewer interventions, and the avoidance of photosensitivity, PDT has also been shown to aid patients with recurrent dysphagia due to stent overgrowth/ingrowth while avoiding thermal damage to the stent [19].

The efficacy of PDT using porfimer sodium for the treatment of Barrett's esophagus with high-grade dysplasia was initially reported to achieve successful eradication of HGD in 76–100% of patients [15, 20] (Table 1). However, less than half of patients achieved complete ablation of all Barrett's epithelium, and stricture rates of 25–34% were reported [4]. In addition, most of these studies were small single-center experiences, although two studies had 80 and 58 patients, respectively [21, 22]. This led to a US FDA-approved regulatory trial featuring an international, multicenter randomized controlled trial design with centralized pathology evaluation [5]. Patients were randomized in a 2:1 fashion to PDT + BID omeprazole therapy or BID omeprazole therapy alone. A total of 208 (138 PDT:70 omeprazole-only) patients were treated at 30 centers, with the absence of HGD on all biopsies at any single surveillance endoscopy defined as a treatment success. The PDT group had a 77% response rate at a mean follow-up of 24 months, compared to 39% for the omeprazole-only group with an 18-month average follow-up. Complete Barrett's ablation was achieved in 52% versus 7% for the PDT and omeprazole-only groups, respectively. The risk of progression to cancer was doubled in the omeprazole-only group, and PDT-treated patients maintained HGD ablation about 10 times as long as omeprazole monotherapy patients (987 versus 98 days). These preliminary findings led to FDA approval of the use of PDT with porfimer sodium for the treatment of HGD. Five-year follow-up data showed similar results, with a persistence in the reduction in the risk of progression to cancer [23]. Figure 3 illustrates a successful endoscopic ablation of HGD by PDT.

Little data exist comparing PDT to other treatment modalities. Two trials of PDT versus acid suppression have been discussed previously in this chapter have demonstrated superior results with PDT ablation [5, 10]. In addition, there have been studies comparing PDT using ALA and porfimer sodium to APC ablation [24]. The trials comparing PDT using ALA to APC showed that APC was comparable or superior to PDT in ablating Barrett's epithelium. A single trial of 26 patients comparing PDT with porfimer sodium to APC showed they were equally effective in ablating Barrett's epithelium, but that PDT was superior in eradicating dysplasia. Unfortunately, all of these trials were quite small and are likely underpowered to determine clinically important differences between the modalities. In addition, there are no currently published comparative trials of PDT against newer ablation modalities such

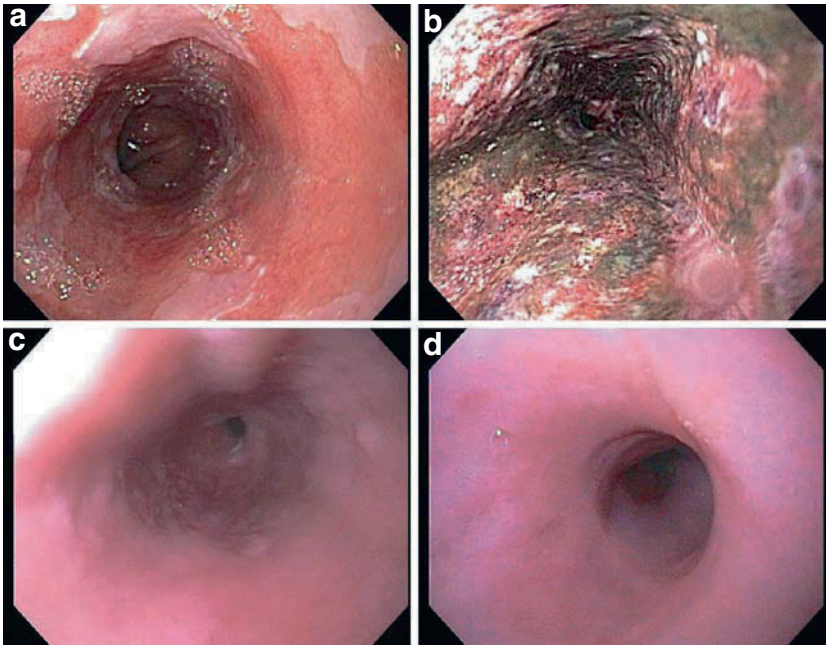

Fig. 3. **A**. A 5 cm region of Barrett's epithelium with HGD was observed pre-ablation. **B**. Confluent necrosis of the treated segment as seen 48 h after photoactivation. **C**. Successful ablation complicated by stricture formation at 6-week follow-up. **D**. Successful ablation and stricture resolution at 1-year follow-up.

as radiofrequency (RF) ablation or cryotherapy. Larger, prospective randomized trials comparing these modalities will be necessary to define the future role of PDT in the endoscopic management of esophageal dysplasia and cancer.

Subsquamous intestinal metaplasia (SSIM), or "buried glands," have been reported to occur in between 4.9 and 51.5% of PDT-treated patients [25, 26], with subsquamous dysplasia and cancers reported in 3.8–27.3% of these patients. A single center study found 7.4% of all post-ablation biopsies showed buried neoplasms [27]. These numbers have led to concern about the risks of ablation and have highlighted the need for complete eradication of all intestinal metaplasia. A review of most trials of PDT reveals that while substantial "downstaging" of esophageal dysplastic or malignant changes usually occurs, most patients will have some persistent glandular epithelium that will require follow-up treatment [4]. The use of focal argon plasma coagulation, radiofrequency ablation, or cryotherapy in conjuction with PDT

to achieve complete eradication of intestinal metaplasia may be the best method to reduce the risk of SSIM or buried dysplasia associated with PDT monotherapy. In addition, endoscopic techniques such as EMR can aid PDT in the treatment of dysplastic or malignant esophageal disease [28]. EMR provides expanded histologic information (including depth of invasion) via its increased specimen size, and it aids treatment by partial or complete lesion removal. It appears likely that the maximal ablation efficacy of PDT may be achieved by the use of pre-PDT EMR for diagnosis, staging, and removal of large mucosal irregularities followed by focal ablation of residual intestinal metaplasia post-PDT by other modalities.

COMPLICATIONS

Acute symptoms occur after PDT in 10–40% of patients and include nausea and vomiting, non-cardiac chest pain, pyrexia, dysphagia, odynophagia, constipation, asymptomatic pleural effusions, dehydration, and singultus [2, 5]. Rare complications include esophageal perforation, anemia resulting from bleeding due to mucosal ulceration, respiratory compromise, and atrial arrythmias [29]. Post-ablation pain is usually treated via a combination of topical, oral, and transdermal medications. Viscous lidocaine is often used alone or in combination with a liquid antacid, hydrocortisone, diphenhydramine, and nystatin prior to eating to mitigate odynophagia. In addition, hydrocodone elixir (1–3 teaspoons every 2–4 h as needed) and a fentanyl patch (25–50 μg/h; change every 72 h) may also be used to treat persistent chest pain [6]. Anti-emetic suppositories, acetaminophen, and stool softeners with osmotic laxatives are recommended to avoid and treat post-PDT nausea/vomiting, fever, and constipation. A weight loss of 5–8 kg is typically observed [30], and adequate oral intake of liquids in the first week post-ablation is critical to avoid dehydration. As mentioned in a previous section, post-PDT hospitalization occurs in only 10% of patients, and is usually secondary to dehydration.

Strictures have been reported to occur after PDT in 15–58% [31, 32, 33, 34], with the wide range likely resulting from a variety of treatment indications and stricture definitions. While clinical dysphagia typically develops within 3–4 weeks of treatment and is known to occur with a luminal diameter of <13 mm, strictures in studies have frequently been defined by the inability to pass a diagnostic endoscope (typically 10 mm) through the narrowing. This may result in some reported stricture rates underestimating the true number of symptomatic patients. PDT strictures appear more difficult to resolve than typical benign peptic strictures, possibly due to an ischemic component that may result in

a formation mechanism more similar to strictures induced by external-beam radiation. A review of the literature suggests that a median to 3–5 dilations are needed over a median dilation period of 12 weeks [7, 35]. While many prefer aggressive balloon dilation of these strictures every 10–14 days as the primary method of dilation, bougienage may also be used as there are currently no available studies to suggest the superiority of either method. While a previous trial of prophylactic oral steroids was ineffective in stricture prevention [32], some recommend that patients not responding to three dilations in a 30-day period receive intramural triamcinolone injections (80 mg total; 20 mg/quadrant) at the site of maximal structuring during dilation [1]. Anecdotally, use of a needle knife to cut the stricture and the placement of removable esophageal stents have also been proposed to treat highly refractory strictures.

Given the frequency and severity of post-PDT strictures, several studies have evaluated risk factors for stricture development. The largest study of 131 patients at a single center undergoing 162 PDT procedures for ablation of HGD found that 27% of patients developed strictures, with EMR prior to PDT, a prior history of stricture, and multiple PDT applications being predictive of stricture formation on multivariate analysis [7]. Of interest was the finding that the centering balloon did not appear to significantly reduce stricture formation. A second large, single-center study of 116 patients undergoing 160 PDT treatments for HGD and intramucosal or T1 cancers found an index PDT stricture rate of 16%, with a 23% rate for all courses [36]. Increasing lengths of Barrett's esophagus, multiple PDT courses, and the presence of intramucosal carcinoma were predictive of stricture formation in a stepwise logistic regression that controlled for treatment length. In contrast to the first study, previous EMR did not appear to increase stricture risk. A third study found that pre-treatment of esophageal nodules and repeated treatments on the same segment increased stricture formation [5]. While these studies differ on several risk factors, a common finding is that repeated or overlapping segmental treatments increases the likelihood of stricture development.

Cutaneous photosensitivity is a particularly difficult complication to avoid, as it may not manifest until hours after solar exposure due to the delay between photoactivation and tissue injury. Patients become photosensitive within 1 h of drug administration and remain so for a period of 30–60 days. Despite education on the need for solar exposure precautions, photosensitivity reactions have been reported to occur in approximately 20–30% of treated patients [1, 2]. Most cases are relatively mild and involve erythema and edema. However, blistering and even necrosis are possible with longer exposure to sunlight. The most frequent sites

of photosensitivity reactions are the hands and face, which are the most difficult locations for patients to remember to protect. Patient education is the key to reducing the frequency of such occurrences. Key points include the fact that sunblock does not protect against photosensitivity, and that patients must ensure that all clothing worn completely blocks all light from penetrating the clothing. In addition, the duration of photosensitivity may be shortened via exposure to very limited amounts of sunlight beginning about 2 weeks after infusion. It is believed this leads to a slow bleaching of the drug from the skin. Once developed, mild symptoms typically resolve within 2 days and are best treated with diphenhydramine to reduce swelling [6]. More severe reactions such as blistering typically require dermatologic consultation for the consideration of a course of pulsed steroids. It is of interest that despite the seasonal variations in solar exposure, the frequency of cutaneous photosensitivity is not seasonal [1].

KEY ISSUES REQUIRING FURTHER STUDY

The most important goals of any Barrett's ablation therapy for HGD or early cancer are to achieve a durable ablation, reduce the risk of progression to cancer, and achieve outcomes similar to esophagectomy. Due to its greater than 15-year history of use for esophageal ablation, PDT has the longest follow-up data among the ablation modalities to assess these critical outcomes. A randomized trial of PDT versus PPI therapy initially showed a median duration of dysplasia regression of 987 days for PDT compared to only 98 days for omeprazole [5]. At 5 years, 48% of patients maintained complete ablation compared to 4% of PPI-treated patients [23]. The median duration of complete response was 44.8 months in the PDT group compared to 3.2 months for the PPI group. Patients without HGD at 2 years were found to have a 90% chance of remaining free of HGD at 5 years. The same study also showed PDT to achieve a statistically significant decrease in cancer progression rates (13% versus 28%) when compared to anti-secretory therapy at a 1-year mean follow-up interval, and this difference was preserved (15% versus 29%) at 5-year follow-up [5, 23]. Several studies have recently appeared comparing ablation therapy to esophagectomy. A non-randomized study of 199 patients with HGD, of whom 129 received PDT and 70 received esophagectomy, showed statistically similar overall mortality rates of 9 and 8.5%, respectively, over a median follow-up of 5 years [37]. No patients in either group died of esophageal cancer, but 30% of PDT-treated patients developed recurrent HGD and 5.4% progressed to cancer. Another recent comparison

involved 62 patients receiving endoscopic ablation with a combination of argon plasma coagulation (APC), PDT, and EMR ($N = 62$) to 32 patients receiving esophagectomy [38]. All patients had either HGD or intramucosal cancer, and 42 patients received PDT as part of their ablation therapy. The study found no difference in adjusted 4-year survival rates and no deaths due to esophageal cancer in either group. Six percent of endotherapy patients progressed to cancer and 13% had persistent dysplasia. Esophagectomy was associated with higher costs and more frequent minor complications. A third study using population-based data also showed no esophageal cancer-specific mortality differences between esophagectomy and endoscopic ablation [39]. Based on these data, PDT appears to show promising results regarding the key outcomes of durability, reduction of cancer risk, and mortality when compared to esophagectomy.

While histologic reversal of dysplasia and intestinal metaplasia has been the defining criteria for successful ablation, concerns exist regarding whether eradication of abnormal biomarkers is also achieved with ablation. An initial retrospective study identified three PDT-treated patients with low- or high-grade dysplasia who had initial improvement or resolution of their dysplasia, only to subsequently develop HGD during a follow-up of between 16 and 38 months and require esophagectomy [40]. When post-PDT biopsy specimens were analyzed for hyperproliferation, aneuploidy, p53 mutations/protein overexpression, and p16 promoter hypermethylation, all patients had at least one persistent biomarker abnormality despite histologic improvement. A subsequent, prospective study of 31 patients with HGD by the same group analyzed biomarkers before and after PDT, with a median follow-up of 9 months [41]. Fluorescence in-situ hybridization (FISH) was used to assess for p16 and p53 loss, gain of *C-MYC*, *HER2/*neu, and 20q13 gains, or the presence of multiple gains. PDT was shown to achieve a statistically significant reduction in the number of abnormal biomarkers, but FISH-detected persistent abnormalities in 25% of the 24 patients without HGD on post-ablation histology. Of these six patients, two (33%) developed recurrent HGD, while none of the 18 patients without FISH abnormalities developed HGD over a median follow-up of 22 months. In addition, five of seven PDT non-responders had abnormal biomarkers. In addition to predicting recurrent dysplasia, biomarkers may also predict successful response to PDT ablation [42]. A prospective evaluation of 71 patients undergoing PDT found that p16 allelic loss predicted lack of treatment response at 3-month follow-up, possibly due to resistance of the these cells to PDT-induced apoptosis. These studies suggest that genetic biomarkers may aid in predicting treatment response and disease recurrence.

OPTIMAL UTILIZATION OF PDT

The use of PDT for esophageal ablation is currently limited to the eradication of Barrett's esophagus with high-grade dysplasia and for the palliative relief of dysphagia in patients with inoperable obstructing esophageal cancers. It is also reasonable to use this technique to treat patients with early-stage esophageal cancer who either refuse surgery or are poor surgical candidates. Due to its high cost, risk of complications, and lack of FDA-approval, it should not be used to ablate Barrrett's esophagus with low-grade dysplasia or non-dysplastic Barrett's esophagus. Given recent data on its efficacy, radiofrequency ablation may be a better choice to ablate non-nodular HGD due to its lower cost and reduced complications. PDT, however, may be best suited for patients with multifocal nodular high-grade dysplasia that is not amenable to removal of all nodules via endoscopic mucosal resection. For patients with malignant dysphagia, PDT may be advantageous in patients with gastroesophageal junction (GEJ) tumors by avoiding the severe reflux that occurs after endoscopic stenting across the GEJ. It also provides a useful option in patients with high cervical malignancies not amenable to endoscopic stenting, especially if the proximal stent has to traverse the upper esophageal sphincter in order to achieve complete coverage of the tumor. A final indication for relief of dysphagia may be in patients with recurrent obstruction after tumor overgrowth/ingrowth into a previously placed esophageal stent. For patients with superficial cancers that are non-surgical candidates, PDT or cryoablation therapy may be appropriate as means of attempting tumor eradication, although no head-to-head data exist comparing these modalities. However, if future studies confirm currently available preliminary data, cryoablation therapy may be the preferred option for these patients due to its reduced costs and improved side effect profile.

SUMMARY

PDT has been used in medicine to ablate and destroy unwanted tissue for nearly 50 years. Its unique mechanism of action is non-thermal and utilizes the activation of a photosensitizer by local application of a specific wavelength of light and the subsequent generation of oxygen radicals by the "excited" photosensitizer. These oxygen radicals create localized cellular injury and necrosis in the region of photoactivation. While a variety of photosensitizers have been studied, only porfimer sodium is approved for use in the United States. Approved gastrointestinal applications include the treatment of both squamous cell cancer and adenocarcinoma of the esophagus in non-surgical candidates for

the purpose of palliation of malignant dysphagia or tumor eradication. More recently, approval for the treatment of Barrett's esophagus with high-grade dysplasia (HGD) has been granted. The technique achieves success rates of 70–100% for these indications, but residual Barrett's epithelium usually remains. Due to its status as the most-widely used ablation technique with more than 15 years of clinical data, PDT is the only method of ablation that has currently been shown to be durable, reduce the risk of cancer recurrence, and achieve outcomes similar to esophagectomy for the treatment of Barrett's with HGD. Despite its high cost and known complications (development of photosensitivity reactions and esophageal strictures in nearly a third of patients), PDT appears to meet established criteria for cost-effectiveness. While initial studies of newer ablative techniques offer promising efficacy results with the advantages of cost-reduction and decreased complications, it is uncertain if these methods are durable, reduce the risk of subsequent cancer, or achieve outcomes similar to surgical therapy. Until data regarding these issues are available, PDT remains the best-validated endoscopic treatment option to surgery for patients with Barrett's esophagus with HGD and early esophageal cancer.

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Cryoablation of Barrett's Esophagus

Michael J. Krier, and Pankaj Jay Pasricha, MD

CONTENTS

Summary

Cryotherapy or the application of exceptionally cold temperatures for tissue destruction has long been used as a mainstay therapy in a wide variety of medical fields such as dermatology, gynecology, and otolaryngology. However, not until relatively recently over the past decade has the use of cryotherapy in therapeutic endoscopy been seriously investigated. Beginning with seminal work at Johns Hopkins in the early 1990s, this treatment modality is now increasingly being evaluated for human use in the ablation of Barrett's esophagus (BE), vascular abnormalities, and the treatment and palliation of

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gastric and esophageal malignancy. This chapter will focus on the application of this therapy for Barrett's esophagus.

Key Words: Cryoablation, Barrett's esophagus, Esophageal dysplasia, Esophageal cancer

INTRODUCTION

Cryotherapy or the application of exceptionally cold temperatures for tissue destruction has long been used as a mainstay therapy in a wide variety of medical fields such as dermatology, gynecology, and otolaryngology [1–3]. However, not until relatively recently over the past decade has the use of cryotherapy in therapeutic endoscopy been seriously investigated. Beginning with seminal work at Johns Hopkins in the early 1990s, this treatment modality is now increasingly being evaluated for human use in the ablation of Barrett's esophagus (BE), vascular abnormalities, and the treatment and palliation of gastric and esophageal malignancy [4–7]. This chapter will focus on the application of this therapy for Barrett's esophagus.

ADVANTAGES OF CRYOTHERAPY IN COMPARISON TO OTHER ABLATIVE TECHNOLOGIES

Several ablative technologies have been proposed for the endoscopic treatment of Barrett's esophagus with focused thermal energy representing a final common pathway. Examples include electrocoagulation, argon plasma coagulation (APC), heater probe, radiofrequency, and Nd:YAG/KTP laser. However, along with the mechanism of action, these modalities also share some major shortcomings. When ablating with heat, maintaining adequate control over the ablation process can be difficult and as a result, there is a high potential for unintended tissue injury with complications including fever, pleural effusion, esophageal stricture, and perforation [8–11]. These concerns are particularly important when balanced against the actual risk for malignant transformation of Barrett's esophagus, estimated at about only 0.5% per year [12]. In addition to these complications, most thermal modalities are also plagued by the drawbacks of cost, patient discomfort and pain during and after the procedure, excessive time for treatment, and the requirement for tissue contact. As discussed further in this chapter, endoscopic cryotherapy has the potential to overcome several of these issues.

PRINCIPLES AND MECHANISMS OF CRYOTHERAPY CELLULAR INJURY

The goal of cryotherapeutic ablation is to produce freezing of a defined volume of tissue while minimizing collateral tissue damage. Rapid intense cooling followed by slow thawing results in lethal injury for most tissues. Specifically an optimal lethal range for freeze-induced cellular injury appears to be between –5 and –50°C [13]. In addition to a repetitive freeze–thaw cycle, factors determining the magnitude of cellular injury include the initial freeze rate (injury proportional to speed), absolute tissue temperatures, duration of freeze, and thaw rates (injury inversely related to speed) [14, 15].

Several complex mechanisms of injury have been described when discussing the specific nature of cell death during the freeze–thaw cycle. In terms of the immediate effects, when significant cellular hypothermia occurs down to freezing temperatures, extracellular ice crystalline formation dehydrates cells via setting up an osmotic gradient, causing them to shrink thus damaging intracellular components and eventually cellular membranes. As cooling duration lengthens, intracellular ice formation occurs which is also cytotoxic. And finally as the initial thawing process begins, there exists a brief period of extracellular hypotonicity setting up a reverse osmotic gradient producing cellular swelling and eventual death through cell membrane rupture. At super-cold temperatures (–76°C to –158°C), cryoablation can also induce cellular apoptosis [16].

Delayed injurious effects have been related to the loss of microcirculation followed by progressive cellular anoxia. Furthermore, immune-related processes may also contribute. Thus, cryoablative techniques for prostate cancer leave tumor-associated proteins and antigens intact, and against a backdrop of a significantly inflammatory microenvironment from the freeze–thaw process, these can effectively stimulate cytotoxic T cells as part of an anti-tumor immune response [17]. Although this has not been specifically tested in gastrointestinal applications, these observations suggest that cryotherapy can invoke a broad spectrum of biological responses to dysplastic and neoplastic tissue, attesting to its promise as a potentially effective therapeutic option cryotherapy.

DELIVERY DEVICES

Pasricha and colleagues first described a cryotherapeutic device (Cryomedical Sciences Inc., Bethesda, MD) suitable for use through an endoscope consisting of a long, insulated catheter through which liquid nitrogen (–196°C) was delivered. The initial prototype's

maneuverability was inhibited by the unintended consequence of excessive endoscopic rigidity during delivery of the super-cooled liquid nitrogen. Subsequently, iterative prototypes were developed to overcome this issue including the most recent device, the Polar Wand (GI Supply, Camp Hill, PA) (Fig. 1A). This device forces a cryogenic refrigerant (carbon dioxide) at or near ambient temperature through a catheter. When the refrigerant reaches the distal catheter tip, a sudden expansion of gas from a higher pressure to atmospheric pressure causes a massive drop in temperature (Joule–Thompson effect). Because the cooling effect is initiated at the distal catheter tip, the rest of the catheter in the accessory channel remains at ambient temperature thus preserving normal endoscopic maneuverability. At flow conditions of 6–8 L/min, end effector temperatures of nearly –78°C can be achieved [18].

The major advantages of this system are the lack of a need for expensive cryogenic equipment as required for liquid nitrogen and the ability to spray the mucosa at will, producing rapid injury of large areas without the need for contact. However, because of the large volume of CO_2 exiting the catheter, venting is required and newer generations of equipment have that built into the catheter.

More recently, another cryotherapy device has been developed by Johnston and colleagues. Instead of the Joule–Thomson effect, this utilizes a more conventional cryogenic system based on the delivery of liquid nitrogen through a multi-layered catheter including an outer sheath coated with a special polymer that is warmed during device operation (CSA Medical Inc., Baltimore, MD) (Fig. 1B). Liquid nitrogen is delivered at a temperature of –196°C to the catheter tip at a minimal ambient pressure [19] (Table 1).

CLINICAL AND EXPERIMENTAL DATA

Initial Esophageal Experiments

Pasricha and colleagues in the late 1990s completed an initial series of clinical endoscopic cryotherapy studies testing an early device in a canine esophageal model [5]. In a circumferential manner, pressurized gas was sprayed at a flow rate approaching (30 mL/min) for freeze durations between 5 and 10 s to ablate the distal 5 cm of esophageal mucosa. A nearly instantaneous freezing of the superficial mucosa was observed and the epithelium was completely sloughed off from the treated area within 24 h. Histological specimens revealed re-epithelialization starting to occur between days 1 and 4 (Fig. 2). All dogs survived the cryoablative therapy and the mucosa appeared fully healed by day 10.

Fig. 1. The Polar Wand endoscopic cryotherapy system (GI Supply, Camp Hill, PA) (**A**). The CSA Medical CryoConsole and catheter (CSA Medical Inc., Baltimore, MD) (**B**). The CSA Medical CryoConsole catheter available in either straight or directional tip (C).

Table 1
Cryotherapy device comparison

Attribute	*CSA™ system (CSA Medical Inc.)*	*Polar Wand (GI supply)*
Cooling method	Super-cooled liquid nitrogen gas	Joule–Thompson effect
Gas	Liquid nitrogen	Ambient temperature carbon dioxide
Temperature target achieved	–196°C	–78°C
Cryotherapy system	Multi-layered, heated catheter delivering refrigerant through low-pressure traditional cryogenic system. Foot pedal and temperature probe included	Ambient temperature system with catheter delivering refrigerant at 6–8 L/min. Foot pedal included

These early embodiments were succeeded by the current Polar Wand device. Further experiments showed a clear relationship between the duration of cryospray application and the corresponding extent of transmural injury. In animal experiments with 8 pigs, esophageal necrosis was limited to the mucosa with 15 s or less of cryospray, whereas 15–30 s extended to involve the submucosa, and frank transmural necrosis occurred after 120 s of application [20]. In the same study, it was also noted that the prophylactic measure of submucosal saline injection conferred a protective effect limiting injury to the submucosa with up to a full 60 s of cryotherapy application.

Johnston and colleagues have also successfully tested their cryogenic system delivering cold nitrogen to the distal esophagus of 20 Yorkshire swine with a 28-day follow-up period [4]. Spray time ranged from 10 to 60 s. These authors found that the depth of injury and transmural inflammation was mainly related to circumferential application of cryorefrigerant with hemi-circumferential application producing a more superficial involvement. Mucosal ablation was also noted to

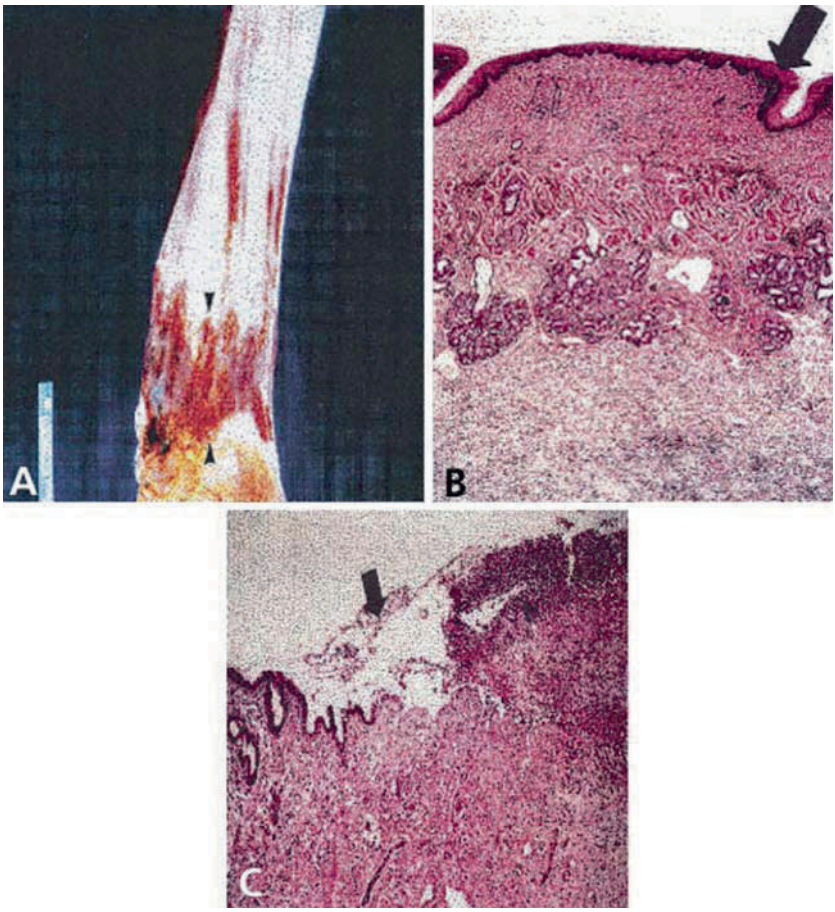

Fig. 2. Cryoablation of dog esophageal mucosa. Freezing of the esophageal mucosa (**A**), with sharp demarcation from untreated mucosa (*arrow*), was visible within seconds of spraying liquid nitrogen endoscopically. Biopsies taken before treatment (**B**) show normal squamous epithelium that was completely sloughed off (*arrow*) after cryotherapy with preservation of the submucosa and deeper layers (**C**). No significant inflammatory response or hemorrhage was seen in most cases.

occur at much higher temperatures (between 0 and –10°C) than previously reported with direct contact cryotherapy which would often cause esophageal perforations at much lower temperatures [4]. Complications observed at week 4 was a 27% incidence of stricture exclusively in those treated circumferentially with no stricture formation being noted in hemi-circumferentially treated pigs.

Cryotherapy with Human Validation

Recently liquid nitrogen-based cryotherapy was evaluated for its safety and efficacy in treating Barrett's esophagus in a pilot study of 11 patients [7]. All patients had a longstanding history of Barrett's esophagus with varying degrees of dysplasia (none to multifocal high-grade). Cryotherapy was applied hemi-circumferentially to the distal esophagus with two repeat freezing applications of 20 s each. Monthly interval treatments (up to a maximum of three) were made until reversal (at least 1 cm length reduction) or complete reversal (no endoscope evidence of BE) was confirmed by biopsy. Patients were then followed for a mean of 12 months with 6-month interval endoscopies. In this series, 9/11 patients completed the protocol and 78% (7/9) of them achieved complete histological resolution of BE. Complications reported included esophageal ulcers in two patients and chest discomfort and solid food dysphagia in two other patients.

An abstract is also available by Canto and colleagues evaluating the Polar Wand system in Barrett's esophagus with low-grade (7 patients) and high-grade dysplasia (26 patients) and esophageal adenocarcinoma (6 patients) in a prospective phase I single center trial [18]. A total of 39 patients were treated with a median follow-up of 7.1 months. An average of four cryotherapy sessions were performed per patient resulting in 95% partial response (reduction in BE and/or dysplasia) and a near-complete response in high-grade dysplasia in 23/25 (88.5%) patients. For any dysplasia, it was noted that 29/36 (80.6%) patients had a complete response to cryotherapy. Complications occurred in only two patients, mainly described as "transient mild discomfort." Polar Wand has also been used in other applications in the GI tract such as vascular malformations, attesting to its practicality and safety [21].

An abstract by Greenwald and coworkers presented recent data using a low-pressure liquid nitrogen device evaluating 77 patients undergoing a median number of four cryotherapy treatments (323 total treatments over a 2-year period) for conditions of Barrett's esophagus (7 patients – 9.1%), high-grade dysplasia (45 patients – 58.4%), intramucosal cancer (13 patients – 16.9%), T1 or T2N0M0 esophageal cancer (10 patients – 13%), and squamous dysplasia (2 patients – 2.6%) [22]. Serious complications encountered included one gastric perforation in a patient with Marfan's syndrome, three esophageal strictures (3.9%), and a lip ulcer from scope contact. Otherwise common less serious side effects encountered included mild chest pain, dysphagia/odynophagia, and sore throat. In total, side effects were encountered in 168 procedures (52%).

CONCLUSION

Although in its infancy, cryotherapy represents a new and exciting approach to endoscopic ablative therapy for Barrett's esophagus. Its promise of relatively low cost, simple technique, portability, and low complication rate makes it an attractive alternative to other "thermal" ablative technologies. Further confirmation with larger clinical trials will need to be undertaken before cryotherapy can be considered a mainstay therapy for Barrett's esophagus.

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Cost-Effectiveness of Endoscopic Therapy for Barrett's Esophagus

Patrick Yachimski, MD, MPH and Chin Hur, MD, MPH

CONTENTS

Summary

Management options for Barrett's esophagus with high-grade dysplasia include intensive endoscopic surveillance, surgical esophagectomy, or endoscopic ablation therapy. Controlled, prospective trials comparing these treatment strategies have not been performed.

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In addition, clinical uncertainty may exist with respect to the accuracy of diagnosis of Barrett's high-grade dysplasia, risk of cancer progression, and likelihood of durable treatment outcome. Disease models can simulate risk over time in an attempt to account for these uncertainties. Cost-effectiveness analyses, based on these models, can be used to compare the relative costs and outcomes of endoscopic therapy for Barrett's esophagus with high-grade dysplasia, compared to surgery or surveillance strategies.

Key Words: Barrett's esophagus, Cost-effectiveness, Photodynamic therapy, Esophagectomy

INTRODUCTION

Barrett's esophagus refers to specialized intestinal metaplasia of the distal esophageal mucosa and is the principal risk factor for esophageal adenocarcinoma [1]. Esophageal adenocarcinoma represents the fourth most common gastrointestinal malignancy in the United States, and its incidence is rising at a rapid rate [2].

Yet for an individual patient with Barrett's esophagus, the annual and lifetime cancer risk may be relatively small. Among individuals with Barrett's esophagus, 1 in 200 per year (0.5% per year) will develop esophageal adenocarcinoma [3]. Among those with Barrett's containing high-grade dysplasia (HGD), the estimated annual adenocarcinoma incidence is between 6 and 7% [4].

In part due to these relatively low rates of progression to cancer, controlled prospective data with respect to treatment of Barrett's esophagus are limited. A trial comparing esophagectomy versus endoscopic ablation for Barrett's HGD, for instance, would need to enroll large numbers of patients in order to have the power to detect a meaningful difference in durable cancer-free survival. In addition, uncertainties surrounding issues such as natural history of dysplasia progression/regression, and inaccuracies with respect to biopsy sampling and histopathologic interpretation of Barrett's HGD, further hamper development of a rational evidence-based approach to treatment of Barrett's HGD.

Moreover, amid this uncertainty, patients with Barrett's esophagus may be incurring increasing health care costs. In a West Virginia Medicaid cohort, for example, the estimated total cost of Barrett's esophagus increased more than threefold between 1995 and 1999, with pharmacy charges accounting for nearly two-thirds of total costs [5]. Widespread adoption of long-term endoscopic surveillance for patients with Barrett's is likely to represent another considerable expense [6].

As a consequence, clinical research in Barrett's esophagus has been an attractive area for simulation disease modeling. In the absence of prospective data, studies employing cost-effectiveness analysis (CEA) have provided a rationale for Barrett's surveillance and treatment strategies.

The focus of this chapter is CEA of endoscopic therapy for Barrett's esophagus. The chapter is divided into the following sections: (1) a brief overview of CEA; (2) special challenges in simulation disease modeling of Barrett's esophagus, including quality of life estimates; (3) a review of CEA of screening and surveillance strategies for Barrett's esophagus; and (4) a detailed discussion of CEA of endoscopic therapy for Barrett's esophagus, with an emphasis on photodynamic therapy.

CEA: A BRIEF OVERVIEW

Inputs and Outputs

CEA is a method which uses estimated health outcomes and costs in order to describe the net utility of a healthcare intervention. By reporting outcomes and costs in standardized units, a measure of cost-effectiveness can be calculated. CEA enables comparison of the relative cost-effectiveness of competing interventions, and can be used as a strategy to allocate finite health care resources [7].

Designing a CEA requires defining values for two classes of model inputs: costs, and disease-specific outcomes.

Costs are typically considered from society's perspective, though the perspective of the health care organization or third-party payer may also be used. CEA should include costs directly attributable to the intervention-related disease. Costs of the intervention/treatment as well as costs associated with treatment outcomes, including potential side effects, are also taken into account. For instance, in care of patients with Barrett's esophagus, foreseeable costs could include: cost of long-term proton pump inhibitor therapy; cost of endoscopy with biopsies; cost of endoscopic therapy; cost of esophagectomy; cost of chemotherapy, radiation, or other cancer care of patients who develop Barrett's-associated esophageal adenocarcinoma. Cost estimates may be obtained from reimbursement data or other estimates of expenditure or billing. Indirect costs, such as lost wages or productivity due to illness, are also included when the CEA is performed from the societal perspective [8].

Effectiveness is measured in terms of net gain or loss of a prespecified health outcome of interest. Depending on the nature of the

clinical scenario posed by the analysis, measures of effectiveness may include lives saved, cases of cancer prevented, or life years gained. A frequently used outcome measure in CEA or cost-utility analysis is the quality adjusted life year (QALY). The QALY is based on the premise that not all life years gained or lost are of equal value, but rather the value is dependent (quality-adjusted) on the hypothetical patient's underlying health state. In other words, a year of impaired health may be valued less than a year of perfect health. The issue of utility assessment in patients with Barrett's will be further discussed later in this chapter.

The ultimate goal of CEA is to use the net costs and net outcomes/effectiveness of a proposed intervention in order to calculate a single cost-effectiveness measure. For instance, in a typical CEA, output is reported in dollar cost per quality adjusted life year gained ($/QALY). By calculating estimates for competing interventions, or a single intervention in competing clinical contexts, the relative cost-effectiveness can be categorically ordered and compared side by side: the incremental change in cost (in dollars) and incremental change in outcome (in QALY) are used to calculate an incremental cost-effectiveness ratio (ICER). For example, the relative merits of annual surveillance, surveillance every 3 years, or surveillance every 5 years for Barrett's esophagus may be compared by calculating the ICER of the more frequent compared to the less frequent strategies.

This may permit society or the third-part payer to establish a willingness-to-pay threshold, below which health care interventions are permissible (e.g., will be or should be funded). A value of $55,000–$80,000/QALY is frequently cited as a threshold below which interventions are sufficiently cost-effective to justify implementation [9]. For instance, the cost-effectiveness of colorectal screening when compared to no screening is generally valued between $10,000 and $25,000 per life year saved, depending on the screening strategy [10].

Methods and Models

CEA models are often a hybrid of standard decision analysis and disease modeling techniques. A commonly used technique is the Markov model, a mathematical model that can be used to define outcomes and calculate costs for patients as they progress through disease states and undergo diagnostic tests and/or therapeutic intervention. Patients begin the simulation in a single health state, and over time, may remain in that health state or transition to a different health state. A simple model with three disease states is depicted in Fig. 1.

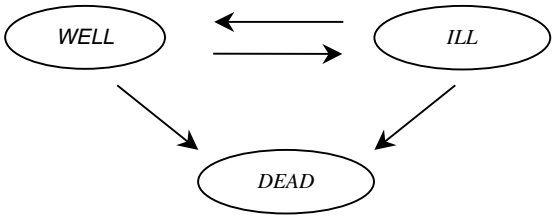

Fig. 1. Simple Markov model. Three health states are depicted, with *arrows* indicating possible transitions between health states.

Monte Carlo Markov models are particularly useful in modeling clinical situations where there is a repeated risk over time, and where events can occur at various times with potentially different outcomes. For example, one patient might progress to cancer at age 70 while another patient develops cancer at age 80. The age at which cancer develops can have important clinical implications and may affect the patient's clinical outcome.

Figure 2 presents a schematic of a simulation disease model of Barrett's esophagus, in which there are seven states: *BARRETT'S; LGD; HGD; CANCER; INOPERABLE/UNRESECTABLE; POST-ESOPHAGECTOMY; DEAD.* Each patient begins in the Barrett's state

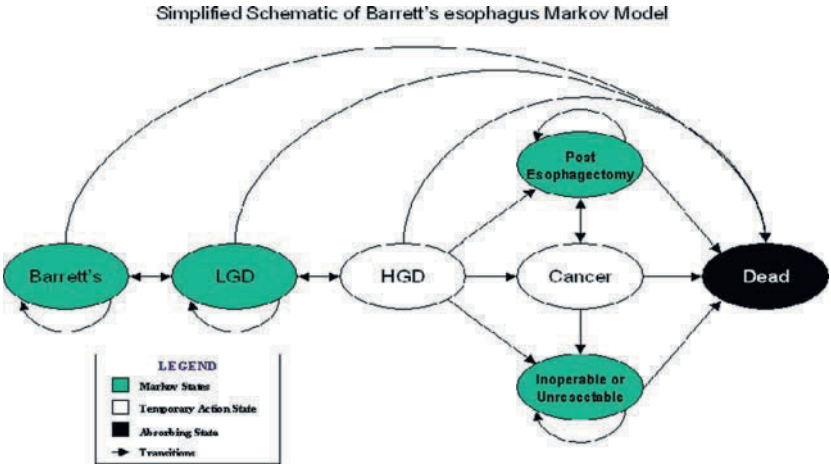

Fig. 2. This model depicts seven distinct health states, with *arrows* indicating possible transitions between health states. Subjects may cycle within certain health states over time (e.g., Barrett's, or LGD) without necessarily progressing to an alternative state. "Dead" is a final state. From Hur et al. [31] (permission requested).

with a set starting age. Depending on defined probabilities and randomly generated numbers (conceptually akin to rolling dice), this individual patient can either stay in the Barrett's state, progress to LGD, or die from age related causes. *DEAD* is an "absorbing" state and the simulation would start with the next patient. If the patient continues to have Barrett's, he/she will start the next cycle in the *BARRETT'S* state and repeat the process. If the patient were to progress to *LGD*, he/she would accordingly start the next cycle at the *LGD* state. Using specialized computer software, this process would be repeated for a large cohort of simulated patients (e.g., 100,000) while collecting specific individual outcomes such as life expectancy and total accrued costs.

Base case and Sensitivity Analyses

One of the strengths of this type of disease modeling is that the effect of any model input estimate can be analyzed to determine its effect on the outcome or model prediction. This is particularly useful when there is uncertainty or a range of possibilities surrounding any of the model inputs.

A model is first run as a base case analysis, using best guess estimates (typically based on published literature) of model inputs. The model can then be run repeatedly holding all parameters constant except for a single variable in question, which is varied over a wide-range of plausible values. By performing such a *univariate sensitivity analysis* and examining the outcomes for each value assigned to the variable in question, it is possible to determine whether this variable is pivotal to the model outcomes. A threshold value of the variable at which the conclusion changes or reverses (e.g., strategy A is no longer superior to strategy B) can be determined. If the determined threshold value is not clinically realistic or not consistent with published literature, then it may be reasonable to conclude that the variable in question does not affect the outcome of the model – or, in other words, the model is not "sensitive" to the particular parameter estimate. A *two-way sensitivity analysis* refers to a sensitivity analysis in which values for two parameter estimates are allowed to simultaneously vary.

Additional Terminology

Most CEA models identify a *reference case*, meant to reflect the typical individual at risk at whom the intervention will be targeted. In the case of a model proposing endoscopic screening for Barrett's esophagus, the reference case might be a 50-year-old male with typical reflux symptoms, representing the demographic of patients at greatest pre-test probability of harboring Barrett's esophagus.

In addition to specifying a reference case, a CEA should also specify a *time horizon*. The time horizon explicitly states the time period over which costs and outcomes should be considered. A range of time horizons is possible, and depending on the goals of the analysis the time horizon may be limited to the duration of a patient's hospital stay, or may be lifelong.

Discount rate refers to the concept that dollars spent and health outcomes gained today may be valued to a higher degree by the patient than costs or health outcomes at some future point in time. Most CEA specify a discount rate of 3%, although a 5% value is occasionally used.

Challenges in Modeling Barrett's Esophagus: Clinical Uncertainty and Utility Assessment

Challenges in both research and clinical management of Barrett's esophagus include uncertain estimates of cumulative cancer risk, which may be subject to publication bias [3]. Particularly relevant to consideration of endoscopic therapy for Barrett's HGD are accuracy of diagnosis of HGD, as well as stability of the diagnosis over time.

Accurate histopathologic diagnosis of Barrett's HGD may present a considerable challenge. Less than a third of community pathologists may correctly identify Barrett's HGD, and strikingly, 5% of community pathologists may interpret Barrett's with dysplasia as invasive adenocarcinoma [11]. Moreover, there may be considerable interobserver variability in grading Barrett's dysplasia even among experienced gastrointestinal pathologists [12].

In addition, some HGD patients, particularly those with focal HGD, may experience spontaneous regression of dysplasia on follow-up endoscopy [13]. Whether this is a function of the accuracy of initial histopathologic diagnosis, the effect of acid suppression therapy, biopsy sampling error, or true spontaneous disease regression is uncertain.

Nonetheless, if endoscopic therapy is to be judged on its ability to eliminate HGD, then assurances need to be provided that achievement of this outcome is in fact due to endoscopic therapy, rather than misdiagnosis or spontaneous disease regression. Whether there is a risk of disease recurrence following successful endoscopic therapy, particularly over the longer term, is also a concern. For instance, in use of photodynamic therapy for elimination of Barrett's HGD, limited data exist beyond 5 years of post-treatment follow-up [14]. Fortunately, the ability of CEA to include sensitivity analysis allows the CEA model to test and explore these clinical uncertainties.

Another challenge in Barrett's models involves utility assessment for estimates of quality of life. On a utility assessment scale, a value of

1 reflects perfect health, whereas a value of 0 indicates death. Every other health state between perfect health and death lies on a gradient within this range. Minor illness will result in a lesser loss of utility than major illness or impairment. Quality of life utility values may be calculated by survey of patient preferences (utility) using specialized techniques such as standard gamble or time tradeoff. From a methodological perspective, utility scores and patient preferences are not equivalent, however, depending on the clinical scenarios being compared, higher versus lower utility scores may be suggestive of patient preferences.

Data regarding utility assessment in Barrett's esophagus are limited. The extent to which endoscopic therapy or surgical therapy is expected to impact post-procedure quality of life is of considerable importance. An early Barrett's surveillance CEA by Provenzale and colleagues established a post-esophagectomy quality of life score of 0.8 [15]. This was upgraded to 0.97 in a subsequent model, with this value derived from utility assessment of patients who had undergone esophagectomy for HGD or cancer at a single academic center [16]. The estimate of 0.97 for post-esophagectomy quality of life score has been used in numerous subsequent Barrett's CEA models.

In another published survey, Barrett's patients without dysplasia valued their actual health state at a utility value of 0.95 [17]. When faced with the hypothetical scenario of developing HGD and confronted with the potential outcomes of therapy, including likelihood of disease recurrence and likelihood of post-treatment dysphagia, the post-esophagectomy state was valued at 0.92, and the post-PDT state was valued between 0.91 and 0.93, depending on the presence or absence of dysphagia [17]. A strategy of intense surveillance for HGD was valued at 0.90, lower than that for either esophagectomy or PDT [17]. When subjects were asked to define their treatment preferences for HGD, however, 70% chose frequent endoscopy, while only 15% chose esophagectomy and 15% chose PDT [18] – indicating that patient preferences may be driven by features not accounted for or not included in the utility assessment.

Another study from the surgical literature surveyed patients who had actually undergone either transhiatal or transthoracic esophagectomy [19]. Subjects were interviewed between 3 and 12 months post-operatively, and presented with eight health states. Utility assessment by standard gamble and overall ranking of the health states are presented in Table 1. Of note, patients valued their current health post-esophagectomy highly overall (0.97). The presence and nature of complications significantly impacted the perceived value they assigned to several other post-esophagectomy states (Table 1) [19].

Table 1
Utility assessment for post-esophagectomy health states

Rank	*Health state*	*Standard gamble score*
1	Own current health state	0.97
2	Home, disease-free	0.96
3	Home, recovering	0.92
4	Hospitalized without complications	0.90
5	Hospitalized with pneumonia	0.82
6	Cancer recurrence in digestive tract	0.41
7	Cancer recurrence in bones	0.35
8	Unresectable cancer	0.34

Adapted from de Boer et al. [19].

As with other uncertain estimates, sensitivity analysis can accommodate a range of utility values in CEA. However, in examining individual Barrett's models, it is worth taking note of quality of life estimates, as their assigned value can have a pivotal impact on model results or projections.

CEA OF BARRETT'S SCREENING AND SURVEILLANCE

Prior to the advent of effective endoscopic therapy for Barrett's esophagus, and in a context in which esophagectomy was the only therapeutic option for Barrett's HGD or esophageal cancer, models analyzed the cost-effectiveness of screening and/or surveillance for Barrett's.

A Markov decision analysis model by Provenzale and colleagues published in 1994 assessed 12 potential surveillance strategies, with the reference case defined as a 55-year-old male with non-dysplastic Barrett's [15]. Strategies included no surveillance followed by esophagectomy for HGD or cancer, versus surveillance at intervals ranging from 1 to 5 years followed by esophagectomy for HGD or cancer. Key model estimates included an annual cancer incidence of 1.3% (1 per 75 patient years), surgical mortality ranging from 9.5 to 19%, and a post-esophagectomy quality of life utility score of 0.8. In this model, annual surveillance with esophagectomy for HGD was the preferred strategy if life expectancy was the only consideration. However, only a strategy of surveillance every 5 years was acceptable from a cost-effectiveness standpoint (assuming a willingness to pay threshold of $50,000/QALY), with an ICER of $27,400/QALY when compared to

no surveillance. The model results were sensitive to estimates of cumulative cancer incidence and post-esophagectomy quality of life [15].

This model was updated in 1999, with revised estimates of a 0.4% annual cancer incidence for patients with Barrett's, and a post-esophagectomy quality of life utility score of 0.97 [16]. As previously discussed, this estimate was reported to be obtained from survey of post-esophagectomy patients (0.97 with interquartile range 0.83–1.0) [16]. The updated model likewise reported 5 years as the optimal surveillance interval, but with a significantly higher ICER (compared to no surveillance) than the original analysis, at $98,000/QALY. Once again, the model results were sensitive to estimates of cancer incidence and post-esophagectomy quality of life. At an annual cancer incidence of 1%, the ICER of surveillance every 5 years dropped to $26,600/QALY. This measure compared favorably with contemporary estimates of accepted practices such as colon cancer screening ($20,000/LY), breast cancer screening with mammography ($22,000/LY), and cervical cancer screening with Papanicolau smear ($250,000/LY) [16].

With respect to quality of life, surveillance every 5 years remained a preferred strategy as long as post-esophagectomy quality of life utility scores exceeded 0.87. Below this threshold, post-operative morbidity outweighed any survival benefit conferred by cancer surveillance [16]. To the extent that endoscopic ablation therapy might be favorable in preserving post-procedure quality of life, this analysis hinted at a future opportunity for such therapy.

Subsequent simulation disease models have addressed the cost-effectiveness of screening for Barrett's in patients with gastroesophageal reflux disease [20], endoscopic surveillance in patients with established Barrett's [21], or both screening and surveillance [22]. In a hypothetical cohort of white men aged 50 with reflux symptoms as the reference case, Inadomi and colleagues identified screening endoscopy at age 50 as cost-effective (ICER $10,440/QALY) compared to no screening [22]. Further surveillance, at 5-year intervals, was cost-effective only for individuals in whom the initial screening endoscopy identified the presence of dysplasia [22]. These models' predictions are consistently sensitive to quality of life estimates, with cost-effectiveness of esophagectomy attenuated by reductions in post-surgical quality of life [20–22].

In summary, earlier CEA models analyzing screening and surveillance of Barrett's esophagus predate the widespread emergence of endoscopic ablation therapy. In each model, Barrett's screening and surveillance could be cost-effective under certain circumstances. In actual practice, a surveillance strategy of endoscopy every three years

for patients without dysplasia has been endorsed by the American College of Gastroenterology [23], though this recommendation was based on collective available data regarding the natural history and clinical course of Barrett's, and not exclusively on CEA model results.

CEA OF ENDOSCOPIC THERAPY FOR BARRETT'S HGD

CEA of endoscopic therapy for Barrett's HGD have focused on photodynamic therapy (PDT). Whereas multiple endoscopic techniques are currently available for esophageal mucosa, PDT among them has arguably the greatest wealth of controlled prospective as well as retrospective data with longer-term follow-up. In a multicenter study of subjects randomized to porfimer sodium PDT plus acid suppression therapy, 77% experienced complete ablation of HGD following PDT [24]. This 77% rate of HGD ablation was maintained in 5-year follow-up [14]. Over 5 years of follow-up, 15% of PDT-treated patients progressed to cancer, compared to a 29% rare of progression among patients receiving acid suppression therapy alone [14].

CEA models incorporating PDT appeared in the literature well in advance of published 5-year efficacy data. The impact of PDT can be measured not only with respect to cost-effectiveness of Barrett's therapy, but also with respect to Barrett's screening and surveillance – expanding the range of available treatment options beyond esophagectomy can be expected to influence the relative costs, risks, and benefits of screening and surveillance for certain individuals under certain conditions. For instance, there may be little justification for surveillance in a Barrett's patient with advanced age or medical comorbidities who is not an acceptable esophagectomy candidate; however, the calculus changes if the patient would be a potential candidate for endoscopic therapy of Barrett's HGD.

We will first describe a disease simulation model addressing the impact of endoscopic ablation on cost-effectiveness of Barrett's screening and surveillance, followed by discussion of several models addressing the cost-effectiveness of PDT as a primary therapy for Barrett's HGD.

THE IMPACT OF ENDOSCOPIC THERAPY ON BARRETT'S SCREENING AND SURVEILLANCE

Gerson and colleagues re-examined the cost-effectiveness of Barrett's screening and surveillance, including endoscopic ablation as an alternative to esophagectomy in the event that screening/surveillance detected Barrett's HGD [25]. The outcome of interest in this model was

cost-effectiveness of screening/surveillance (incorporating the impact of endoscopic ablation therapy), and not a comparison of cost-effectiveness of endoscopic ablation versus esophagectomy for HGD therapy. This model demonstrates the influence of available endoscopic therapy not as an end in itself, but with respect to the cost-effectiveness of the upstream practices of screening and surveillance.

The model structure was relatively complex in this case. The reference case was a 50-year-old male with heartburn who either would or would not undergo endoscopic screening for Barrett's esophagus. Based on the findings of screening endoscopy, subjects would be allocated to one of several disease categories: normal, Barrett's without dysplasia, Barrett's with dysplasia, etc. Frequency of further endoscopic surveillance for those with Barrett's (ranging from once every 3 months to once every 3 years) was determined on the presence and grade of dysplasia. Ultimate treatment arms could consist of a "non-aggressive" approach of esophagectomy only for early esophageal cancer, several "moderate-intensity" approaches of esophagectomy for HGD and/or cancer, or several "high-intensity" approaches of esophagectomy for HGD and/or cancer *or* endoscopic ablation for individuals with early-stage cancer who were not surgical candidates. Endoscopic therapy was not limited to PDT, but consisted of endoscopic mucosal resection (EMR) for nodular lesions, or PDT for flat lesions. Laser ablation was used for residual early-stage cancer following incomplete EMR or PDT [25].

It was assumed that 85% of HGD patients would undergo esophagectomy. Further base case assumptions included a 15% operative mortality rate, and a cancer remission rate of 45% following PDT. The possibility of false-positive and/or false-negative biopsy results was not incorporated in the base case analysis. Utility assessments were not incorporated in the model and quality life adjustments were not performed [25].

In this model, under a strategy in which esophagectomy was offered for HGD and endoscopic ablation was offered for early cancer, the ICER of screening and surveillance for Barrett's (compared with no screening) was $12,140/LY. This strategy "dominated" all other moderate- or high-intensity strategies – in other words, this strategy was both more effective and less costly than all other competing strategies [25].

PDT VERSUS ESOPHAGECTOMY AS PRIMARY THERAPY FOR BARRETT'S HGD

Three models are described below, and a comparison of key model estimates and outcomes is presented in Tables 2 and 3.

PDT Versus Esophagectomy Versus Surveillance for HGD: Hur et al. [26]

Hur et al. designed a disease simulation model to examine three competing strategies for hypothetical 55-year-old male subjects with Barrett's HGD: continued surveillance, PDT, or esophagectomy [26]. All patients were assumed to be potential operative candidates at baseline. Key assumptions in the model included the following: (1) patients who experienced complete elimination of Barrett's mucosa following PDT were not at risk for progression to cancer; (2) patients with HGD who underwent PDT and subsequently developed cancer were less likely to achieve complete surgical cancer resection compared to patients with HGD who proceeded to esophagectomy without delay; (3) patients who failed PDT underwent esophagectomy, without an attempt at repeat PDT or alternative endoscopic therapies [26].

Further model specifications and base case assumptions are as detailed in Table 2. The model assumed a base case esophagectomy mortality rate of 2.7% for individuals with HGD, and 3.5% for individuals with cancer. False negative and false positive biopsy results were possible, at rates ranging up to 17.5% (cancer interpreted as HGD, LGD interpreted as Barrett's). The post-esophagectomy quality of life score for this model was 0.8, considerably lower than the 0.97 [16, 22] to 1.0 [20, 21] range estimates used in the surveillance and screening models. In the absence of published data objectively measuring post-PDT quality of life, a post-PDT quality score of 1.0 (perfect health) was assumed for the base case analysis [26].

PDT for HGD was more effective and resulted in a longer unadjusted life expectancy than either esophagectomy or surveillance in this model, but was also more expensive. Altogether, the main model outcomes in base case analysis indicated that PDT for HGD was cost-effective compared to surveillance (ICER $12,400/QALY) and also compared to esophagectomy ($3,300/QALY) [26].

Sensitivity analyses indicated that the model results were sensitive to patient age at the start of therapy/surveillance. As patient age increased above 55 years, PDT became increasingly more cost-effective. The model results were additionally sensitive to post-PDT quality of life estimates, however only at relatively extreme values. Surveillance became a preferred strategy only if post-PDT quality of life was valued

Table 2
Cost-effectiveness of endoscopic therapy for Barrett's esophagus, as compared to surveillance or esophagectomy: selected model base case estimates, comparison among models

Author	*Year*	*Endoscopic treatment*	*Reference case*[a]	*Time horizon*	*Post-esophagectomy QOL*	*Post-PDT QOL*	*Allows for histologic misdiagnosis?*	*Eradication of HGD post-PDT (%)*	*Allows for recurrence post-PDT?*
Hur et al. [26]	2003	PDT	55 year old M	Death	0.80	1.0	Yes	77	No
Shaheen et al. [28]	2004	PDT	50 year old WM	Death or age 80	0.97	1.0	Yes	88	No
Vij et al. [29]	2004	PDT + laser	55 year old WM	Death	0.97	0.97[b]	Yes	77	Yes

All models assumed a 3% annual discount rate.
[a]M: male; WM: white male.
[b]QOL estimate for post-PDT with stricture.

Table 3
Cost-effectiveness of endoscopic therapy for Barrett's esophagus, as compared to surveillance or esophagectomy: selected model base case estimates, comparison among models

Author	*Year*	*Surgical mortality (%)*	*PDT stricture rate (%)*	*Monetary unit*	*Base cost estimate: esophagectomy*	*Base cost estimate: PDT*	*Base cost estimate: endoscopy with biopsy*
Hur et al. [26]	2003	2.7–3.5	34	Year 2000 US $	$22,600	$9,000	$800
Shaheen et al. [28]	2004	2.7–5	18.5	Year 2001 US $	$19,000	$20,000	$830
Vij et al. [29]	2004	4	30	Year 2001 US $	$8,900[a] $22,347[b]	$13,408	$680

[a]Cost of esophagectomy without complications.
[b]Cost of esophagectomy with complications.

below a score of 0.85, and esophagectomy was preferred only if post-PDT quality of life was valued below 0.8 [26]. The principal local complication likely to impact quality of life following PDT is esophageal stricture, which has been reported to occur in up to 34% of patients [27]. However, model outcomes were not sensitive to post-PDT stricture rate over a wide range of estimates (0–70%). Model results were not sensitive to multiple additional parameters including operative mortality estimates, false positive biopsy rates, rates of HGD recurrence after PDT, or rate of progression from HGD to cancer [26].

PDT, Esophagectomy, or Surveillance Versus a No-Surveillance Strategy: Shaheen et al. [28]

Shaheen and colleagues published a CEA model for management of Barrett's HGD, but with a slightly different frame of reference. Rather than reporting ICER of PDT or esophagectomy relative to surveillance or to one another, the reference/default option in this model was an approach of no preventive or surveillance strategy [28].

The reference case for the model was a Caucasian male aged 50 with Barrett's HGD. Key model estimates include eradication of HGD in 88% of patients following PDT, and a surgical mortality as high as 5% for patients with symptomatic esophageal cancer. A quality of life utility value of 0.97 was used for the post-esophagectomy state. While a single post-PDT quality of life adjustment was not uniquely specified, additional estimates included a 1.0 value for subjects with Barrett' s esophagus, and a 0.5 value for esophageal cancer. These latter two estimates were derived from direct survey of 56 "surveillance eligible" patients with Barrett's at a Veterans Affairs medical center [28].

All treatment strategies, including surveillance, resulted in fewer cases of cancer than a no prevention/no surveillance strategy. In terms of cost-effectiveness, surveillance dominated esophagectomy for HGD – meaning that surveillance was both less costly and more effective (gain in QALY of 14.96 for surveillance versus 14.89 for esophagectomy). Either surveillance (ICER $32,053/QALY) or endoscopic ablation ($25,621/QALY) was cost-effective relative to a no prevention/no surveillance strategy. In comparison of surveillance versus ablation, whereas ablation was more costly than surveillance ($41,998 per patient versus $34,724 per patient), endoscopic ablation was preferred due to a greater overall gain in QALY (15.51 versus 14.96). Sensitivity analysis indicated that ablation therapy resulted in a superior average cost-effectiveness when the cost of ablation dropped below $15,000 [28].

Additional sensitivity analyses demonstrated that the model was sensitive to cancer incidence among patients with HGD, and also to quality of life post-esophagectomy. As the rate of cancer progression increased, esophagectomy became increasingly cost-effective relative to endoscopic surveillance. Esophagectomy resulted in longer life expectancy than ablation only when annual cancer incidence exceeded 30% [28]. Among unvariate estimates, ICER was most sensitive to changes in post-esophagectomy utility measures [28].

PDT Plus Laser Versus Esophagectomy: Vij et al. [29]

A third model by Vij and colleagues included four competing strategies for Barrett's HGD: (1) surveillance, (2) esophagectomy, (3) PDT with laser therapy for residual Barrett's during follow-up, (4) PDT followed by esophagectomy for persistent Barrett's HGD [29]. A distinguishing feature of this model is that, due to sampling error and initial misdiagnosis, a substantial portion of HGD patients were assumed to have prevalent cancer – including "late" cancer in 23% of HGD patients. Neither surgery nor PDT was assumed to be curative for patients with late cancer [29].

PDT followed by surveillance resulted in higher incremental cost than esophagectomy, but led to the greatest overall gain in life expectancy. Compared to esophagectomy, PDT followed by surveillance was cost-effective with an ICER of $47,410/QALY. Assumptions regarding misdiagnosis of HGD, as well as the efficacy of PDT in treating early cancer, impacted model outcomes. For instance, if the efficacy of PDT in treating early cancer (misdiagnosed as HGD) drops below 50%, then the ICER of PDT compared to esophagectomy exceeds $50,000/QALY [29].

Further sensitivity analyses again demonstrated the importance of quality of life values in determining the preferred strategy. Significant reductions in post-esophagectomy quality of life values improved the cost-effectiveness of PDT. Of note, if participation in an ongoing endoscopic surveillance program following PDT was deemed to have a significant negative impact on quality of life, then PDT became a less attractive option [29]. A two-way sensitivity analysis incorporated the impact of post-PDT stricture on post-procedure quality of life. PDT remained cost-effective compared to esophagectomy even with a post-PDT utility score of 0.8, as long as post-esophagectomy quality of life was valued at a utility below 0.95 [29].

Additional critical parameter estimates in sensitivity analyses included operative mortality and prevalent cancer rates. If operative mortality was below 2%, then esophagectomy became a preferred

strategy. Similarly, if operative mortality exceeded 15%, then either PDT or surveillance was preferred over esophagectomy. Surveillance was also preferred over esophagectomy if the prevalent cancer rate was below 15% [29].

FUTURE ISSUES IN COST-EFFECTIVENESS OF ENDOSCOPIC ABLATION

Endoscopic ablation options for Barrett's are not limited to PDT, but may also include radiofrequency ablation, multipolar electrocoagulation, endoscopic mucosal resection (EMR), or cryotherapy. Future analyses will need to address the cost-effectiveness of not only these individual ablation strategies, but also the cost-effectiveness of combination endoscopic ablation therapy. For instance, in current practice a patient may undergo EMR for diagnostic or therapeutic purposes, followed by PDT for ablation of residual Barrett's HGD. While such an approach may be based on sound clinical reasoning, its cost-effectiveness has not been established. Efforts to identify the relative cost-effectiveness of these therapies must include consideration of costs, efficacy, side effects, and requirement for long-term follow-up.

In considering the cost-effectiveness of endoscopic ablation therapy, a primary component of cost is the actual cost of an ablation session. For instance, a component of the cost of PDT is the cost of the photosensitizing agent (estimated at $2,740 per 75 mg vial in one model [25], with a typical dose being 2 mg/kg intravenous). From the perspective of individual patient care, the cost of a pharmaceutical agent or single-use ablation device is of interest to providers and third-party payers. And from a CEA perspective, the extent to which endoscopic ablation techniques can minimize the cost of pharmaceutical or device components may impact the cost and subsequently cost-effectiveness of therapy.

A second critical cost feature relates to the practice of long-term endoscopic surveillance with biopsy even following successful endoscopic ablation of Barrett's HGD. Recurrent Barrett's containing dysplasia or carcinoma has been described following PDT, occasionally "buried" beneath squamous re-epithelialization [30]. An endoscopic ablation technique that could abrogate or minimize the need for ongoing surveillance endoscopy would have a significant impact on cost-effectiveness of therapy.

Side effects of endoscopic ablation therapy have the potential to impact future CEA. The principal esophageal side effect of PDT is esophageal stricture formation, which may require multiple subsequent endoscopic procedures for stricture dilation. The cost of repeat endoscopy may be significant – although among the CEA models of PDT presented in this chapter, the model results were generally not

sensitive to post-PDT stricture rate across a wide range of estimates. Nevertheless, the incidence of measurable post-ablation side effects (stricture formation, esophageal perforation requiring surgery, need for a post-procedure inpatient hospital stay) may impact the cost-effectiveness of individual ablation techniques.

SUMMARY AND CONCLUSIONS

Cost-effectiveness models of endoscopic therapy for Barrett's HGD have focused on PDT. In some instances, estimates and assumptions for earlier Barrett's screening or surveillance models have been incorporated in CEA of endoscopic therapy. By extrapolation of existing data, simulation disease modeling is a methodology that tries to address the lack of data and clinical uncertainty with respect to natural history of Barrett's HGD, biopsy sampling error, and risk of HGD or cancer recurrence following ablation therapy.

Despite differences in model structure, CEA using simulation disease models consistently demonstrates that PDT ablation for Barrett's HGD can be cost-effective relative to continued endoscopic surveillance, esophagectomy, or both. This cost-effectiveness is relatively preserved over a range of model estimates that are consistent with the published literature and our current understanding of Barrett's natural history and outcomes.

Model results are consistently sensitive to quality of life estimates, particularly post-esophagectomy quality of life. Estimates for quality of life scores may be imprecise and may be based on cohorts of patients that are not easily generalizable to the Barrett's population at large. To the extent that developments in surgical technique and post-operative care have the potential to enhance post-esophagectomy quality of life, implications for CEA results may need to be re-addressed.

CEA for endoscopic ablation of Barrett's HGD has assessed PDT ablation. Based on current data, PDT ablation of Barrett's HGD can be supported and justified on a cost-effectiveness basis. Long-term data should begin to emerge with respect to additional ablation techniques such as endoscopic mucosal resection or radiofrequency ablation. Assuming these techniques are similarly effective as PDT, they should also have comparable cost-effectiveness.

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