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Current management of Barrett esophagus and esophageal adenocarcinoma

ABSTRACT

Barrett esophagus is found in 5% to 15% of patients with gastroesophageal reflux disease and is a precursor of esophageal adenocarcinoma, yet the condition often goes undiagnosed. Patients with reflux disease who are male, over age 50, or white, and who smoke or have central obesity or a family history of Barrett esophagus or esophageal adenocarcinoma, should undergo initial screening endoscopy and, if no dysplasia is noted, surveillance endoscopy every 3 to 5 years. Dysplasia is treated with endoscopic eradication by ablation, resection, or both. Chemoprotective agents are being studied to prevent progression to dysplasia in Barrett esophagus. The authors discuss current recommendations for screening and management.

KEY POINTS

Screening is recommended for patients with long-standing reflux symptoms (> 5 years) and 1 or more key risk factors: male sex, age over 50, white race, central obesity, and history of smoking.

In Barrett esophagus without dysplasia, surveillance endoscopy is recommended every 3 to 5 years to detect dysplasia and early esophageal adenocarcinoma.

The recommended treatment of dysplasia is endoscopic eradication followed by surveillance endoscopy.

A LL CASES OF ESOPHAGEAL adenocarcinoma are thought to arise from Barrett esophagus.[1] But most cases of Barrett esophagus go undiagnosed. And Barrett esophagus is seen in 5% to 15% of patients with gastroesophageal reflux disease.[2] These facts clearly emphasize the need for screening. Here, we review the rationale and recommendations for screening and surveillance, as well as the range of treatment options.

■ SCOPE OF THE PROBLEM

The American Cancer Society estimated there were 17,290 new cases of esophageal cancer and 15,850 deaths from it in the United States in 2018.[3] Of the 2 main histologic types of esophageal cancer, adenocarcinoma and squamous cell cancer, adenocarcinoma is more common in the United States.

The precursor lesion is Barrett esophagus, defined as an extension of salmon-colored mucosa at least 1 cm into the tubular esophagus proximal to the gastroesophageal junction, with biopsy confirmation of intestinal metaplasia.[4]

The natural course of progression to dysplasia and cancer in Barrett esophagus is unknown but is thought to be stepwise, from no dysplasia to low-grade dysplasia to high-grade dysplasia and cancer, and the cancer risk depends on the degree of dysplasia: the annual risk is 0.33% if there is no dysplasia, 0.54% with low-grade dysplasia, and 7% with high-grade dysplasia.[4]

Although all cases of esophageal adenocarcinoma are thought to arise from Barrett

esophagus,[1] more than 90% of patients with newly diagnosed esophageal adenocarcinoma do not have a prior diagnosis of Barrett esophagus.[5] Therefore, there is a substantial unmet need to expand screening for Barrett esophagus in people at risk.

■ GASTROESOPHAGEAL REFLUX DISEASE IS A RISK FACTOR FOR CANCER

The rationale behind screening is that detecting Barrett esophagus early and intervening in a timely manner in patients at higher risk of developing adenocarcinoma will decrease mortality.

Chronic gastroesophageal reflux disease is a strong risk factor for esophageal adenocarcinoma (odds ratio [OR] 7.7, 95% confidence interval [CI] 5.3–11.4), and the risk increases when symptoms are long-standing (> 20 years) or severe (OR 43.5, 95% CI 18.3–103.5) or occur daily (OR 5.5, 95% CI 3.2–9.3).[6]

Reflux symptoms are scored as follows:
- Heartburn only, 1 point
- Regurgitation only, 1 point
- Heartburn with regurgitation, 1.5 points
- Nightly symptoms (2 points if yes, 0 if no)
- Symptoms once a week, 0 points; 2 to 6 times a week, 1 point; 7 to 15 times a week, 2 points; more than 15 times a week, 3 points.[6]

A score of 4.5 or higher indicates severe reflux disease. However, it is worth noting that the annual incidence of esophageal adenocarcinoma in patients with long-term gastroesophageal reflux disease is less than 0.001%.[7]

■ RISK FACTORS FOR BARRETT ESOPHAGUS

Risk factors for Barrett esophagus include:

Male sex. Barrett esophagus is more prevalent in men than in women, at a ratio of 2 to 1; but in individuals under age 50, the ratio is 4 to 1.[8]

Age 50 or older. Barrett esophagus is usually diagnosed in the sixth to seventh decade of life, and the prevalence increases from 2.1% in the third decade to 9.3% in the sixth decade.[9]

White race. It is more prevalent in whites than in blacks (5.0% vs 1.5%, *P* < .0001).[10]

Central obesity. Waist circumference is an independent risk factor: every 5-cm increase carries an OR of 1.14 (95% CI 1.03–1.27, *P* = .02).[11]

Cigarette smoking increases the risk of Barrett esophagus (OR 1.42; 95% CI 1.15–1.76).[12]

A family history of Barrett esophagus or esophageal adenocarcinoma is a strong risk factor (OR 12, 95% CI 3.3–44.8). In 1 study, the risk in first- and second-degree relatives of patients with Barrett esophagus was 24%, compared with 5% in a control population (*P* < .005).[13]

■ SCREENING GUIDELINES AND DRAWBACKS

American College of Gastroenterology guidelines recommend screening for Barrett esophagus in men who have chronic reflux disease (> 5 years) or frequent symptoms (weekly or more often), and 2 or more risk factors.[4] In women, screening is recommended only in the presence of multiple risk factors.[4]

The standard screening method is esophagogastroduodenoscopy with sedation, with careful visual inspection and 4-quadrant biopsies every 2 cm using the Seattle protocol, ie, including biopsy of any mucosal irregularities in salmon-colored mucosa above the gastroesophageal junction (**Figure 1**).[4]

Endoscopic screening is cost-effective, costing $10,440 per quality-adjusted life-year saved, which is well below the accepted threshold of less than $100,000.[14] However, it is still expensive, invasive, and not ideal for screening large populations.

Less-invasive methods under study

Less-invasive, less-expensive methods being tested for mass screening include:

Unsedated transnasal endoscopy. Done with only topical anesthesia, it has high diagnostic accuracy and is quicker and more cost-effective than standard esophagogastroduodenoscopy, with fewer adverse effects. However, the procedure has not yet gained widespread acceptance for regular use by gastroenterologists.[15]

A swallowable sponge. Another promising test is cell collection using the Cytosponge Cell Collection Device (Medtronic, Minneapolis, MN). An encapsulated compressed

There is a substantial unmet need to expand screening for Barrett esophagus in people at risk
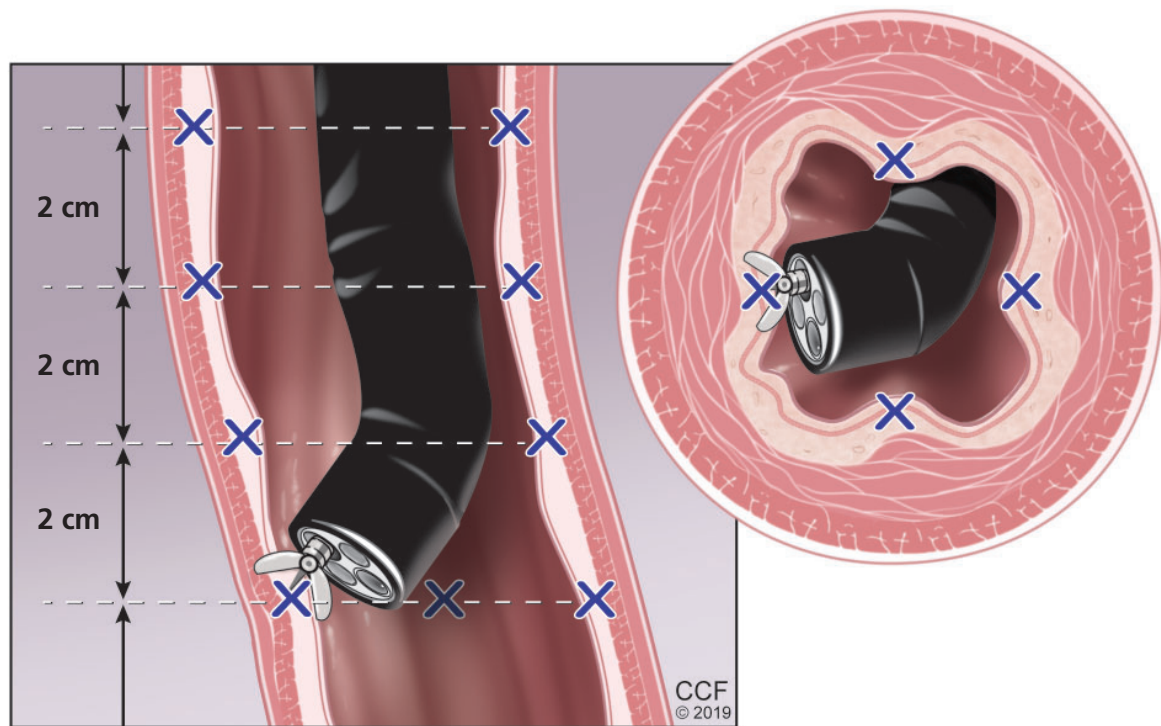
Figure 1. Four-quadrant biopsies are taken every 2 cm, plus at any mucosal irregularities in salmon-colored mucosa above the gastroesophageal junction.

Chemoprevention with aspirin, other NSAIDs, PPIs, metformin, and statins is under study

sponge with a string attached is swallowed; in the stomach, the capsule dissolves, and the sponge expands and is then withdrawn using the attached string. The obtained cytology sample from the lower esophagus is then tested for trefoil factor 3, a protein biomarker for Barrett esophagus.[16]

A retractable balloon. The EsoCheck Cell Collection Device is a retractable balloon attached to a string. When swallowed, it gathers distal esophageal cells for detecting methylated DNA markers for Barrett esophagus.[17]

Esophageal capsule endoscopy uses a camera to visualize the esophagus, but lacks the ability to obtain biopsy samples.

Other screening methods are being tested, although data are limited. Liquid biopsy uses a blood sample to detect microRNAs that are dysregulated in cancer. The "electronic nose" is a device that detects exhaled volatile organic compounds altered in Barrett esophagus. Another test involves taking an oral wash sample to study the oral microbiome for a pattern associated with adenocarcinoma.[18–21]

■ SURVEILLANCE: WHAT'S INVOLVED, WHAT'S AVAILABLE

Surveillance in Barrett esophagus aims to detect premalignant changes or early-stage adenocarcinoma to provide longer survival and lower cancer-related mortality. Recent evidence suggests that patients with esophageal adenocarcinoma that is diagnosed in a Barrett esophagus surveillance program have an earlier stage of disease and therefore a survival benefit.[22]

Patient education is essential

Before enrolling a patient in a surveillance program, the clinician should explain the risks, benefits, and limitations, the importance of periodic endoscopy, and the possible eventual need for endoscopic therapy or surgery.

The endoscopic procedure

Surveillance involves examination by high-definition white-light endoscopy, with random 4-quadrant biopsies every 2 cm (or every 1 cm in patients with a history of dysplasia) and biopsy of any mucosal irregularity (nodule,

ulcer, or other visible lesion). The degree of dysplasia determines the frequency of follow-up surveillance intervals and the need for endoscopic eradication therapy, as presented in professional society guidelines (**Table 1**).[4,23,24]

Advanced methods for detecting dysplasia

Newer endoscopic surveillance techniques include dye-based chromoendoscopy, narrow-band imaging, confocal laser endomicroscopy, volumetric laser endomicroscopy, and wide-area transepithelial sampling with computer-assisted 3-dimensional analysis. All these techniques are used to increase the detection of dysplasia. Of these, dye-based chromoendoscopy, narrow-band imaging, and confocal laser endomicroscopy meet current criteria of the American Society for Gastrointestinal Endoscopy for preservation and incorporation of valuable endoscopic innovations.[23]

■ MANAGEMENT OF NONDYSPLASTIC BARRETT ESOPHAGUS

A proton pump inhibitor (PPI) is recommended to control reflux symptoms in patients with nondysplastic Barrett esophagus. But it is important to counsel patients on additional ways to protect against esophageal adenocarcinoma, such as:

- Low to moderate alcohol consumption
- Regular physical activity
- Increased dietary intake of fruits, vegetables, folate, fiber, beta-carotene, and vitamin C
- Weight control
- Smoking cessation.[25]

Surveillance endoscopy with 4-quadrant biopsies at 2-cm intervals is recommended every 3 to 5 years (**Table 1**).

■ DOES CHEMOPREVENTION HAVE A ROLE?

Chemoprevention is an exciting area of research in preventing progression to adenocarcinoma in patients with Barrett esophagus. Various drugs such as aspirin, other nonsteroidal anti-inflammatory drugs (NSAIDs), PPIs, metformin, and statins have been studied.

Aspirin

Aspirin has been shown to prevent development of Barrett esophagus in patients with re-

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TABLE 1

Surveillance guidelines for Barrett esophagus[a]

Nondysplastic Barrett esophagus
AGA, ACG, and ASGE recommend surveillance every 3–5 years

'Indefinite for dysplasia'
AGA: no recommendation
ACG: repeat esophagogastroduodenoscopy (EGD) after 3–6 months of proton pump inhibitor (PPI) therapy; if repeat EGD indicates "indefinite for dysplasia," then surveillance every 12 months
ASGE: additional pathology review, PPI dose escalation, and repeat EGD with biopsy

Low-grade dysplasia
AGA: surveillance every 6–12 months
ACG: either endoscopic eradication therapy for confirmed low-grade dysplasia for patients without a life-limiting comorbidity, or surveillance every 12 months
ASGE: repeat EGD in 6 months to confirm low-grade dysplasia, then surveillance every year, with eradication therapy in select patients

High-grade dysplasia
AGA: eradication therapy or surveillance every 3 months
ACG: eradication therapy for confirmed high-grade dysplasia in patients without a life-limiting comorbidity
ASGE: eradication therapy or surveillance every 3 months

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[a]All guidelines recommend confirmation of dysplasia by an expert gastrointestinal pathologist.

ACG = American College of Gastroenterology[4]; AGA = American Gastroenterological Association[24]; ASGE = American Society for Gastrointestinal Endoscopy[23]

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flux disease,[26] but more studies are needed to validate those findings.

PPIs

Gastroesophageal reflux disease is a primary risk factor for esophageal adenocarcinoma, and gastric acid suppression with PPIs reduces cancer risk. PPI therapy is associated with a 71% decrease in the risk of high-grade dysplasia and adenocarcinoma in patients with Barrett esophagus (OR 0.29, 95% CI 0.12–0.79).[27] Long-term therapy (> 2 to 3 years) has a higher protective effect (adjusted OR 0.45, 95% CI 0.19–1.06) than short-term therapy (< 2 to 3 years) (adjusted OR 1.09, 95% CI 0.47–2.56).[27]

NSAIDs

NSAIDs, including aspirin, have been associated with decreased risk of colon, stomach,

lung, breast, and esophageal cancer due to their potential to inhibit cyclooxygenase 2 (COX-2) enzymes.

A meta-analysis demonstrated that aspirin and NSAIDs led to a 32% reduction in the risk of adenocarcinoma (OR 0.68, 95% CI 0.56–0.83). The benefit was even greater if the drug was taken daily or more frequently (OR 0.56, 95% CI 0.43–0.73, $P < .001$) or was taken for 10 or more years (OR 0.63, 95% CI 0.45–0.90, $P = .04$).[28]

PPI plus aspirin

The best evidence for the role of PPIs and aspirin in reducing the risk of dysplasia comes from the Aspirin and Esomeprazole Chemoprevention in Barrett's Metaplasia Trial.[29] This randomized, controlled trial compared 4 regimens consisting of esomeprazole (a PPI) in either a high dose (40 mg twice daily) or a low dose (20 mg once daily) plus either aspirin (300 or 320 mg per day) or no aspirin in 2,557 patients with Barrett esophagus. The composite end point was the time to all-cause mortality, adenocarcinoma, or high-grade dysplasia.

At a median follow-up of 8.9 years, the combination of high-dose esomeprazole plus aspirin had the strongest effect compared with low-dose esomeprazole without aspirin (time ratio 1.59, 95% CI 1.14–2.23, $P = .0068$). The number needed to treat was 34 for esomeprazole and 43 for aspirin.[29]

Based on these data, we can conclude that aspirin and PPIs can prevent dysplasia and all-cause mortality in Barrett esophagus.

Metformin: No evidence of benefit

Metformin was studied as a protective agent against obesity-associated cancers including esophageal adenocarcinoma, as it reduces insulin levels.

In a randomized controlled trial[30] in 74 patients with Barrett esophagus, metformin (starting at 500 mg daily, increasing to 2,000 mg/day by week 4) was compared with placebo. At 12 weeks, the percent change in esophageal levels of the biomarker pS6K1—an intracellular mediator of insulin and insulin-like growth factor activation in Barrett epithelium—did not differ significantly between the 2 groups (1.4% with metformin vs −14.7% with placebo; 1-sided $P = .80$). This

suggested that metformin did not significantly alter proliferation or apoptosis in Barrett epithelium, despite reducing serum insulin levels and insulin resistance. Thus, metformin did not demonstrate a chemoprotective effect in preventing the progression of Barrett esophagus to adenocarcinoma.

Vitamin D: No evidence of benefit

Vitamin D affects genes regulating proliferation, apoptosis, and differentiation, and has therefore been studied as a potential antineoplastic agent. Its deficiency has also been associated with increased risk of esophageal adenocarcinoma. However, its efficacy in chemoprevention is unclear.[31]

One study found no association between serum 25-hydroxyvitamin D levels and prevalence of dysplasia in Barrett esophagus ($P = .90$). An increase in vitamin D levels had no effect on progression to dysplasia or cancer (for every 5-nmol/L increase from baseline, hazard ratio 0.98, $P = .62$).[32]

In another study, supplementation with vitamin D_3 (cholecalciferol 50,000 IU weekly) plus a PPI for 12 weeks significantly improved the serum 25-hydroxyvitamin D levels without significant changes in gene expression from Barrett epithelium.[33] These findings were confirmed in a meta-analysis that showed no consistent association between vitamin D exposure and risk of esophageal neoplasm.[34]

Thus, there is currently no evidence to support vitamin D for chemoprevention in Barrett esophagus or esophageal adenocarcinoma.

Statins

In addition to lowering cholesterol, statins have antiproliferative, pro-apoptotic, anti-angiogenic, and immunomodulatory effects that prevent cancer, leading to a 41% reduction in the risk of adenocarcinoma in patients with Barrett esophagus in one study (adjusted OR 0.59, 95% CI 0.45–0.78); the number needed to treat with statins to prevent 1 case of adenocarcinoma was 389.[35]

A meta-analysis also showed that statin use was associated with a lower risk of progression of Barrett esophagus (OR 0.48, 95% CI 0.31–0.73).[36]

In general, statins appear promising for chemoprevention, but more study is needed.

Endoscopic resection techniques include mucosal resection, submucosal dissection, radiofrequency ablation, and cryotherapy
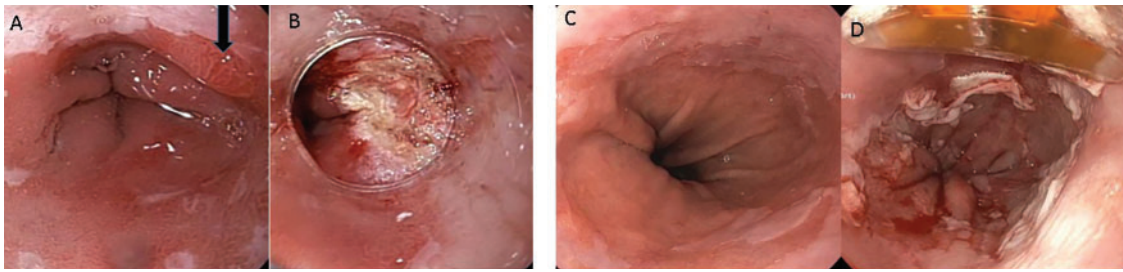
Figure 2. A: Endoscopic picture of Barrett esophagus with arrow pointing to nodule. B: After endoscopic mucosal resection of nodule. C: Barrett esophagus before radiofrequency ablation. D: Barrett esophagus after ablation.

When is chemoprevention appropriate?

Chemoprevention is not recommended for all patients with Barrett esophagus, given that the condition affects 1% to 2% of the US adult population, and very few patients have progression to esophageal adenocarcinoma. Rather, chemoprevention may be considered in patients with Barrett esophagus and multiple risk factors for adenocarcinoma.

■ INDEFINITE DYSPLASIA

In Barrett esophagus with indefinite dysplasia, either the epithelial abnormalities are insufficient for a diagnosis of dysplasia, or the nature of the epithelial abnormalities is uncertain due to inflammation or technical difficulties with specimen processing. The risk of high-grade dysplasia or cancer within 1 year of the diagnosis of indefinite dysplasia varies between 1.9% and 15%.[37] The recommendation for management is to optimize acid-suppressive therapy for 3 to 6 months and then to repeat esophagogastroduodenoscopy. If indefinite dysplasia is noted again, repeat endoscopy in 12 months is recommended.[2]

■ ENDOSCOPIC ERADICATION: AN OVERVIEW

Because dysplasia in Barrett esophagus carries a high risk of progression to cancer, the standard of care is endoscopic mucosal resection of visible lesions, followed by ablation of the flat mucosa, with the aim of achieving complete eradication of intestinal metaplasia.[4,38] The initial endoscopic treatment is followed by outpatient sessions every 8 to 10 weeks until the dysplasia is eradicated. A key part of treatment during this time is maximal acid suppression with a PPI twice daily and a histamine-2 blocker at night. In rare cases, fundoplication is required to control reflux refractory to medical therapy.

After eradication is confirmed, continued surveillance is necessary, as recurrences have been reported at a rate of 4.8% per year for intestinal metaplasia, and 2% per year for dysplasia.[39]

Current endoscopic resection techniques

Endoscopic resection techniques include mucosal resection, submucosal dissection, radiofrequency ablation, cryotherapy, argon plasma coagulation, and photodynamic therapy (**Figure 2**).

In mucosal resection, the lesion is either suctioned into a band ligator, after which a band is placed around the lesion, or suctioned into a cap fitted at the end of the endoscope, after which the lesion is removed using a snare.

In submucosal dissection, a liquid is injected into the submucosa to lift the lesion, making it easier to remove. The procedure is technically complex and requires additional training.

In radiofrequency ablation, a special catheter is passed through the endoscope to ablate the affected epithelium by thermal injury. Argon plasma coagulation works in a similar way, but uses ionized argon gas to induce thermal coagulation of metaplastic epithelium.

Cryotherapy produces cellular injury by rapid freezing and thawing of tissue using a cryogen such as liquid nitrogen or nitrous oxide.

In photodynamic therapy, a photosensitizer (porfimer sodium) is administered and taken up preferentially by metaplastic epithelium; it is then activated by transmission of

Radiofrequency ablation has compelling evidence for efficacy, and hence is the most commonly used endoscopic resection technique

red light using the endoscope, leading to destruction of the metaplastic epithelium.

Of the different techniques, radiofrequency ablation has the most evidence for efficacy and hence is the most commonly used.

All of these procedures are generally well tolerated and have favorable side-effect profiles. After radiofrequency ablation with or without mucosal resection, esophageal strictures are noted in 5.6% of patients, and bleeding and perforation occur rarely (1% and 0.6% of patients, respectively).[40] Submucosal dissection is associated with a higher rate of complications such as stricture formation (11% of patients) and bleeding or perforation (1.5% of patients).[41]

■ LOW-GRADE DYSPLASIA: RECOMMENDED MANAGEMENT

Most patients with low-grade dysplasia (73%) are down-staged to nondysplastic Barrett esophagus or to indefinite for dysplasia after review by expert pathologists.[42] Patients with confirmed and persistent low-grade dysplasia are at higher risk of progression.[43]

Once low-grade dysplasia is confirmed by a second gastrointestinal pathologist, the patient should undergo endoscopic ablation. A landmark study by Shaheen et al[44] demonstrated the benefit of radiofrequency ablation in achieving complete eradication of dysplasia (90.5% vs 22.7% for a sham procedure) and complete eradication of intestinal metaplasia (77.4% vs 2.3% for a sham procedure). In another trial of 136 patients with low-grade dysplasia followed for 3 years, Phoa et al[45] demonstrated that radiofrequency ablation reduced the rate of progression to high-grade dysplasia by 25% and to adenocarcinoma by 7.4% compared with endoscopic surveillance.

Patients with confirmed low-grade dysplasia who do not undergo eradication therapy should have surveillance endoscopy every 6 to 12 months (**Table 1**).

■ HIGH-GRADE DYSPLASIA: RECOMMENDED MANAGEMENT

As with low-grade dysplasia, the diagnosis of high-grade dysplasia needs to be confirmed by a second pathologist with gastrointestinal expertise. In the past, the treatment was

Long-term PPI therapy and surveillance are recommended after dysplasia ablation

esophagectomy, but due to lower morbidity and equivalent efficacy of radiofrequency ablation,[46] the current treatment of choice is endoscopic mucosal resection of raised lesions, followed by radiofrequency ablation of the entire affected segment.

In the study by Shaheen et al,[44] 42 patients with high-grade dysplasia were randomized to radiofrequency ablation and 21 to a sham procedure, and 81% of ablation patients achieved complete eradication of dysplasia vs 19% with the sham procedure. Eradication of intestinal metaplasia was achieved in 77% of ablation patients vs 2% of patients with the sham therapy. Results of 3-year follow-up from the same cohort showed complete eradication of dysplasia in 98% and of intestinal metaplasia in 91%.[47]

Endoscopic eradication therapy is recommended for all patients with Barrett esophagus and high-grade dysplasia without a life-limiting comorbidity. Alternatively, surveillance every 3 months is an option if the patient does not wish to undergo eradication therapy. Radiofrequency ablation is more cost-effective than esophagectomy or endoscopic surveillance followed by treatment once patients develop adenocarcinoma.[48,49]

■ EARLY ESOPHAGEAL ADENOCARCINOMA: RECOMMENDED MANAGEMENT

Adenocarcinoma limited to the mucosa and without evidence of nodal involvement can be resected endoscopically. In patients with localized cancer, mucosal resection is done not only for therapeutic purposes but also for staging. Ideal management is multidisciplinary, including a gastroenterologist, thoracic surgeon, oncologist, pathologist, and radiation oncologist.

If lesions have features suggesting submucosal invasion or are greater than 1.5 cm in size, or if it is difficult to separate (ie, lift) the mucosa from the submucosal layer with injection of saline, then submucosal dissection is recommended.[50] Because of the risk of metachronous lesions, ablation of the remaining Barrett esophagus mucosa is recommended after resection of cancer.

Endoscopic eradication is highly effective and durable for the treatment of intramucosal esophageal adenocarcinoma. In a study of 1,000 patients, 963 patients (96.3%) had

achieved a complete response; 12 patients (3.7%) underwent surgery after eradication failed during a follow-up of almost 5 years.[51] Metachronous lesions or recurrence of cancer developed during the follow-up period in 140 patients (14.5%) but were successfully treated endoscopically in 115, resulting in a long-term complete remission rate of 93.8%.

■ POSTABLATION MANAGEMENT

Because of the risk of recurrence of dysplasia after ablation, long-term PPI therapy and surveillance are recommended.

Surveillance endoscopy involves 4-quadrant biopsies taken every 1 cm from the entire length of segment where Barrett esophagus had been seen before ablation.

The timing of surveillance intervals depends on the preablation grade of dysplasia. For low-grade dysplasia, the recommendation is every 6 months for the first year after ablation and, if there is no recurrence of dysplasia, annually after that.[2] After treatment of high-grade dysplasia or intramucosal adenocarcinoma, the recommendation is every 3 months for the first year, every 6 months in the second year, and then annually.[2]　　■

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