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Current Strategies in the Management of Barrett's Esophagus

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Abstract

Barrett's esophagus has become a very important topic in gastroenterology. Its management may vary from essentially a surveillance strategy to highly invasive esophagectomy. The variation in management strategies has occurred because of the current perceptions regarding cancer risks, which range from almost negligible to an incidence of 30% in high-grade dysplasia. Although it is clear that most patients with Barrett's esophagus without dysplasia will not require therapy, the prospect of continued surveillance is unpleasant at best. Promising future tools and techniques for surveillance and treatment are described in this review.

Introduction

Many new tools and techniques are in development for management of Barrett's esophagus. Promising tools for predicting cancer development include biomarkers, such as fluorescence in situ hybridization, and measurements of cellular DNA content (flow or image cytometry). Novel ablative techniques are being studied to help decrease the risk of cancer development in patients with Barrett's esophagus. The first endoscopic therapy approved, photo-dynamic therapy, has been shown to decrease cancer risk, with a 50% risk reduction in cancer. Multiple smaller series have been conducted that verify this benefit. Newer techniques, such as endoscopic mucosal resection and endoscopic submucosal dissection, are also being used in Barrett's esophagus and may lead to further developments in elimination of Barrett's with high-grade dysplasia and superficial cancer. These promising treatments highlight the rapid development in new management strategies for Barrett's esophagus.

Cancer Risk

The primary diagnostic priority in evaluation of patients with Barrett's esophagus is to determine the degree of cancer risk. The current strategy is to use endoscopic biopsies to identify the degree of dysplasia present in the mucosa. Endoscopic surveillance should be performed by obtaining biopsies acquired in four quadrants in every 2 cm of Barrett's mucosa if nondysplastic or low-grade dysplasia is found, but in every centimeter if high-grade dysplasia is observed. It has not been established clearly that jumbo forceps are better than standard forceps except possibly in high-grade dysplasia. The current accepted lifetime risk of cancer in Barrett's mucosa without dysplasia is between 2% and 5%, in low-grade dysplasia it is 8% to 10%, and in high-grade dysplasia it is 28% to 30%, which may be high due to a publication bias [1]. These numbers are based on studies with 1 to 8 years of follow-up. However, improvement in strategy is needed in a number of areas. The first area is the large number of biopsies required to monitor Barrett's esophagus. Endoscopists clearly are not able to obtain as much tissue as might be desirable. Second, when tissue is obtained, even expert pathologists vary a great deal in their interpretation of whether high-grade dysplasia or cancer is present [2]. Finally, knowledge is lacking regarding the natural history of Barrett's esophagus.

Although large prospective cohorts have been observed with serial biopsies, a study similar to the National Polyp Trial has not been conducted in Barrett's esophagus. Patients have never been simply observed with long intervals of time without biopsy. The extensive biopsies used to perform surveillance may change the course of the disease as intense biopsy strategies can actually eliminate the Barrett's mucosa and dysplasia in a substantial proportion of patients. In a prospective randomized trial for photodynamic therapy in Barrett's esophagus, fully 39% of the patients in the control arm had loss of high-grade dysplasia during follow-up over 2 years. These areas need to be addressed in future studies.

Due to these difficulties in determining cancer risk using dysplasia, clinicians have sought newer techniques to provide this critical information. Newer techniques involving biomarkers are being developed, including cell cytometric assays for assessment of aneuploidy and fluorescence in situ hybridization for loss of heterozygosity [3]. Aneuploidy is usually assessed by the measurement of total DNA content in the tissue. A dye is used to stain the DNA, such as a Feulgen stain, that binds stoichiometrically to DNA on a one-to-one basis. Therefore, the amount of dye bound to the DNA can directly quantify the amount of DNA present. These methods can also be applied using fluorescent agents, such as propidium iodine, which is usually employed with flow cytometry to assess cell ploidy status. Fluorescence in situ hybridization, however, employs small DNA probes that can be used in permeabilized cell nuclei. These probes are then hybridized to the nuclei of cells "in situ" or in tissue or cell preparations. Then the markers are assessed for binding. Loss of marker binding generally indicates a deletion of that area. However, other genetic mechanisms that can be determined include duplication of the marker gene. Gene amplification is a common technique for cells to obtain growth advantages. Finally, loss of genetic material, as detected either by fluorescence in situ hybridization or ploidy studies, can be a sign of genomic instability and problems with the mitotic process.

These potential biomarkers might be better able to identify patients at high risk of developing carcinoma. In particular, patients with aneuploid or abnormal amounts of DNA indicating abnormal mitotic processes seem to be at a higher risk of cancer development [4]. In addition, loss of function of highly important cell-cycle regulatory genes such as *p16* and *p53* has also been shown to be predictive of cancer [5]. One hopes that these biomarkers might be combined and made more clinically available in the future so that assessment of cancers can be improved. Although flow cytometry can be done on paraffin fixed tissues, no prospective trial has demonstrated the validity of this strategy in comparison with fresh tissues, which have been used in current prospective trials.

Drug Therapy

No prospective clinical trial has supported the use of any drug treatments to modify cancer risk in Barrett's esophagus. The most obvious choice would be proton pump inhibitors, but studies that have investigated standard and high-dose proton pump inhibitors have not shown them to decrease cancer risk, although proton pump inhibitors have been demonstrated to increase the formation of squamous islands [6]. Only one study has shown that lack of proton pump inhibitor use was a significant factor in the development of cancer in patients with high-grade dysplasia [7]. Also, surgical control of reflux disease has not been found to be associated with a decrease in the incidence of esophageal cancer in large population-based epidemiology studies [8•]. Although there is some speculation about the effects of cyclooxygenase (COX)-2 inhibitors on cancer development that is supported by epidemiologic and animal studies, no human trials have been conducted at this point [9,10,11•]. An esophageojejunostomy model in rats showed a significant decrease in cancer development in rats treated with COX-2 inhibitors [12•]. However, numerically, nonselective COX agents are even superior to COX-2 inhibitors in

decreasing cancer development. This is significant because of the recent cardiotoxicities described with COX-2 inhibitors.

Goals of Endoscopic Therapy

It is important to define the ultimate goals of the treatment. The gastroenterologist must consider multiple factors before embarking on any therapeutic program. These include patient-related factors, such as age, health, comorbidities, and support systems. If endoscopic therapy is proposed for a young patient, the therapy must be capable of eliminating nearly all risk of esophageal adeno-carcinoma. This would mean that all the Barrett's mucosa should probably be ablated in order to obtain a reasonable result. In addition, long-term control of reflux disease would be needed to prevent recurrence of Barrett's esophagus. However, for patients who are elderly, being able to reduce neoplastic risk by a percentage or simply treating the primary tumor may be sufficient. Thus, eliminating an intramucosal cancer may be all that is done because evolution of other areas of high-grade dysplasia in patients with limited life expectancies may not occur before concomitant comorbidities become more severe.

These goals dictate the type of therapy that is required. If elimination of neoplastic risk is required, a combination of endoscopic therapies will probably be necessary, such as mucosal resection and photodynamic therapy, and the patient must be aware that continued endoscopic surveillance will still be needed [13]. Surgical resection should also be discussed with the patient to be certain that alternative therapies have been explained. However, if complete elimination of neoplastic risk is not the goal, as in patients with multiple comorbidities or those with limited life expectancies, reduction of neoplastic risk could be accomplished with a single treatment or with ablative techniques used only when the patient is scheduled for surveillance. An example of this strategy might be surveillance with the use of mucosal resection of any visible lesion. Although early cancers may be found, they can be resected endoscopically without further therapies to modify the risk of future recurrences. This approach is associated with minimal morbidities and mortality rates because the patients tolerate it quite well with only 1 to 2 days of chest pain.

Endoscopically Treatable Lesions

The ideal lesions to be treated with endoscopic therapy are those that are more limited in size, macroscopically identifiable, and confined to the mucosa. Given these criteria, areas of high-grade dysplasia or superficial cancers are potentially treatable. The key to endoscopic therapy is to treat lesions that can be identified either through their appearance, such as elevated or polypoid lesions, or through prior biopsies that have established that an area of Barrett's mucosa contains a high-grade lesion. Despite advances in imaging and chromoendoscopy, the sensitivity and specificity of simple techniques, such as methylene blue and advanced techniques, such as autofluorescence, could not identify areas of dysplasia as well as random biopsies in one recent study [14]. Methylene blue had a sensitivity of only 21% for dysplasia or cancer, whereas the sensitivity for autofluorescence was 37%.

Small segments of Barrett's esophagus can be treated with mucosal resection or with photodynamic therapy with reasonable success. Entire segments of Barrett's mucosa have been removed with mucosal resection techniques, as recently demonstrated [15,16]. Mucosal resection was applied to Barrett's esophagus with a median length of 5 cm and required a median of 2.5 sessions during which five resections were completed in each session [16]. Bleeding occurred in four of the sessions, and two strictures were reported in this series of 12 patients. Though feasible, the ability of extending these procedures to the general population would seem unlikely. Photo-dynamic therapy can rarely "reverse" more than 5 cm of Barrett's mucosa in a single treatment, though it has been shown in randomized prospective studies to decrease cancer risk. Its ability to completely eliminate Barrett's mucosa is more limited.

Lesions that are ulcerated or depressed or contain high-grade cancers are also probably less likely to respond to endoscopic therapy. In a series of patients treated with endoscopic mucosal resection, those lesions that were ulcerated or depressed had a remission rate of 59%, versus 97% in patients who had elevated or polypoid lesions [17].

Endoscopic Mucosal Resection

Endoscopic mucosal resection was pioneered by Japanese endosurgeons over a decade ago [18-20]. In the United States, this technique has been limited by a lack of need because squamous cell cancers that are routinely detected in early stages are rarely found. However, with the advent of surveillance endoscopy for Barrett's esophagus, endoscopic mucosal resection has increased in use [21,22]. Previously, the technique had been performed with variceal ligation devices. The targeted mucosa was first "lifted" with an injection of saline and epinephrine (1:100,000 to 1:500,000 dilution). If no evidence was shown of metastasis or deep invasion on endoscopic ultrasound, the lesion would be amenable to resection. The variceal ligator was placed on the lesion, and the pseudopolyp formed could be removed with a snare.

Now there is a commercially available kit (Olympus EMR-001 kit; Melville, NY) that includes a spray catheter, a crescent snare, and a clear cap for the endoscope that can perform the same function. These caps range from being blunt tipped to having an oblique end that may be flexible or made of hard plastic. Generally, the caps that can resect the most tissue are flexible and have an oblique orientation. However, those caps with the firmer plastic end are easier to control and have a greater ability to determine the amount of tissue resected. After the lesion has been lifted using an injection needle, a crescent snare can be placed around the cap, and the lesion can be excised without difficulty after application of suction to the cap. The lesion is sucked into the cap and the snare closed.

Complication rates have been low. In a series of 101 patients treated with endoscopic mucosal resection, bleeding was the only complication found in 22% of patients [23]. These findings were similar to those from a series in Japan in which a variety of endoscopic techniques were used only in the esophagus in 113 patients, and a complication rate of 21% was noted, including perforation [24]. In our own experience, our complication rate in 240 mucosal resections has been 6%, primarily bleeding or stenosis. This procedure definitely requires some experience and training, although with familiarity, it can be applied safely.

Thermal Ablative Methods

Thermal therapies have long been applied to nondysplastic Barrett's mucosa. Results from argon plasma coagulation (APC) in high-grade dysplasia and early cancer have been encouraging in small series. One study of 10 patients found that APC could eliminate high-grade lesions in eight of 10 patients [25]. In another report, two thirds of patients with early cancers of less than 4 mm in size responded to APC [26]. Clearly, this modality might be useful in very small early lesions and would certainly be more tolerable for patients. Nd:YAG laser therapy has also been described as a potential thermal therapy for high-grade dysplasia and early cancer. One series of 14 patients had all patients cleared of high-grade dysplasia or cancer, and 79% had complete elimination of Barrett's esophagus [27]. A prospective randomized trial compared APC with multipolar coagulation for elimination of Barrett's mucosa. In this 52-patient series, there were no differences in efficacy in elimination of Barrett's esophagus regardless of the technique. In fact, multipolar coagulation actually enjoyed a numerical, although not significant, advantage over APC.

One problem with using thermal modalities is the lack of ability to determine the precise depth of penetration of the lesion and whether the correct lesion was treated. It is hoped that the lesion is destroyed, but there is no histologic confirmation with thermal ablative therapies.

Unfortunately, an increase in metastasis has been reported once cancers invade past the muscularis mucosae [28,29•]. Thermal therapies would not be able to stage these lesions histologically. Nonetheless, in appropriate patients, reports suggest that thermal therapies are beneficial in eliminating early cancers or areas of high-grade dysplasia.

Elimination of All Barrett's Mucosa

Recent studies suggest that therapy targeted only toward neoplastic lesions will have high rates of recurrent high-grade dysplasia or cancer. In one series, 115 patients (of whom 96 (83%) had intraepithelial cancer) were treated with mucosal resection, photodynamic therapy, or APC [30]. The patients were followed for an average of 10 months, during which time 30% developed meta-chronous lesions. This study suggests that metachronous lesions occur commonly in residual Barrett's esophagus after treatment of their primary lesion.

Previous studies have shown that residual Barrett's mucosa within squamous epithelium appears to be unstable epithelium with persistence of increased proliferation, as evidenced by Ki-67 marker positivity, increased COX-2 expression, and increased ornithine decarboxylase activity. In addition, patients with downstaging of dysplasia have shown persistence of biomarker positivity, including p16 promoter hypermethylation and p53 mutation [31].

Complete and immediate elimination of Barrett's mucosa appears to be a reasonable goal if long-term reduction in cancer risk is needed. Barrett's cancer appears to occur through clonal evolution, during which time some clones may evolve to cancer but others remain stable in the Barrett's mucosa [32]. Elimination of all the premalignant clonals would be necessary to disrupt progression to cancer on a long-term basis.

Photodynamic Therapy for Barrett's Ablation

Photodynamic therapy involves the use of three separate components: a photosensitizing drug, which is sodium porfimer; light that can activate the photosensitizer; and oxygen [33]. The drug is administered intravenously at a dosage of 2 mg/kg/d before photoradiation. The light is administered using a cylindrical diffusing fiber through an endoscope or by a photoradiating balloon. The balloon was used in a recent multicenter trial to help distend mucosal folds and allow the treatment for upwards of 7 cm of esophagus with a single application. This is now available from commercial vendors as a kit that comes in three different sizes (3, 5, and 7 cm) that retails with the treating fibers at \$1450.00 (Wilson-Cook, Xcell PDT Balloon; Winston-Salem, NC).

Photodynamic therapy was used to treat Barrett's esophagus with high-grade dysplasia in a prospective multicenter randomized prospective trial with 208 patients with standardized central pathology. In this study, patients were randomly assigned two to one to photodynamic therapy with omeprazole or to omeprazole alone. The study participants were followed for at least 2 years. High-grade dysplasia was reduced from 77% in the control group to 39% in the treatment group. This is a very interesting finding, because 39% of the patients in the control group actually did not have high-grade dysplasia during the 2-year follow-up. Cancer risk was reduced from 28% in the control group to 13% in the treated group. Although this was a 50% reduction in cancer, clearly there still is a significant cancer risk in patients treated with photodynamic therapy alone.

In Europe and in the United States a new photosensitizing agent, aminolevulinic acid (ALA), is being tested [34]. This oral agent can be administered the day of endoscopy and leads to a much shorter period of cutaneous photosensitivity. With the sodium porfimer mentioned previously, patients must take light sensitivity precautions for 30 to 90 days after injection of the drug. With ALA, the period of photosensitivity decreases markedly to less than a week.

However, the ALA-based therapy has a very limited depth of penetration, which may make it inappropriate for treatment of such conditions as high-grade dysplasia.

Endoscopic management of Barrett's esophagus must be individualized for affected patients. Use of ablative therapy for nondysplastic Barrett's esophagus is still controversial, but such treatment may be beneficial, given the need for surveillance endoscopy. Therapy for high-grade dysplasia and even early cancer has been shown to be beneficial in prospective trials and may be considered in selected patients.

Surgical Therapy

Esophagectomy has been recommended as the standard therapy for Barrett's with high-grade dysplasia or superficial cancer. This strategy is obviously very efficacious in this application because it can completely eliminate the mucosa at risk, which is one of the principles in treatment of Barrett's esophagus. However, it is associated with a high degree of morbidity and mortality [35]. Recent studies have shown that hospitals in which fewer than 28 esophagectomies are performed in a year have mortality rates that exceed 18% [36•]. The great majority of esophagectomies performed in the United States are actually done in low-volume hospitals. Surgical experience with this procedure has also been correlated with mortality rates [37].

In addition, morbidity from these procedures is fairly crippling. Anastomotic leaks, infectious complications, and strictures are frequently seen. Advances in surgical techniques have included minimally invasive surgeries in which the partial gastrectomy portion of the procedure is performed laparoscopically and the thoracic esophageal anastomosis is performed through a neck incision [38]. However, length of hospital stay and overall complications have not been much reduced with these procedures. Vagal-sparing esophagectomy has also been proposed, and some evidence suggests that vagal function can be retained after this type of procedure, although one loses the benefit of esophagectomy, which is elimination of local lymph nodes in case any cancer is found after resection. This technique depends upon adequate preoperative staging, which has always been difficult with high-grade dysplasia.

Conclusions

A wide range of therapeutic options exists for patients with Barrett's esophagus. In patients without dysplasia, who are in the vast majority, it is unlikely that, in the absence of any biomarkers, there is a significant risk of progression of cancer. If it can be assured that no evidence of dysplasia is present, surveillance in this group could probably be deferred for a long period of time (3–5 years). In patients with low-grade dysplasia, evidence suggests a substantial risk of cancer, requiring some degree of surveillance on a yearly basis. Ablation therapy could be considered in these patients, although the risk—benefit ratio has not been established for this subgroup of Barrett's patients. Should therapies be developed that would be highly efficacious in eliminating all Barrett's esophagus, these patients might benefit from this therapy, as opposed to lifetime surveillance. Finally, patients with high-grade dysplasia probably require some form of intervention. In patients who have comorbidities and limited life expectancies, expectant management with continued surveillance and elimination of mucosal abnormalities as they appear may be quite reasonable. In patients with extended longevity, surgical options, including esophagectomy, should definitely be considered. Finally, ablative strategies using photodynamic therapy in combination with endoscopic mucosal resection might be beneficial for those that decline surgical therapy or continued surveillance.

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References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

• Of importance

•• Of major importance

1. Shaheen NJ, Crosby MA, Bozyski EM, Sandler RS. Is there publication bias in the reporting of cancer risk in Barrett's esophagus? *Gastroenterology* 2000;119:333–338. [PubMed: 10930368]
2. Montgomery E, Bronner MP, Goldblum JR, et al. Reproducibility of the diagnosis of dysplasia in Barrett esophagus: a reaffirmation. *Human Pathol* 2001;32:368–378. [PubMed: 11331953]
3. Krishnadath KK, Reid BJ, Wang KK. Biomarkers in Barrett esophagus. *Mayo Clin Proc* 2001;76:438–446. [PubMed: 11322362]
4. Rabinovitch PS, Longton G, Blount PL, et al. Predictors of progression in Barrett's esophagus III: baseline flow cyto-metric variables. *Am J Gastroenterol* 2001;96:3071–3083. [PubMed: 11721752]
5. Reid BJ, Prevo LJ, Galipeau PC, et al. Predictors of progression in Barrett's esophagus II: baseline 17p (p53) loss of heterozygosity identifies a patient subset at increased risk for neo-plastic progression. *Am J Gastroenterol* 2001;96:2839–2848. [PubMed: 11693316]
6. Sampliner RE. Effect of up to 3 years of high-dose lansoprazole on Barrett's esophagus [see comments]. *Am J Gastroenterol* 1994;89:1844–1848. [PubMed: 7942680]
7. Buttar NS, Wang KK, Sebo TJ, et al. Extent of high-grade dysplasia in Barrett's esophagus correlates with risk of adenocarcinoma. *Gastroenterology* 2001;120:1630–1639. [PubMed: 11375945]
8. Ye W, Chow WH, Lagergren J, et al. Risk of adenocarcinomas of the esophagus and gastric cardia in patients with gastroesophageal reflux diseases and after antireflux surgery. *Gastroenterology* 2001;121:1286–1293. [PubMed: 11729107] This important paper examines the effect of antireflux surgery on the development of adenocarcinoma, esophagus, and gastric cardia in the Swedish population. Basically, the authors found that there is no risk reduction of adenocarcinomas with antireflux surgery.
9. Buttar NS, Wang KK, Anderson MA, et al. The effect of selective cyclooxygenase-2 inhibition in Barrett's esophagus epithelium: an in vitro study. *J Natl Cancer Inst* 2002;94:422–429. [PubMed: 11904314]
10. Buttar NS, Wang KK, Leontovich O, et al. Chemoprevention of esophageal adenocarcinoma by COX-2 inhibitors in an animal model of Barrett's esophagus. *Gastroenterology* 2002;122:1101–1112. [PubMed: 11910360]
11. Corley DA, Kerlikowske K, Verma R, Buffler P. Protective association of aspirin/NSAIDs and esophageal cancer: a systematic review and meta-analysis. *Gastroenterology* 2003;124:47–56. [PubMed: 12512029] This important study is a review of the literature about nonsteroidal anti-inflammatory drugs (NSAIDs) and aspirin as protective for esophageal carcinoma. It demonstrates that in multiple epidemiologic studies, NSAIDs and aspirin have a protective effect for both squamous and esophageal adenocarcinoma. Aspirin seems to have a greater effect of risk reduction in adenocarcinoma than NSAIDs.
12. Pacifico RJ, Wang KK, Wongkeesong LM, et al. Combined endoscopic mucosal resection and photodynamic therapy versus esophagectomy for management of early adenocarcinoma in Barrett's esophagus. *Clin Gastroenterol Hepatol* 2003;1:252–257. [PubMed: 15017665] This retrospective review assessed the use of endoscopic mucosal resection in combination with photodynamic therapy and compared these modalities with results in a cohort of patients who underwent esophagectomy during a similar time period for early adenocarcinoma. There was no statistical difference in outcomes except for increased complications in those patients who underwent surgery. This suggests that endoscopic therapy might be useful in patients with early esophageal carcinoma.

13. Egger K, Werner M, Meining A, et al. Biopsy surveillance is still necessary in patients with Barrett's oesophagus despite new endoscopic imaging techniques. *Gut* 2003;52:18–23. [PubMed: 12477753]
14. Satodate H, Inoue H, Yoshida T, et al. Circumferential EMR of carcinoma arising in Barrett's esophagus: case report. *Gastrointest Endosc* 2003;58:288–292. [PubMed: 12872107]
15. 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. [PubMed: 12776032]
16. Ell C, May A, Gossner L, et al. Endoscopic mucosal resection of early cancer and high-grade dysplasia in Barrett's esophagus. *Gastroenterology* 2000;118:670–677. [PubMed: 10734018]
17. Inoue H, Endo M. Endoscopic esophageal mucosal resection using a transparent tube. *Surg Endosc* 1990;4:198–201. [PubMed: 2291159]
18. Inoue M, Shiozaki H, Tamura S, Monden M. Endoscopic mucosal resection for early esophageal cancer. Review 15 refs Japanese. *Nippon Rinsho Jpn J Clin Med* 1996;54:1286–1291.
19. Inoue H, Kawano T, Tani M, et al. Endoscopic mucosal resection using a cap: techniques for use and preventing perforation. *Can J Gastroenterol* 1999;13:477–480. [PubMed: 10464347]
20. Pacifico RJ, Wang KK. Role of mucosal ablative therapy in the treatment of the columnar-lined esophagus. *Chest Surg Clin North Am* 2002;12:185–203.
21. Nijhawan PK, Wang KK. Endoscopic mucosal resection for lesions with endoscopic features suggestive of malignancy and high-grade dysplasia within Barrett's esophagus. *Gastrointest Endosc* 2000;52:328–332. [PubMed: 10968845]
22. Ahmad NA, Kochman ML, Long WB, et al. Efficacy, safety, and clinical outcomes of endoscopic mucosal resection: a study of 101 cases. *Gastrointest Endosc* 2002;55:390–396. [PubMed: 11868015]
23. Noguchi H, Naomoto Y, Kondo H, et al. Evaluation of endoscopic mucosal resection for superficial esophageal carcinoma. *Surg Laparosc Endosc Percutan Tech* 2000;10:343–350. [PubMed: 11147906]
24. Van Laethem JL, Jagodzinski R, Peny MO, et al. Argon plasma coagulation in the treatment of Barrett's high-grade dysplasia and in situ adenocarcinoma. *Endoscopy* 2001;33:257–261. [PubMed: 11293760]
25. May A, Gossner L, Gunter E, et al. Local treatment of early cancer in short Barrett's esophagus by means of argon plasma coagulation: initial experience. *Endoscopy* 1999;31:497–500. [PubMed: 10494693]
26. Weston AP, Sharma P. Neodymium:yttrium-aluminum garnet contact laser ablation of Barrett's high grade dysplasia and early adenocarcinoma. *Am J Gastroenterol* 2002;97:2998–3006. [PubMed: 12492182]
27. Endo M, Kawano T. Detection and classification of early squamous cell esophageal cancer. *Dis Esophagus* 1997;10:155–158. [PubMed: 9280071]
28. Ruol A, Merigliano S, Baldan N, et al. Prevalence, management and outcome of early adenocarcinoma (pT1) of the esophago-gastric junction. Comparison between early cancer in Barrett's esophagus (type I) and early cancer of the cardia (type II). *Dis Esophagus* 1997;10:190–195. [PubMed: 9280078]
29. May A, Gossner L, Pech O, et al. Local endoscopic therapy for intraepithelial high-grade neoplasia and early adeno-carcinoma in Barrett's oesophagus: acute-phase and intermediate results of a new treatment approach. *Eur J Gastroenterol Hepatol* 2002;14:1085–1091. [PubMed: 12362099] This large review of patients who underwent endoscopic therapy primarily for early adenocarcinomas demonstrates that those patients who only received local treatment for a neoplastic lesion had a high rate of recurrence during follow-up observation.
30. Krishnadath KK, Wang KK, Taniguchi K, et al. Persistent genetic abnormalities in Barrett's esophagus after photo-dynamic therapy. *Gastroenterology* 2000;119:624–630. [PubMed: 10982754]
31. Wong DJ, Paulson TG, Prevo LJ, et al. p16(INK4a) lesions are common, early abnormalities that undergo clonal expansion in Barrett's metaplastic epithelium. *Cancer Res* 2001;61:8284–8289. [PubMed: 11719461]
32. Wang KK, Kim JY. Photodynamic therapy in Barrett's esophagus. *Gastrointest Endosc Clin N Am* 2003;13:483–489. [PubMed: 14629104]

33. Barr H. Barrett's esophagus: treatment with 5-aminolevulinic acid photodynamic therapy. *Gastrointest Endosc Clin N Am* 2000;10:421–437. [PubMed: 10899256]
34. Rice TW, Falk GW, Achkar E, Petras RE. Surgical management of high-grade dysplasia in Barrett's esophagus [see comments]. *Am J Gastroenterol* 1993;88:1832–1836. [PubMed: 8237928]
35. Finlayson EV, Goodney PP, Birkmeyer JD. Hospital volume and operative mortality in cancer surgery: a national study. *Arch Surg* 2003;138:721–725. [PubMed: 12860752]discussion 726
36. Birkmeyer JD, Stukel TA, Siewers AE, et al. Surgeon volume and operative mortality in the United States. *N Engl J Med* 2003;349:2117–2117. [PubMed: 14645640]This recent review of the operative mortality in the United States for multiple types of procedures demonstrates the effect of performing surgical volume on operative mortality in esophagectomy.
37. Luketich JD, Grondin SC, Pearson FG, et al. Minimally invasive esophagectomy. *Ann Thorac Surg* 2000;70:906–911. [PubMed: 11016332]discussion 911-912
38. Banki F, Mason RJ, DeMeester SR, et al. Vagal-sparing esophagectomy: a more physiologic alternative. *Ann Surg* 2002;236:324–335. [PubMed: 12192319]