

The future of endoscopic treatment of early Barrett neoplasia: The endoscopist's view

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Bibliography

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The field of Barrett's esophagus ablation has advanced dramatically in recent years. Endoscopic ablation is now viewed as a legitimate first-line treatment option for healthy patients with high grade dysplasia and early adenocarcinoma, on the basis of ongoing research. Furthermore, the notion of complete ablation of Barrett's esophagus has moved from concept to reality. Many questions have been answered, but many remain including issues relating to optimal technique,

Introduction

The field of Barrett's esophagus ablation has come a long way since the original pioneering work of Brandt and Berenson in the early 1990s [1,2]. In fact, ablation is now viewed as a legitimate first-line treatment option for healthy patients with high grade dysplasia and early adenocarcinoma, based on studies performed to date. Furthermore, the notion of complete ablation of Barrett's esophagus has moved from concept to reality. That being said, many questions about endoscopic ablation of Barrett's esophagus remain unanswered. This section will try to address the following issues regarding the endoscopic ablation of Barrett's esophagus:

1. Where have we been?
2. Where are we now?
3. What are currently unresolved issues in endoscopic ablation?
4. What are potential solutions for these issues?

Where have we been?

The concept of endoscopic ablation emerged in 1992 with the work of Brandt and then Berenson, who demonstrated that re-injury to metaplastic epithelium followed by healing in an environment characterized by aggressive control of acid could lead to re-epithelialization with a neosqua-

appropriate patient selection, predictors of response, and behavior of the cardia after ablation. This paper attempts to address the following questions with regard to endoscopic ablation of Barrett's esophagus: (i) Where have we been? (ii) Where are we now? (iii) What issues regarding endoscopic ablation are currently unresolved? (iv) What are potential solutions for these issues?

mous lining of the esophagus [1,2]. That early concept gave rise an explosion of techniques and publications that all demonstrated the feasibility of endoscopic ablation, using methods such as lasers, multipolar electrocoagulation, heater probe, argon plasma coagulation, radiofrequency ablation, cryotherapy, photodynamic therapy with either sodium porfimer or 5-aminolevulinic acid, and endoscopic mucosal resection. This early work also suggested that the biologic properties of the neosquamous epithelium were comparable to those of the normal squamous lining of the esophagus [3].

These early studies, while innovative, were flawed. They were typically uncontrolled, single-center case series, characterized by short-term follow-up, variable and nonstandardized treatment and follow-up protocols, and different primary end points as measures of success. There was only one randomized controlled trial in the early days of ablation therapy [4]. Furthermore, this early literature examined ablation in a heterogeneous group of patients, having intestinal metaplasia without dysplasia, low grade and high grade dysplasia, and both superficial and more deeply invasive adenocarcinoma. This being the case, there was no agreement on the best way to evaluate these approaches. Was the goal a "bottom up approach" starting with intestinal metaplasia, or a "top down" approach start-

ing with superficial carcinoma as recommended by the Amsterdam group [5]?

Furthermore, these reports and many editorials did not pay adequate attention to following rules of evidence in evaluating new treatment approaches. In particular, those involved in endoscopic ablation repeatedly failed to recognize several important principles of evidence-based evaluation of new treatment modalities. First, nonrandomized trials routinely overestimate the benefit of therapy [6]. Secondly, proof of principle and larger studies, including randomized controlled trials, continued to examine large numbers of patients without dysplasia. These studies repeatedly failed to acknowledge that, assuming a risk reduction of 50% for the development of cancer, that is, from an estimated 0.50% per year to 0.25% per year, then the number needed to treat to prevent one cancer in nondysplastic Barrett's epithelium was approximately 400 [7].

Studies routinely found incomplete macroscopic regression of the Barrett's segment and buried intestinal metaplasia beneath the neosquamous epithelium; hence, not surprisingly, there were reports of subsquamous cancers developing in patients with previously nondysplastic Barrett's epithelium [8–10]. Furthermore, persistent genetic abnormalities were noted after photodynamic therapy, despite histological downstaging from high grade dysplasia to lesser abnormalities, along with subsequent redevelopment of high grade dysplasia [11]. Also, some authors demonstrated persistent molecular abnormalities in residual dysplastic and nondysplastic epithelium after ablative therapy [12–14]. Other complications were noted as well, including perforation, stricture formation, and prolonged photosensitivity. It also became clear that the homogeneous application of these techniques to the entire surface area of the esophagus was a challenge.

Most importantly, ablation therapy in its early days was also hampered by the limited amount of data, derived from either animal or human studies, regarding the optimal dosing and administration of a given technique to achieve the most beneficial depth of injury; such studies were the exception rather than the rule [15–18].

Where are we now?

The field of endoscopic ablation has matured considerably as we reach the end of 2008. Long-term studies extending over 5 years are now available, dealing with endoscopic mucosal resection, photodynamic therapy, and a combination of the two; these demonstrate long-term survival comparable to that following esophageal surgery for high grade dysplasia or superficial carcinoma, and low rates of cancer-associated death [19]. A recent population-based study of patients with early esophageal cancer found long-term survival for patients managed with endoscopic therapy to be comparable to survival in those treated with surgical resection [20].

Randomized controlled trials have now compared a variety of ablation techniques with one another. 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 [21–23]. Randomized controlled studies have evaluated photodynamic therapy and radiofrequency ablation compared with a strategy of continued surveillance for patients with high grade dysplasia and low grade dysplasia [24,25]. These

studies represent a dramatic improvement in the quality of the work in this field and demonstrate the potential as well as the limitations of these techniques. The 5-year results of a randomized controlled trial of photodynamic therapy alone versus continued surveillance for high grade dysplasia showed that at 5 years, complete ablation of high grade dysplasia was achieved in only 48%, and progression to cancer occurred in 15% [26]. While the results were superior to those of the control arm, one can argue that the “juice is not worth the squeeze” for this technique, given the continued risk of cancer and need for surveillance, along with the cost and morbidity of this procedure. The 1-year results for radiofrequency ablation compared with sham therapy in high grade and low grade dysplasia have been submitted for publication (N. Shaheen, personal communication). Multicenter studies are now the norm rather than the exception. These studies all demonstrate the long-term efficacy of endoscopic therapy compared with other treatments for intraepithelial neoplasia. Furthermore, there is an emerging consensus on the need to completely remove all at-risk mucosa rather than leave any metaplastic epithelium behind. This has led to the increasing popularity of multimodal therapy with endoscopic mucosal resection plus either continued wide area endoscopic mucosal resection or thermal ablative techniques to eliminate the remaining at-risk mucosa. Recent studies now indicate that complete ablation of Barrett's esophagus with endoscopic mucosal resection in combination with radiofrequency ablation is now feasible (● Fig. 1).

In addition, new techniques are now routinely evaluated in animal models to determine the depth and type of injury from various ablative techniques, as well as the time course of the injury. The studies on radiofrequency ablation have involved a stepwise progression from animal studies, to human studies prior to esophagectomy, to human dosimetry studies, single-center studies, multicenter nonrandomized studies, and now multicenter randomized controlled trials [25,27–30]. This process has also led to modifications in the radiofrequency ablation technique and the development of the focal ablation device. Regardless of the eventual role of radiofrequency ablation, this series of studies illustrates the steps that need to be taken in the development and application of ablative technologies in the future. This is perhaps easier said than done, given the economic realities involved in the development of endoscopic therapeutic technologies. Nevertheless, the importance of animal work prior to widespread clinical application cannot be overstated.

The emergence of endoscopic mucosal resection as both a diagnostic and therapeutic tool has changed the landscape of ablation therapy (● Fig. 2).

Endoscopic mucosal resection of visible lesions in patients with high grade dysplasia and superficial adenocarcinoma has come of age, thanks in part to the pioneering work of the Wiesbaden group which has demonstrated 5-year survival of 98% for meticulously selected patients with early esophageal adenocarcinoma treated by endoscopic mucosal resection [31]. Endoscopic mucosal resection of visible lesions in patients with high grade dysplasia is now recommended in clinical practice guidelines [32].

Finally, the emerging concept of the combination of endoscopic mucosal resection of visible lesions with either circumferential endoscopic mucosal resection or thermal injury treatment of the remaining at-risk mucosa is becoming established. The rationale for this relates to the high metachronous cancer rate found by the Wiesbaden group along with the concept that at-

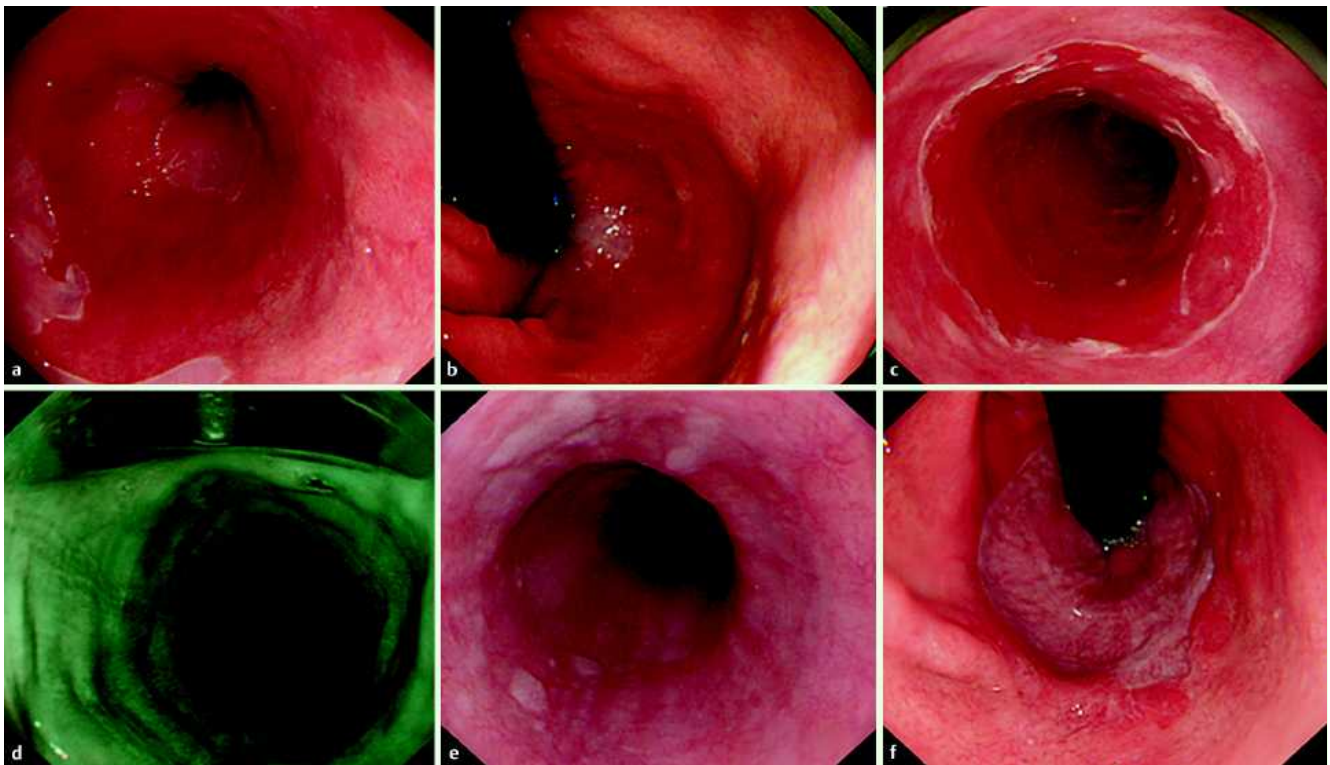


Fig. 1 Endoscopic images of a C9M10 Barrett esophagus (“C&M,” circumference and maximal extent) with multifocal high grade dysplasia, treated with stepwise circumferential and focal radiofrequency ablation. **a, b** Antegrade and retrograde view on a C9M10 Barrett segment, without visible lesions. **c** Effect after primary circumferential ablation using the HALO³⁶⁰

system. **d** At 2 months after circumferential ablation, two small residual islets of Barrett epithelium were detected with narrow-band imaging, and treated with secondary focal ablation using the HALO⁹⁰ system (12-o’clock position). **e, f** At 2 months after the last ablation session, the esophagus has completely regenerated with normal-appearing neosquamous epithelium.

risk mucosa, with its persistent molecular abnormalities remains after endoscopic mucosal resection. In 2008, exciting work from the Amsterdam group described the technique of circumferential and focal ablation in a small number of Barrett’s patients with residual dysplasia after endoscopic mucosal resection of visible lesions [33, 34]. 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. These findings suggest that the concept of complete ablation of Barrett’s esophagus and superficial cancer is now feasible.

It appears that many techniques evaluated to date have fallen by the wayside or are about to do so. These include multipolar electrocoagulation, the heater probe, argon plasma coagulation, laser treatment, and, in all likelihood, photodynamic therapy in its current variations. The reasons for the probable demise of these techniques include difficulty in obtaining uniform ablation, cost, side effects and persistent endoscopically evident or microscopic columnar epithelium after therapy. Current techniques still in play include radiofrequency ablation, cryotherapy, endoscopic mucosal resection, endoscopic submucosal dissection, and combinations of these techniques. The only conceivable role at present for techniques such as multipolar electrocoagulation and argon plasma coagulation is for dealing with small islands and areas of residual Barrett’s esophagus after treatment with another, more effective modality. While no comparative data are available, studies to date suggest that the focal radiofrequency ablation probe may be a better choice at present.

It is now clear that for any technique to have value, it must be inexpensive, safe, simple to apply, require a limited number of ses-

sions for application, completely eliminate columnar epithelium, eliminate or decrease cancer or progression risk, and possibly decrease the need for surveillance. Furthermore, it is essential that techniques provide a uniform application to the esophagus. This requires compensation for movement related to respiration and esophageal motility. With this in mind, the centering balloons used in photodynamic therapy and the balloon-based radiofrequency devices which isolate esophageal segments during the ablation procedure are appealing features of those methods.

We also need to keep in mind that the application of these techniques also requires rigorous patient selection, high quality imaging and staging prior to application, and meticulous long-term follow-up.

What are currently unresolved issues in endoscopic ablation?



While the field of endoscopic ablation has advanced dramatically in recent years, there is much we still need to know.

What is the role of cryotherapy?

Cryotherapy remains under study as an ablative technique, either as a stand-alone approach or in combination with endoscopic mucosal resection. Animal studies have already been undertaken to determine depth of injury with this technique and the time course of the response to injury. However, data as to its efficacy in Barrett’s esophagus are very limited. Johnston et al. studied 11 patients, of whom seven showed complete endo-



Fig. 2 Endoscopic and histological images of endoscopically resected lesions in a Barrett esophagus. **a** A short segment Barrett esophagus with a type 0-IIa lesion at the 12-o'clock position. **b** The lesion was endoscopically resected in four pieces using the "lift, suck and cut" technique. Mild bleeding was treated by placement of a clip. **c** Histological evaluation of the resected specimens showed a moderately differentiated (G2) adenocarcinoma infiltrating into the submucosa, T1sm1, 300 μ m (hematoxylin and eosin [H&E]; original magnification \times 40). Based on these histological findings, the

preferred approach in this patient is esophagectomy. **d** A type 0-IIa-IIc lesion at the 1-6 o'clock position. **e** The lesion was removed during a piecemeal procedure with five resections using the lift, suck, and cut technique. **f** Histological evaluation of the resected specimens showed an adenocarcinoma, with minimal infiltration into the muscularis mucosae, T1m3. Two peri-esophageal glands are seen below the muscularis mucosae (H&E; original magnification \times 40). Based on these histological findings, endoscopic treatment is suitable in this patient.

scopic and histologic reversal at 6 months [35]. Preliminary reports of cryotherapy were presented at Digestive Diseases Week (DDW) 2008 for a small group of patients with high grade dysplasia and cancer, and a randomized sham controlled study is now under way [36].

The appeal of cryotherapy is ease of use and relatively low cost. However, the uneven application inherent in spraying of the cryogen, rather than direct balloon-based application to isolated segments of the esophagus, is a matter of concern with this technique besides the lack of published data.

What is the role of radiofrequency ablation?

Studies to date have evaluated radiofrequency ablation in both nondysplastic and dysplastic Barrett's epithelium. We now know that a combination of circumferential and focal probes provides 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 [25]. Finally, published results for radiofrequency ablation are primarily from centers of excellence.

However, only a limited number of patients have been studied, we still do not know about either long-term results beyond 2.5 years, or the safety and efficacy of the technique when used outside of expert centers. In contrast, longer-term results are available for photodynamic therapy, which suggest a favorable outcome when it is compared with esophageal resection [19].

What is the optimal role of endoscopic mucosal resection?

As mentioned above, endoscopic mucosal resection has come of age, either as a stand-alone technique or in combination with complete ablation of the Barrett's segment. The key unresolved issue is the role of circumferential endoscopic mucosal resection. Studies to date suggest that circumferential endoscopic mucosal resection results in complete remission of intraepithelial neoplasia and Barrett's epithelium in 75% to 100% of patients [37-40]. Complication rates vary, but early bleeding, the occasional perforation, and late strictures remain issues. Key unanswered questions related to endoscopic mucosal resection include the following:

1. What is the optimal technique?
2. Should it be limited to patients with nodules only, or should it be applied in patients with flat dysplasia?
3. What is the optimal role and setting for circumferential endoscopic mucosal resection?
4. What is the best way to avoid islands of residual epithelium between resection specimens?
5. Can complications, especially strictures, be avoided?

Where does endoscopic submucosal dissection fit in?

Endoscopic mucosal dissection has disseminated from Asia to Europe and North America. Studies suggest that it is feasible and effective in superficial adenocarcinoma of the gastroesophageal junction [41]. This technique allows for en bloc removal of larger tumors and avoids the problems in interpreting the lateral

margins of piecemeal endoscopic mucosal resection specimens. However, more data are needed and the issues that need to be addressed include training, optimal techniques, and improved equipment, as well as the duration of the procedure.

Patient selection

Which patient should get which 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 undergo thermal techniques and what parameters should be used to determine which patient should get which combination techniques? Is it time for aggressive ablation in patients with low grade or indefinite dysplasia? Most importantly, the issue of nondysplastic Barrett's esophagus needs to be confronted.

There are two schools of thought in this regard. The first holds that, given the low risk of progression to cancer in a nondysplastic patient with Barrett's esophagus, it is hard to justify an intervention unless it is safe, inexpensive, and easy to do. The other camp suggests that we should get rid of all Barrett's epithelium, providing the potential to decrease or eliminate surveillance in the future. However, there are no data at present to justify such an approach.

Acid suppression

Aggressive acid suppression is typically part of the treatment plan of endoscopic ablation. However, it is well recognized that normalization of esophageal acid exposure is difficult to achieve in Barrett's esophagus patients, even with high dose therapy [42]. Furthermore, studies have shown that Barrett's esophagus may be reversed with multipolar electrocoagulation therapy despite abnormal esophageal acid exposure [43,44]. There is little if any proof that acid suppression or antireflux surgery prevents the development of cancer or dysplasia in the absence of endoscopic ablation.

Nevertheless, the conditions still exist in patients with Barrett's esophagus for the metaplastic epithelium to redevelop, and we still do not know the best way to prevent this on a long-term basis. Should patients routinely receive double dose or single dose proton pump inhibitor therapy? Should pH or impedance-pH monitoring be used to guide therapy? Given the risks of surgery, it is hard to imagine that routine antireflux surgery in conjunction with ablation will ever become a management strategy.

Buried intestinal metaplasia

While early data for radiofrequency ablation are promising, it is difficult to envisage that any technique will reliably eliminate all subsquamous intestinal metaplasia. Biomarker abnormalities persist in this epithelium, but 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 with pretreatment Barrett's epithelium, raising the question of the neoplastic potential of the buried Barrett's epithelium [45].

Furthermore, better techniques for detecting buried columnar epithelium are needed. Confocal endomicroscopy is one such technique under study. Molecular marker development would also be helpful.

What is the appropriate depth of injury?

We know surprisingly little about the target depth of ablative techniques. As mentioned above, limited animal and human data are available from the full thickness of the esophagus. Biopsy work by Ackroyd et al. suggests that the thickness of Barrett's columnar epithelium is approximately 0.6 mm [46]. Recent work from Leedham et al. suggests that molecular abnormalities may arise in esophageal submucosal glands [47]. If abnormalities may in fact originate that deeply, the target depth of injury may need to be reconsidered.

The cardia

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 [48,49]. The reason for this is unknown. While squamous epithelium may develop below the gastroesophageal junction after ablation, it is unclear what is the natural history of that metaplastic mucosa [50]. Not only can problems develop at the cardia but it is difficult to apply techniques such as radiofrequency ablation to the cardia, even with the focal probe, due to positioning and the anatomic alterations in the setting of a large hiatal hernia.

What happens to the esophagus?

To date, limited human data are available regarding the results of applying ablative techniques to the esophagus. Motility appears to be unchanged. Despite the assumption that multipolar electrocoagulation resulted in only superficial injury to the esophagus, in a single patient who had been treated with multipolar electrocoagulation, subsequent esophagectomy for complications of antireflux surgery revealed complete elimination of intestinal metaplasia in the esophagectomy specimen but fibrosis, friability, and extensive adhesions to the pleura of the intrathoracic esophagus [51].

Predictors of response

What factors predict whether a patient will respond to a given therapy? Possible variables include segment length, hiatal hernia size, adequacy of acid suppression, and biomarker values. To date, one study has evaluated biomarkers as predictors of 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 [52]. While these factors are not ready for "prime time", future studies will need to carefully examine biomarkers or other patient factors that predict response.

What are potential solutions to these issues?



As we look to the future, there is a clear need for answers to the above questions. I agree with the view of the Amsterdam group that future studies should emphasize a "top down" approach to evaluate these interventions in patients with intraepithelial neoplasia or dysplasia. More data, especially from long-term studies, are clearly called for with regard to cryotherapy, radiofrequency ablation, endoscopic mucosal resection, endoscopic submucosal dissection, and combinations of these techniques. The promising pilot work from Amsterdam demonstrating complete

ablation needs confirmation in a larger number of patients at other centers. There is a clear need for multicenter randomized clinical trials that compare these different approaches. These studies should also allow us to refine predictors of response, be they clinical, endoscopic, or biomarker.

Furthermore, those involved in endoscopic ablation should develop some consensus on the components of pre-intervention staging and imaging along with post-intervention end points and surveillance. All parties need to acknowledge that given the high stakes involved in treating esophageal cancer, all bets are off with ablative technologies if endoscopists and patients do not adhere to rigorous and meticulous follow up protocols, the details of which need to be defined.

While the future of natural orifice transluminal endoscopic surgery (NOTES) as applied to gastrointestinal endoscopy remains hazy, clearly one can anticipate the emergence of better “tools of the trade”, especially for endoscopic mucosal resection and endoscopic submucosal dissection. We still need methods that reliably and predictably control the depth and homogeneity of injury to the esophagus. For any new technique that may be developed, the need will continue for well-crafted animal studies to determine depth of injury and dosimetry, like those performed for cryotherapy and radiofrequency ablation.

Barrett's esophagus does not develop in a vacuum. Other factors that contribute to cancer risk in Barrett's esophagus need to be studied in conjunction with ablation, including age, gender, obesity, tobacco use, hiatal hernia size, ongoing reflux, diet, and use of nonsteroidal anti-inflammatory drugs (NSAIDs), to name just a few.

To accomplish these goals is a challenge in the best of circumstances. Given the current global financial problems, provision of funding to achieve these goals will be problematic and will require imaginative approaches. Synergies of funding that involve partnerships between governments, industries, and foundations should be sought.

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References

- 1 Brandt LJ, Kauvar DR. Laser-induced transient regression of Barrett's epithelium. *Gastrointest Endosc* 1992; 38: 619–622
- 2 Berenson MM, Johnson TD, Markowitz NR et al. Restoration of squamous mucosa after ablation of Barrett's esophageal epithelium. *Gastroenterology* 1993; 104: 1686–1691
- 3 Garewal H, Ramsey L, Sharma P et al. Biomarker studies in reversed Barrett's esophagus. *Am J Gastroenterol* 1999; 94: 2829–2833
- 4 Ackroyd R, Brown NJ, Davis MF et al. Photodynamic therapy for dysplastic Barrett's oesophagus: a prospective, double blind, randomised, placebo controlled trial. *Gut* 2000; 47: 612–617
- 5 Bergman JJ, Fockens P. Ablating Barrett's metaplastic epithelium: are the techniques ready for clinical use? *Gut* 2006; 55: 1222–1223
- 6 Schoenfeld P, Scheiman J. An evidence-based approach to studies of gastrointestinal therapies. *Clin Gastroenterol Hepatol* 2003; 1: 57–63
- 7 Spechler SJ. Thermal ablation of Barrett's esophagus: a heated debate. *Am J Gastroenterol* 2006; 101: 1770–1772
- 8 Van Laethem JL, Peny MO et al. Intramucosal adenocarcinoma arising under squamous re-epithelialisation of Barrett's oesophagus. *Gut* 2000; 46: 574–577
- 9 Shand A, Dallal H, Palmer K et al. Adenocarcinoma arising in columnar lined oesophagus following treatment with argon plasma coagulation. *Gut* 2001; 48: 580–581
- 10 Mino-Kenudson M, Ban S, Ohana M et al. Buried dysplasia and early adenocarcinoma arising in Barrett esophagus after porfimer-photodynamic therapy. *Am J Surg Pathol* 2007; 31: 403–409
- 11 Krishnadath KK, Wang KK, Taniguchi K et al. Persistent genetic abnormalities in Barrett's esophagus after photodynamic therapy. *Gastroenterology* 2000; 119: 624–630
- 12 Hage M, Siersema PD, Vissers KJ et al. Molecular evaluation of ablative therapy of Barrett's oesophagus. *J Pathol* 2005; 205: 57–64
- 13 Hage M, Siersema PD, Vissers KJ et al. Genomic analysis of Barrett's esophagus after ablative therapy: persistence of genetic alterations at tumor suppressor loci. *Int J Cancer* 2006; 118: 155–160
- 14 Dvorak K, Ramsey L, Payne CM et al. Abnormal expression of biomarkers in incompletely ablated Barrett's esophagus. *Ann Surg* 2006; 244: 1031–1036
- 15 Pech O, Nagy CD, Gossner L et al. Photodynamic therapy of human Barrett's cancer using 5-aminolaevulinic acid-induced protoporphyrin IX: an in-vivo dosimetry study in athymic nude mice. *Eur J Gastroenterol Hepatol* 2002; 14: 657–662
- 16 Johnston CM, Schoenfeld LP, Mysore JV et al. Endoscopic spray cryotherapy: a new technique for mucosal ablation in the esophagus. *Gastrointest Endosc* 1999; 50: 86–92
- 17 Pasricha PJ, Hill S, Wadwa KS et al. Endoscopic cryotherapy: experimental results and first clinical use. *Gastrointest Endosc* 1999; 49: 627–631
- 18 Johnston MH. Cryotherapy and other newer techniques. *Gastrointest Endosc Clin N Am* 2003; 13: 491–504
- 19 Prasad GA, Wang KK, Buttar NS et al. Long term survival following endoscopic and surgical treatment of high-grade dysplasia in Barrett's esophagus. *Gastroenterology* 2007; 132: 1226–1233
- 20 Das A, Singh V, Fleischer DE et al. A comparison of endoscopic treatment and surgery in early esophageal cancer: an analysis of surveillance epidemiology and end results data. *Am J Gastroenterol* 2008; 103: 1340–1345
- 21 Kelty CJ, Ackroyd R, Brown NJ et al. Endoscopic ablation of Barrett's oesophagus: a randomized-controlled trial of photodynamic therapy vs. argon plasma coagulation. *Aliment Pharmacol Ther* 2004; 20: 1289–1296
- 22 Dulai GS, Jensen DM, Cortina G et al. Randomized trial of argon plasma coagulation vs. multipolar electrocoagulation for ablation of Barrett's esophagus. *Gastrointest Endosc* 2005; 61: 232–240
- 23 Sharma P, Wani S, Weston AP et al. A randomised controlled trial of ablation of Barrett's oesophagus with multipolar electrocoagulation versus argon plasma coagulation in combination with acid suppression: long term results. *Gut* 2006; 55: 1233–1239
- 24 Overholt BF, Lightdale CJ, Wang KK et al. Photodynamic therapy with porfimer sodium for ablation of high-grade dysplasia in Barrett's esophagus: international, partially blinded, randomized phase III trial. *Gastrointest Endosc* 2005; 62: 488–498
- 25 Shaheen NJ, Sharma P, Overholt BF et al. A randomized, multicenter, sham-controlled trial of radiofrequency ablation for subjects with Barrett's esophagus containing dysplasia: interim results of the AIM dysplasia trial. *Gastroenterology* 2008; 134: A37
- 26 Overholt BF, Wang KK, Burdick JS et al. Five-year efficacy and safety of photodynamic therapy with Photofrin in Barrett's high-grade dysplasia. *Gastrointest Endosc* 2007; 66: 460–468
- 27 Ganz RA, Utley DS, Stern RA et al. Complete ablation of esophageal epithelium with a balloon-based bipolar electrode: a phased evaluation in the porcine and in the human esophagus. *Gastrointest Endosc* 2004; 60: 1002–1010
- 28 Dunkin BJ, Martinez J, Bejarano PA et al. Thin-layer ablation of human esophageal epithelium using a bipolar radiofrequency balloon device. *Surg Endosc* 2006; 20: 125–130
- 29 Sharma VK, Wang KK, Overholt BF et al. Balloon-based, circumferential, endoscopic radiofrequency ablation of Barrett's esophagus: 1-year follow-up of 100 patients. *Gastrointest Endosc* 2007; 65: 185–195
- 30 Fleischer DE, Overholt BF, Sharma VK et al. Endoscopic ablation of Barrett's esophagus: a multicenter study with 2.5-year follow-up. *Gastrointest Endosc* 2008; Jun 16 [Epub ahead of print]
- 31 Ell C, May A, Pech O et al. Curative endoscopic resection of early esophageal adenocarcinomas (Barrett's cancer). *Gastrointest Endosc* 2007; 65: 3–10
- 32 Wang KK, Sampliner RE. Practice Parameters Committee of the American College of Gastroenterology. Updated guidelines 2008 for the diagnosis, surveillance and therapy of Barrett's esophagus. *Am J Gastroenterol* 2008; 103: 788–797

- 33 Gondrie JJ, Pouw RE, Sondermeijer CM *et al*. Effective treatment of early Barrett's neoplasia with stepwise circumferential and focal ablation using the HALO system. *Endoscopy* 2008; 40: 370–379
- 34 Gondrie JJ, Pouw RE, Sondermeijer CM *et al*. Stepwise circumferential and focal ablation of Barrett's esophagus with high-grade dysplasia: results of the first prospective series of 11 patients. *Endoscopy* 2008; 40: 359–369
- 35 Johnston MH, Eastone JA, Horwhat JD *et al*. Cryoablation of Barrett's esophagus: a pilot study. *Gastrointest Endosc* 2005; 62: 842–848
- 36 Dumot JA, Vargo JJ, Zuccaro G *et al*. Results of cryospray ablation for esophageal high grade dysplasia (HGD) and intramucosal cancer (IMCA) in high risk non-surgical patients. *Gastrointest Endosc* 2008; 67: AB176
- 37 Seewald S, Akaraviputh T, Seitz U *et al*. Circumferential EMR and complete removal of Barrett's epithelium: a new approach to management of Barrett's esophagus containing high-grade intraepithelial neoplasia and intramucosal carcinoma. *Gastrointest Endosc* 2003; 57: 854–859
- 38 Giovannini M, Bories E, Pesenti C *et al*. Circumferential endoscopic mucosal resection in Barrett's esophagus with high-grade intraepithelial neoplasia or mucosal cancer. Preliminary results in 21 patients. *Endoscopy* 2004; 36: 782–787
- 39 Peters FP, Kara MA, Rosmolen WD *et al*. Stepwise radical endoscopic resection is effective for complete removal of Barrett's esophagus with early neoplasia: a prospective study. *Am J Gastroenterol* 2006; 101: 1449–1457
- 40 Larghi A, Lightdale CJ, Ross AS *et al*. Long term follow-up of complete Barrett's eradication endoscopic mucosal resection (CBE-EMR) for the treatment of high grade dysplasia and intramucosal carcinoma. *Endoscopy* 2007; 39: 1086–1091
- 41 Yoshinaga S, Gotoda T, Kusano C *et al*. Clinical impact of endoscopic submucosal dissection for superficial adenocarcinoma located at the esophagogastric junction. *Gastrointest Endosc* 2008; 67: 202–209
- 42 Spechler SJ, Sharma P, Traxler B *et al*. Gastric and esophageal pH in patients with Barrett's esophagus treated with three esomeprazole doses: a randomized, double-blind, crossover trial. *Am J Gastroenterol* 2006; 101: 1964–1971
- 43 Sampliner RE, Camargo L, Fass R. Impact of esophageal acid exposure on the endoscopic reversal of Barrett's esophagus. *Am J Gastroenterol* 2002; 97: 270–272
- 44 Kovacs BJ, Chen YK, Lewis TD *et al*. Successful reversal of Barrett's esophagus with multipolar electrocoagulation despite inadequate acid suppression. *Gastrointest Endosc* 1999; 49: 547–553
- 45 Hornick JL, Mino-Kenudson M, Lauwers GY *et al*. Buried Barrett's epithelium following photodynamic therapy shows reduced crypt proliferation and absence of DNA content abnormalities. *Am J Gastroenterol* 2008; 103: 38–47
- 46 Ackroyd R, Brown NJ, Stephenson TJ *et al*. Ablation treatment for Barrett oesophagus: what depth of tissue destruction is needed? *J Clin Pathol* 1999; 52: 509–512
- 47 Leedham SJ, Preston SL, McDonald SA *et al*. Individual crypt genetic heterogeneity and the origin of metaplastic glandular epithelium in human Barrett's oesophagus. *Gut* 2008; 57: 1041–1048
- 48 Weston AP, Sharma P, Banerjee S *et al*. Visible endoscopic and histologic changes in the cardia, before and after complete Barrett's esophagus ablation. *Gastrointest Endosc* 2005; 61: 515–521
- 49 Sampliner RE, Camargo E, Prasad AR. Association of ablation of Barrett's esophagus with high grade dysplasia and adenocarcinoma of the gastric cardia. *Dis Esophagus* 2006; 19: 277–279
- 50 Fass R, Garewal HS, Hayden CW *et al*. Preferential repair by squamous epithelium of thermal induced injury to the proximal stomach in patients undergoing ablation of Barrett's esophagus. *Gastrointest Endosc* 2001; 53: 711–716
- 51 Fennerty MB, Corless CL, Sheppard B *et al*. Pathological documentation of complete elimination of Barrett's metaplasia following endoscopic multipolar electrocoagulation therapy. *Gut* 2001; 49: 142–144
- 52 Prasad GA, Wang KK, Halling KC *et al*. Utility of biomarkers in prediction of response to ablative therapy in Barrett's esophagus. *Gastroenterology* 2008; 135: 370–379