

# EDUCATION PRACTICE

## Esophageal Adenocarcinoma

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### Clinical Scenario

A 52-year-old man with a long history of chronic gastroesophageal reflux symptoms manifested by heartburn and acid regurgitation presents for screening colonoscopy. Before the procedure because of his chronic reflux, an investigation of his esophagus was also performed. An upper gastrointestinal endoscopy reveals erosive esophagitis Los Angeles class C and a nodular lesion 1 cm in diameter (Figure 1), which, on biopsy, is interpreted as an adenocarcinoma. Additional biopsies of the area show erosive esophagitis and evidence of Barrett's esophagus with low-grade dysplasia. The entire segment of erythematous mucosa has a maximal length of about 5 cm. How should this patient be evaluated and treated?

### The Clinical Problem

Barrett's esophagus and adenocarcinoma are well-established complications of chronic gastroesophageal reflux disease. Both Barrett's esophagus and adenocarcinoma most commonly occur in white male patients. The adenocarcinoma usually presents in those who are older than 60 years. Patients typically have a long history of gastroesophageal reflux disease, although a substantial number of patients with adenocarcinoma (up to 30%) will not have symptoms of reflux disease before their diagnosis of malignancy. Approximately 7% of patients participating in a colonoscopy screening trial were found to have Barrett's esophagus at screening examinations of the esophagus. Although Barrett's esophagus was more commonly found in patients with reflux symptoms, it was also common (6%) in those patients without any reflux symptoms.

It is still unclear which patients should be screened for Barrett's esophagus. Recently, the British Society of Gastroenterology did not recommend screening for Barrett's esophagus because it is so difficult to identify all the patients at risk for Barrett's esophagus because a large percentage of patients do not have symptoms.

At the current time, the only available method of screening for Barrett's esophagus is through endoscopy and biopsy. Although small-caliber endoscopes have been shown to allow reasonable visualization at the esophagogastric junction and also permit biopsies, this approach is only minimally more cost-effective than standard endoscopy. The advent of capsule endoscopy of the esophagus also has been promoted as a potential screening tool, but the initial costs of the current esophageal capsule examination are almost as high as those of an endoscopic procedure, whereas its ability to detect columnar mucosa is thought to be substantially lower. This would decrease the ability to use capsule endoscopy as a screening tool over standard endoscopy because capsule might not be suffi-

cient to exclude the presence of Barrett's esophagus, and all patients with suspected Barrett's esophagus found on esophageal capsule would still have to undergo standard endoscopy and biopsy for diagnosis.

Once Barrett's esophagus is diagnosed, management is dependent on histology. Barrett's esophagus is known to progress through degrees of dysplasia (from low-grade to high-grade) before advancing to adenocarcinoma. Unfortunately, there is disagreement among pathologists over the diagnosis of dysplasia. It is recommended that if dysplasia is found within Barrett's esophagus, a confirmatory interpretation should be obtained from an experienced gastrointestinal pathologist.

### Management Strategies and Supporting Evidence

Surveillance for Barrett's esophagus is somewhat controversial. There has not been any definitive, prospective study that compares no surveillance versus any fixed interval of surveillance to determine the efficacy of surveillance endoscopy in detecting esophageal adenocarcinoma. Studies have shown that patients who are in surveillance programs have earlier staged cancers (that are potentially curable) compared with those that are discovered in patients who were not in surveillance programs. Patients with nondysplastic Barrett's or low-grade dysplasia are usually observed in surveillance programs with biopsies taken in 4 quadrants every 2 cm. Patients without dysplasia should be followed with endoscopy and biopsy at 3- to 5-year intervals, depending on their overall health status. Patients with low-grade dysplasia should be followed at yearly intervals. Intervention is not advocated until the patient progresses to Barrett's esophagus with high-grade dysplasia or early adenocarcinoma. Patients with high-grade dysplasia verified by a second expert pathologist should be counseled about treatment options including further intensive surveillance (biopsies taken in 4 quadrants every centimeter), esophagectomy, or mucosal ablative therapies such as photodynamic therapy. Esophagectomy can eliminate the mucosa but is associated with substantial morbidity and significant mortality. Photodynamic therapy can decrease cancer risk by 50%, but there still is a 13% chance of development of cancer, and there is a serious risk of esophageal stricture. Surveillance is reasonable but must be very intensive with biopsies obtained every 3 months initially, and it

**Abbreviations used in this paper:** CT, computed tomography; PET, positron emission tomography.

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**Figure 1.** Nodule at the gastroesophageal junction in patient with Barrett’s esophagus.

has the potential to miss cancers. Proton pump inhibitors are recommended for control of reflux symptoms. Antireflux surgery has not been shown in large epidemiologic studies to actually decrease potential cancer development in patients with chronic gastroesophageal reflux disease.

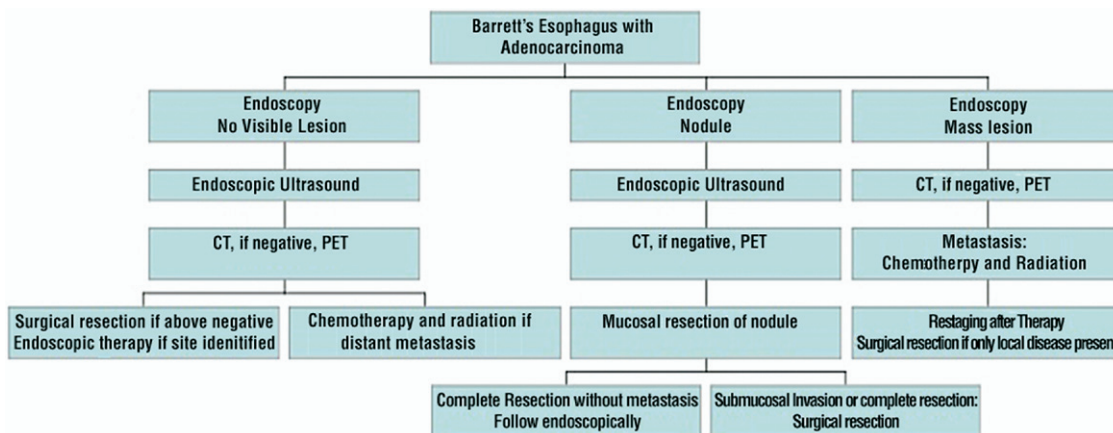
There is no chemopreventative agent recommended for use in Barrett’s esophagus. Acid suppressive therapy is recommended for control of symptoms, but there have been no definitive studies indicating that more aggressive acid inhibition will decrease the formation or progression of Barrett’s esophagus. Acid suppression is recommended before screening or surveillance to avoid confusion with inflammatory changes in the biopsy specimen that could be present in our case, although confusion on histology with adenocarcinoma would be uncommon. Cyclooxygenase inhibitors have been shown in a number of epidemiologic studies to reduce esophageal cancer risk, but prospective studies in patients at risk (eg, chronic gastroesophageal reflux disease) or Barrett’s esophagus with dysplasia have not been performed.

There are prospective cohort studies suggesting that patients with high-grade dysplasia who are carefully followed at tertiary

care centers with a strong interest in Barrett’s esophagus can do reasonably well. Development of cancer after the first year of observation (this is done to exclude potential incident cancers) in Barrett’s esophagus with high-grade dysplasia occurred in 16% of one cohort during the next 7 years. Most of these cancers occurred early on during close observation of the patients. It is generally recommended that if a surveillance strategy is followed, the patient should be followed every 3 months for the first year to make sure there is not any occult cancer present. Afterwards, 3- to 6-month surveillance intervals would be reasonable.

In this patient, it is clear that the evolution to carcinoma has already occurred, and staging of the tumor is definitely indicated (Figure 2). In patients without esophageal symptoms and a known small esophageal lesion, the likelihood of distant metastasis to other organs is low, and evaluation with endoscopic ultrasound is indicated if available in the community. If the ultrasound demonstrated a mucosal cancer, endoscopic mucosal resection could be performed for diagnosis and therapy. Retrospective cohort studies have found that endoscopic therapy can lead to prolonged survival similar to surgical resection for early staged cancer. If the patient had dysphagia (which is the most common symptom in advanced esophageal cancers), the likelihood of metastasis would be high. Evaluation should begin with a computed tomography (CT) scan of the chest and upper abdomen to exclude distant metastasis. If this were negative, the patient should have a positron emission tomography (PET) scan to increase the possibility of detection of distant metastasis. If CT or PET confirms distant metastasis, the patient will need chemotherapy and radiation to extend life.

Patients with mucosal cancers or high-grade dysplasia should also be counseled about surgical intervention. Esophagectomy traditionally can be performed by 2 ways, either a transhiatal approach or a transthoracic approach, the so-called Ivor-Lewis procedure. The transhiatal approach is generally undertaken when the patient has Barrett’s esophagus and high-grade dysplasia, if lymph node dissection is not critical. In patients with more advanced cancers, the transthoracic approach is usually favored, because visualization of the lesion and evaluation of local nodal metastasis tend to be better.



**Figure 2.** Algorithm for the management of esophageal adenocarcinoma complicating Barrett’s esophagus. The management of esophageal adenocarcinoma begins with the endoscopic appearance of the lesion. If the lesion is unapparent, endoscopic ultrasonography should be performed if available. If there is a mass lesion, then CT may be more cost-effective since distant metastases are likely. Earlier-stage lesions need careful staging because they can be managed endoscopically.

Esophagectomy can definitely remove the area at risk but is associated with mortality rates ranging from 1%–20%, depending on the surgical expertise available. Surgical resection is associated with a high incidence of complications, which occur in approximately 30%–40% of patients undergoing esophageal resection. Minimally invasive techniques are becoming available that combine the use of laparoscopy and thoracoscopy to perform the esophagectomy. Chemotherapy and radiation therapy are often given before surgical resection if there is evidence of lymph node involvement.

Ablation with photodynamic therapy is one of the few treatments that has actually been assessed by using a prospective, randomized, multicenter study. Patients from 30 centers in the United States and Europe were enrolled in the multicenter trial examining the use of sodium porfimer (Axcan Pharma, Mt Saint-Hilaire, Quebec, Canada) in the treatment of Barrett's esophagus with high-grade dysplasia. This multicenter study eventually enrolled 208 patients, of whom 70 were in the control arm given omeprazole, 20 mg twice a day, and 138 were in the treatment arm and treated with omeprazole, 20 mg twice a day, as well as photodynamic therapy at a dose of 2 mg/kg intravenously, followed by a light dose of 130 J/cm fiber by using a 630-nm red light laser. Overall, this randomized controlled trial demonstrated a decrease in high-grade dysplasia, with 77% in the treatment group versus 39% in the observational group. Complications of photodynamic therapy are related to cutaneous photosensitivity, which can persist for 30–90 days after injection with the drug. In addition, chronic stricture formation occurs in roughly 30% of treated patients; strictures might be difficult to dilate. Other complications such as nausea, vomiting, and chest pain are relatively short-lived. Thermal ablative therapies with multi-polar coagulation and argon plasma coagulation have been well described with smaller randomized trials comparing the two modalities. No significant differences have been found between these treatments in terms of efficacy or complications. Both have been shown to eliminate Barrett's mucosa in a high percentage of treated patients, although a few cases of cancer occurring under regenerated squamous mucosa have been reported. Argon plasma coagulation has been described treating high-grade dysplasia with good rates of ablation.

Other ablative therapies include radiofrequency ablation, which is applied by using a 3-cm long coil mounted on a balloon, which can be passed through the mouth into the esophagus. The balloon is inflated, maintaining strict contact with the mucosa. This direct contact allows application of high-frequency, high-power therapy for a very short time to create a superficial mucosal destruction. Preliminary evidence suggests that this treatment is promising, although more substantive testing has not occurred. Cryotherapy has also recently been reported in a group of 8 patients with Barrett's esophagus. The cryotherapy did eliminate most of the Barrett's segment.

### Areas of Uncertainty

At the current time, it is really unclear who should be screened for Barrett's esophagus. There are far more patients with some evidence of intestinal metaplasia than will develop cancer. Therefore, the use of screening procedures necessitates quite an expenditure of health care dollars for identification of a very small number of patients who truly will develop esophageal adenocarcinoma. In addition, the ideal screening method

has not been defined. The method to perform endoscopic biopsies for screening or surveillance has not been established by prospective study. The interval between endoscopic examination hinges on the reliability of biopsies that we know are flawed. In addition, long-term outcomes, such as cancer-free survival, have not been assessed by using these surveillance techniques.

Although the results of endoscopic ablative therapy are indeed promising, there has not been a comparison of which treatments might be the most efficacious. A randomized control trial between endoscopic therapy and surgical therapy would be quite interesting scientifically, but it might be quite difficult to recruit to such a study in practice because of the significant differences between these 2 treatments.

High-dose proton pump inhibitor therapy has not been proved to have efficacy in decreasing cancer risk, although proton pump inhibitors definitely should be given to anyone with symptomatic reflux disease and Barrett's esophagus. It is unclear whether the patient without symptomatic reflux should be on acid suppression. Even though the evidence suggests elimination of inflammatory change should theoretically decrease carcinogenesis, this has not been proved. Given the high cost of proton pump inhibitor therapy and the relatively low incidence of esophageal adenocarcinoma, high-dose proton pump inhibitor therapy cannot be recommended at this time.

For early adenocarcinomas, endoscopic mucosal resection has been promoted as a possible therapy. This will not only help diagnose the depth of invasion to a much more certain stage, but it could potentially even be curative in the appropriately selected individual. Endoscopic mucosal resection can be done relatively safely and with immediate results obtained with frozen section. The complication with this procedure is primarily related to bleeding complication in ~3%–4% and rare perforations in 1%. If the lesion is completely confined in the mucosa and has been completely resected by using mucosal resection, the chances of having metastatic disease are quite low (<3%).

### Published Guidelines

The American College of Gastroenterology has published a guideline regarding the treatment of Barrett's esophagus that was published in 2002. The American Gastroenterology Association has a position statement on esophageal adenocarcinoma that was published in 2005. The guidelines are relatively current with the literature, although most of the recommendations are not based on actual data but are more of expert opinion. The guidelines basically only vary on the length of time between surveillance intervals. Both guidelines offer reasonable management options for Barrett's esophagus.

### Recommendations for This Patient

In this patient, who seems to be a relatively good surgical candidate, staging should be completed. It would also be helpful to make sure thorough biopsies have been taken throughout the Barrett's segment to exclude other areas of carcinoma. If this is a single area that is superficial, it is likely that the patient can be cured with endoscopic therapy. On the other hand, the investigation for metastatic disease should be very thorough. The staging should initially be done with endoscopic ultrasonography to confirm depth of invasion and to determine whether there are any regional lymph nodes, because

recent studies suggest that there is a high prevalence of regional lymph node involvement in patients with early cancer or high-grade dysplasia. Mucosal resection should probably be performed if available in the community, both as a diagnostic tool and as a potentially therapeutic modality. The specimen should be carefully examined by pathologists to determine whether the entire cancer has been removed and the precise depth of invasion. Once ultrasonography has excluded the presence of potential metastatic lymph nodes, CT of the chest and upper abdomen as well as PET should be done to exclude more distant metastases. If these reveal evidence of metastasis, medical and radiation therapy should be involved. The goals of management and their potential weaknesses should be carefully discussed with this patient including that of surgical resection if the disease has not metastasized.

### Suggested Reading

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