CLINICAL PRACTICE

Barrett's Esophagus

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This Journal *feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the author's clinical recommendations.*

SUMMARY

Barrett's esophagus develops as a result of chronic acid and bile reflux and carries an increased risk of esophageal adenocarcinoma. Because it has no specific symptoms, many patients do not receive a diagnosis or they present with symptoms of gastroesophageal reflux disease and other related risk factors or complications. Diagnosis relies on endoscopic and histopathological findings, including a visible columnar-cell–lined segment measuring at least 1 cm long that contains intestinal metaplasia with goblet cells. Ongoing surveillance focuses on early detection of malignant progression, particularly high-grade dysplasia and early-stage cancer, which allows curative endoscopic treatment and avoids the adverse effects associated with chemotherapy or esophagectomy. Participation in clinical trials is encouraged to improve detection, risk stratification, and management strategies.

A 61-year-old man presents with a 10-year history of occasional use of antacids for heartburn. However, the symptoms have worsened during the past 6 months despite regular administration of acid-suppressant medication and are affecting his sleep. He has overweight, and he used to smoke cigarettes but stopped several years ago. He is worried about the risk of cancer. How would you treat this patient?

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CME

THE CLINICAL PROBLEM

Barrett's esophagus is detected in 3 to 14% of adults with symptoms of gastroesophageal reflux disease (GERD) who undergo an endoscopy examination.[1] Barrett's esophagus is characterized by the replacement of the squamous mucosa in the lower portion of the esophagus with a columnar epithelium. On endoscopy, the columnar-cell–lined segment appears as reddened mucosa originating from the gastroesophageal junction and is frequently associated with a hiatal hernia. Histopathological findings include a mosaic of intestinal and gastric cell types. Clinically, a diagnosis of Barrett's esophagus is established when endoscopic findings reveal a columnar epithelium measuring at least 1 cm long in combination with confirmed goblet-cell lineages, a condition termed intestinal metaplasia (Fig. 1 and video). Endoscopists record the length of the segment of Barrett's esophagus in centimeters because longer segments are associated with a greater chance of progression to cancer.[2] On the basis of historical studies, 3 cm is used as a cutoff between short segments (<3 cm) and long segments (≥3 cm). Establishing whether a segment is short or long determines how often monitoring should take place owing to the altered pathophysiological features of long segments

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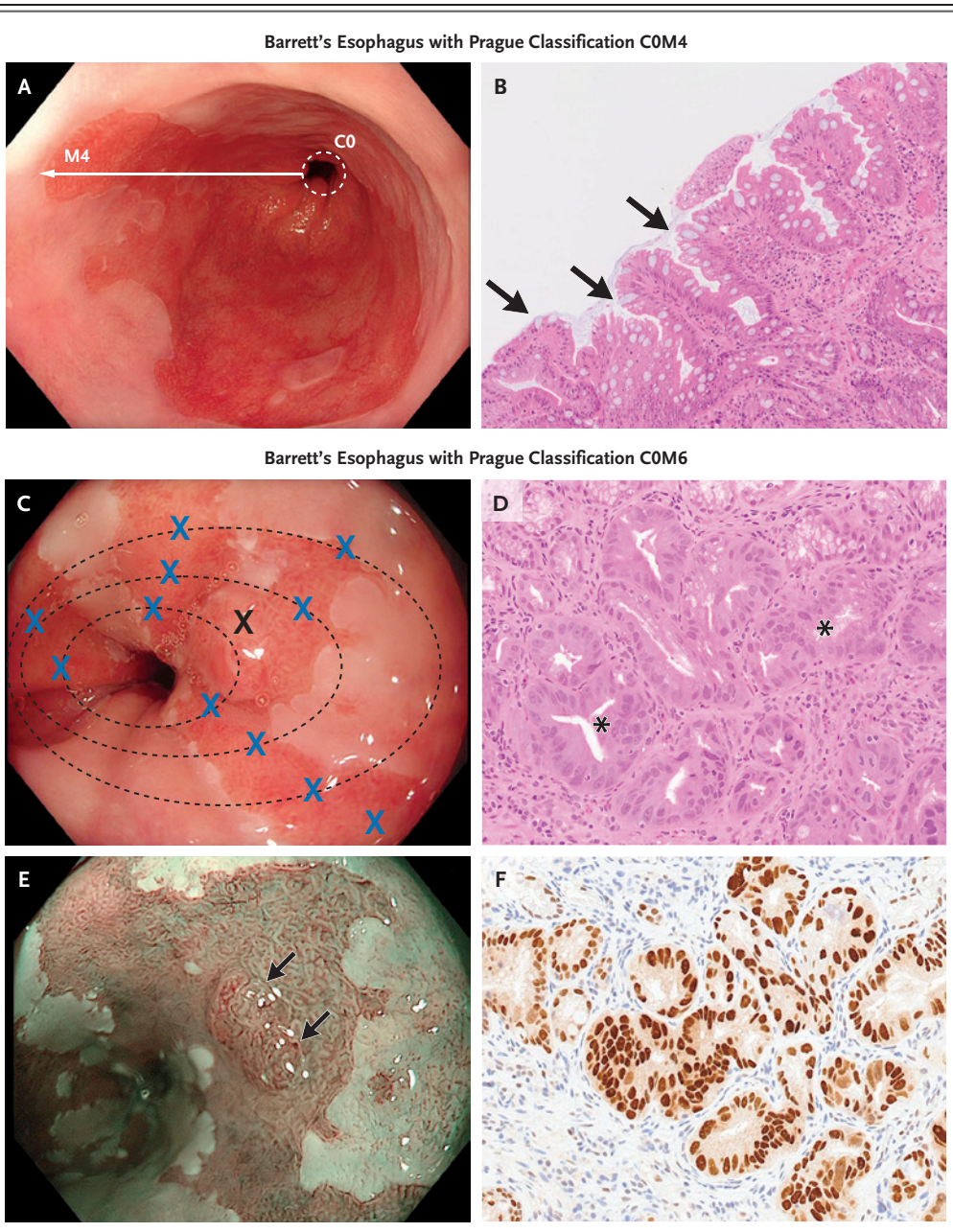

with intestinal-cell lineages coupled with greater molecular instability.

The mechanism through which reflux contributes to metaplasia in Barrett's esophagus has been difficult to prove in the absence of physiologically relevant models. Several hypotheses have been proposed.[3] Advances in molecular tools used to trace cell lineage have shown that Barrett's esophagus probably develops secondary to reprogramming of gastric cardia cells, which expand to replace the reflux-damaged squamous epithelium.[4]

The prevalence of Barrett's esophagus varies according to geographic region, with a predominance seen in Western populations. Consistent reports of increasing incidence in Asia may reflect changing lifestyle patterns and the decline in *Helicobacter pylori* infection.[5]

The identification and treatment of Barrett's esophagus is important because of the associated increased risk of esophageal adenocarcinoma and the potential to decrease the risk of its occurrence. Although only half the patients with

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Figure 1 (facing page). Key Endoscopic and Histopathological Features of Barrett's Esophagus.

Panel A shows a high-definition, white-light endoscopic image of a columnar-lined mucosa looking down toward the gastroesophageal junction in a patient with Barrett's esophagus. This case has extensive tongues (i.e., noncircumferential areas of Barrett's esophagus) extending 4 cm (arrow) above the gastroesophageal junction but no circumferential component (circle) and is therefore scored as Prague classification C0M4. Panel B shows the corresponding histopathological hematoxylin and eosin stain of a biopsy sample taken from the segment of Barrett's esophagus; the image shows a high number of goblet cells (arrows), which indicates florid intestinal metaplasia. Panels C and E show a visible lesion on a white-light endoscopic image (black X, Panel C) and on the corresponding narrow-band image (arrows, Panel E) in a patient with Barrett's esophagus with Prague classification C0M6. Biopsy samples should be taken from the visible lesion, and systematic biopsies should be performed in accordance with the Seattle protocol, which states that a biopsy sample should be obtained for every 2 cm of Barrett's esophagus–affected epithelium in each quadrant; the ellipses in Panel C show each level where biopsy samples are taken, and the blue Xs show the biopsy site. At the most proximal extent of the affected tissue in this case, only one biopsy sample would be taken. Panel D shows the corresponding histopathological hematoxylin and eosin stain, which shows nuclear enlargement and disruption of glandular atypia (asterisks), indicating high-grade dysplasia. Panel F shows the corresponding immunohistochemical stain; the image shows aberrant overexpression of p53 in the affected tissue as compared with the wild-type glands, which confirms the genomic basis for this phenotypic change.

esophageal adenocarcinoma have demonstrable Barrett's esophagus at the time of diagnosis,[6] traces of the molecular hallmarks of Barrett's esophagus are often present, even in patients with advanced cancer.[7,8]

CLINICAL PRESENTATION

Barrett's esophagus is not associated with a specific symptom over and above those related to GERD. Because antireflux medication is widely available over the counter and because reflux can be asymptomatic, it is estimated that up to 80% of persons with Barrett's esophagus have not received a diagnosis. Furthermore, the suppression of acid reflux and its symptoms does not affect the underlying metaplasia. Reflux can be "silent," or asymptomatic[9]; therefore, the diagnosis is often an incidental finding (in up to 16% of cases in a U.S. registry of more than 3 million endoscopies).[10]

MANAGEMENT STRATEGIES AND EVIDENCE

DIAGNOSIS

Whom to Test?

Although reliable risk-prediction tools are lacking, several factors are associated with a higher risk of Barrett's esophagus (Table 1), and these factors can be incorporated into decision making regarding whom should be tested. One systematic review of studies examining the prevalence of Barrett's esophagus estimated that the prevalence was 0.8% (95% confidence interval [CI], 0.6 to 1.1) in a low-risk general population without any risk factors, 3.0% (95% CI, 2.3 to 4.0) among persons with GERD, 12.2% (95% CI, 10.2 to 14.6) among those with GERD plus any other risk factor, 23.4% (95% CI, 13.7 to 37.2) among those with a family history of Barrett's esophagus and esophageal adenocarcinoma, 6.1% (95% CI, 4.6 to 8.1) among persons older than 50 years of age, 1.9% (95% CI, 1.2 to 3.0) among those with obesity, and 6.8% (95% CI, 5.3 to 8.6) among male persons.[9] This meta-analysis controlled for study region (Western vs. non-Western) and showed that the prevalence of Barrett's esophagus in 3 Western studies was 3.0% (95% CI, 1.6 to 5.6), as compared with a prevalence of 1.0% (95% CI, 0.4 to 2.4) in the 14 non-Western studies.[9,12] Another systematic review showed a prevalence of Barrett's esophagus of 7% among persons with confirmed GERD, as compared with 1% among those without confirmed GERD.[13]

Although family history is a strong risk factor for Barrett's esophagus and leads to a diagnostic yield of 20 to 40%, it is uncommon and often poorly documented.[9,14] In the absence of a family history, the heritable contribution to risk, from multiple gene loci, is estimated to be approximately 20%. However, current polygenic risk scores are not sufficiently predictive to be incorporated into a clinical prediction tool.

How to Test?

Endoscopy is the recognized diagnostic standard and can be performed through the oral or transnasal route. Delineation of the landmarks of the gastroesophageal junction is required to distinguish Barrett's esophagus from a hiatal hernia. The extent of disease is measured from the top of the gastric folds with the use of the 10-cm markings on the endoscope and is recorded as the circumferential (C) and maximal (M) length

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Table 1. Steps in the Clinical Pathway of Barrett's Esophagus.*

Steps in Clinical Pathway	Description	Quality Indicators
Risk factors	A history of reflux symptoms and three of the following: White race, male sex, age of >50 yr, central obesity, tobacco use, or first-degree relative with Barrett's esophagus or esophageal adenocarcinoma	Barrett's esophagus and rate of detection of dysplasia or esophageal adenocarcinoma (neoplasia detection rate is inversely correlated with subsequent missed cancer)[11]
Diagnostic method	Triage with a nonendoscopic test in an office setting to increase access and uptake of the screening or diagnostic test; endoscopy and biopsy to determine endoscopic location and extent	Minimum inspection time of 1 min per cm of Barrett's esophagus Photographic documentation of landmarks Eight biopsies for initial diagnosis
Endoscopic dysplasia assessment	High-dose PPI used to heal any esophagitis High-definition white-light endoscopy with access to enhanced imaging (virtual or chromoendoscopy) to delineate focal changes and biopsies, including systematic biopsies Biopsy of all visible lesions and random four-quadrant biopsies for every 2 cm of Barrett's esophagus (Seattle protocol)	Prague criteria Paris classification for any visible lesions Adherence to Seattle protocol Audit of postendoscopy Barrett's neoplasia within 3 yr
Histopathological assessment	Assessment of intestinal metaplasia and any dysplasia (low grade, high grade, or indefinite) or cancer at each biopsy; consensus diagnosis of dysplasia by two independent pathologists Use of immunohistochemical staining for TP53 to confirm inflammatory or malignant changes if any dysplasia is suspected	Intestinal metaplasia and dysplasia status reported for each level (recorded in centimeters) of Barrett's esophagus biopsied Audit of postendoscopy Barrett's neoplasia within 3 yr

* PPI denotes proton-pump inhibitor, and TP53 tumor protein p53.

A video showing endoscopy in a patient with Barrett's esophagus is available at NEJM.org

in accordance with the Prague classification criteria (Fig. 1 and video).[15] Multiple biopsy samples should be taken from the distal esophagus to confirm the diagnosis of Barrett's esophagus; otherwise, intestinal metaplasia may be missed owing to tissue heterogeneity.

Because many cases of Barrett's esophagus are undiagnosed, interest in less invasive triage tests that are more suited to large-scale testing has increased. Prospective, multicenter studies have shown good accuracy of nonendoscopic cell-collection tools coupled with morphologic protein-based markers for detecting Barrett's esophagus, with emerging data on methylation biomarkers.[16-20] In one community-based, pragmatic trial of a nonendoscopic triage test, participants at increased risk of Barrett's esophagus (>50 years of age and receiving acid-suppressing agents for >6 months) were randomly assigned to either the intervention group (in which participants were invited to undergo a screening triage test followed by endoscopy if the screening test was positive for trefoil factor 3) or the usual-care group (in which participants only underwent endoscopy if deemed clinically indicated by their primary care doctor) to determine whether the offer of a screening test increases the detection of Barrett's esophagus.[21] The screening test entails swallowing a capsule, which is tethered to a thread, that dissolves over a few minutes and releases a spherical sponge. The sponge is then withdrawn through the mouth to collect a pan-esophageal sample of cells that are analyzed for evidence of intestinal metaplasia with the use of a trefoil factor 3 protein biomarker. In an intention-to-treat analysis (i.e., including all the participants whether they accepted or did not accept the offer of a screening test), 140 of the 6834 participants (2.0%) in the intervention group and 13 of the 6388 participants (0.2%) in the usual-care group received a diagnosis of Barrett's esophagus during an average follow-up of 12 months (rate ratio adjusted for cluster randomization, 10.6; 95% CI, 6.0 to 18.8; P<0.001). Among the 221 participants in the intervention group with a positive triage test who underwent endoscopy, 131 (59.3%) received a diagnosis of Barrett's esophagus or cancer. For comparison, a national cross-sectional analysis involving patients with symptomatic reflux who were referred by their family practitioner to undergo gastroscopy without a triage test calculated a diagnostic yield for Barrett's esophagus of 4.1%.[22]

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TREATMENT

Control of reflux does not regress Barrett's esophagus but is important for improvement in quality of life and reduction of inflammation-related complications, including stricture. Proton-pump inhibitor (PPI) treatments generally provide effective control of reflux symptoms. Results from five prospective cohort studies involving more than 2 million participants in China, the United Kingdom, and the United States showed that there are long-term adverse effects of PPI use that have dose–response relationships[23]; therefore, a risk-stratified approach is recommended. In a double-blind, randomized trial involving 17,598 patients who received either a PPI or placebo, enteric infection occurred in 1.4% of the patients in the PPI group and in 1.0% of those in the placebo group and was the only clear safety event associated with PPI use.[24] For patients with proven reflux with unacceptable side effects from medication or who do not have a response to medication, antireflux surgery is a good alternative.

Treatment to remove the segment affected by Barrett's esophagus is reserved for patients with histopathologically confirmed dysplasia or early-stage (T1) adenocarcinoma associated with Barrett's esophagus. The techniques are physical rather than medicinal, and the choice and combination of techniques will depend on the focality of the lesion, the depth of invasion, the length of the overall segment, the skills and equipment available, and the physical fitness of the patient to undergo the procedure (Fig. 2). Randomized, controlled trials have shown that endoscopic therapy with radiofrequency ablation substantially decreases the risk of malignant progression in patients with low-grade dysplasia and in those with high-grade dysplasia with no visible lesions.[25,26] In addition, large, multicenter case series have shown that endoscopic resection techniques for focally delineated lesions combined with radiofrequency ablation for residual Barrett's esophagus lead to good oncologic control.[25-27] In a report comparing endoscopic eradication therapies (radiofrequency ablation and the historical photodynamic therapy) with surveillance, the relative risk of disease progression among patients with high-grade dysplasia receiving therapy was 0.42 (95% CI, 0.24 to 0.73; P=0.002) with direct evidence from two randomized, controlled trials and 0.22 with indirect evidence; the relative risk of disease progression among patients with low-grade dysplasia receiving therapy was 0.16 and 0.14, respectively.[28] Because radiofrequency ablation is associated with side effects, including stricture in approximately 5% of patients, this treatment is not recommended for patients with nondysplastic Barrett's esophagus.

"Indefinite for dysplasia" is a term used when grading of the histologic features of the biopsy specimen is difficult, such as with inflamed nondysplastic epithelium. In such cases, repeat biopsies are performed after administration of high-dose acid-suppressing medication to ensure that high-grade dysplasia is not missed. Immunohistochemical staining for tumor protein p53 (TP53) in the affected tissue can be a useful adjunct to distinguish true dysplasia from reactive changes; strong associations between an abnormal or aberrant immunostain for p53 and progression to high-grade dysplasia or cancer have been shown[29] (Fig. 1).

For early-stage (T1) adenocarcinoma, determining the depth of invasion is important because the risk of lymph-node metastases increases sharply as the disease breaches the deeper submucosal layers (layers SM2 or SM3). This fact is especially true if differentiation is poor or invasion of the lymphovascular space is present (Fig. 2).[30] If a biopsy does not determine the depth of invasion, an endoscopic mucosal resection can aid diagnosis and is generally more informative than endoscopic ultrasonography.[31]

After resection or radiofrequency ablation of the Barrett's esophagus–affected segment, acid-suppressing therapy is administered for healing and to maintain the squamous re-epithelialization. Thereafter, ongoing surveillance with high-definition white-light endoscopy and virtual chromoendoscopy is recommended to detect recurrence; the chance of recurrence of histopathological evidence of intestinal metaplasia is 8%, and the chance of recurrence of dysplasia is 2%.[27]

MONITORING FOR AND PREVENTION OF FUTURE CANCER

Most patients with Barrett's esophagus have nondysplastic disease, and their lifetime risk of the development of cancer is low; however, the estimates vary widely, from 0.12% per year to 11.8% per person-year of follow-up, depending on the case selection (Table 2). For example, a

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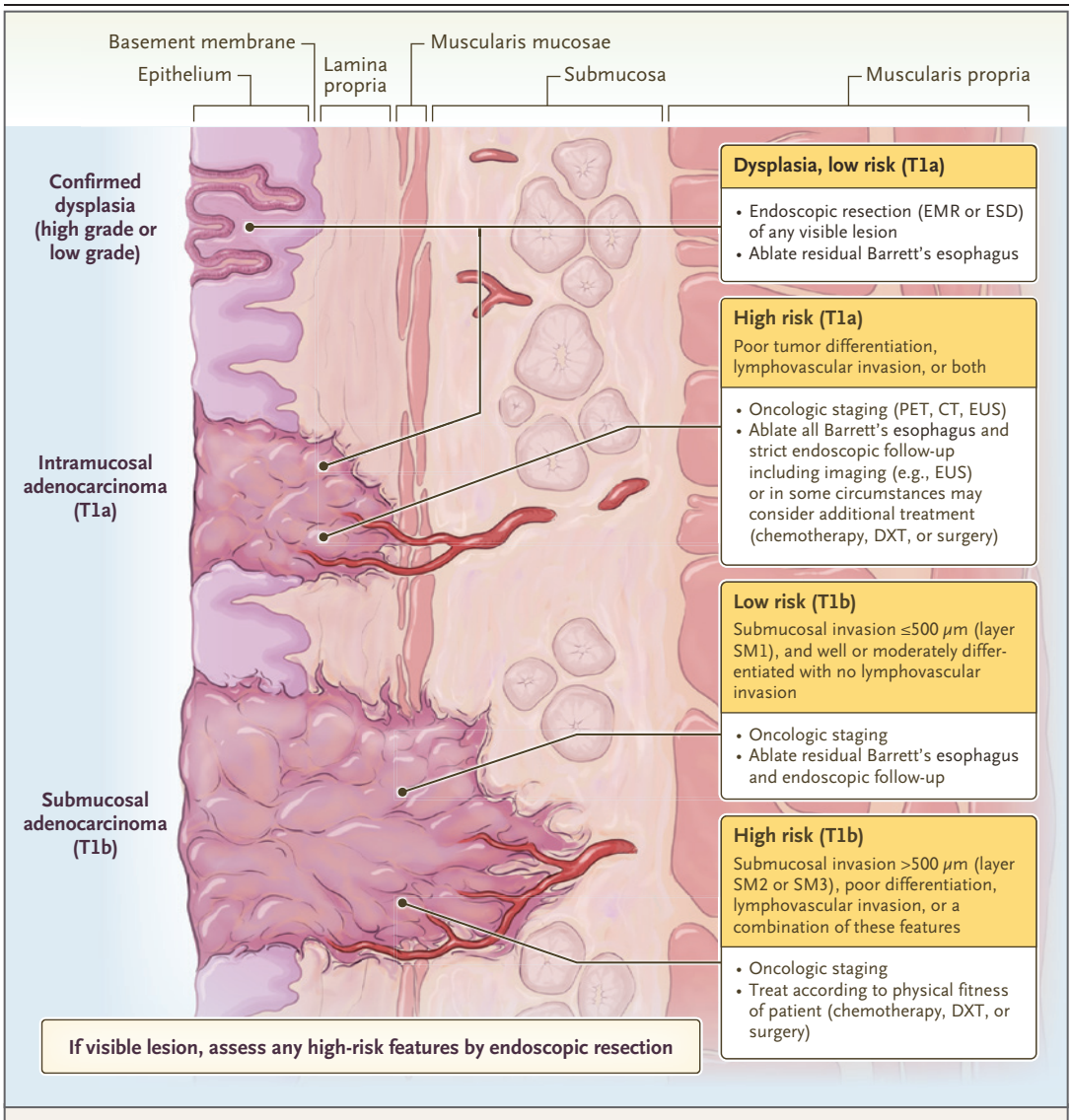

Figure 2. Disease Extent, Features, and Therapy Recommendations in Barrett's Esophagus.

The diagram shows the criteria for assessing the extent of disease and any high-risk features in Barrett's esophagus, as well as subsequent therapy recommendations. The endoscopic resection may entail cap-assisted mucosal resection for lesions less than 20 mm deep that are confined to the mucosal layer or submucosal dissection for deeper lesions (>20 mm) and those suspicious for submucosal invasion (type 0–Is [polypoid or sessile and broad-based] or 0–IIc [superficially depressed] according to the Paris classification) or in fibrotic areas. Pathological information cannot be obtained after ablation therapy; therefore, close follow-up with biopsies is warranted. Additional oncologic treatment should be considered after endoscopic resection in cases of a tumor-positive deep (vertical) resection margin. All treatment decisions should be discussed among members of a multidisciplinary team and will be influenced by patient physical fitness and choice. CT denotes computed tomography, DXT external beam radiation therapy, EMR endoscopic mucosal resection, ESD endoscopic submucosal dissection, EUS endoscopic ultrasonography, and PET positron-emission tomography.

Danish population study used pathological records to identify patients with intestinal metaplasia without confirming that a measurable columnar segment was present,[32] whereas a study assessing data from the United Kingdom General Practice Research Database included patients without intestinal metaplasia on the basis of the broader definition of Barrett's esophagus

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in the United Kingdom.[33] Regarding the rate of progression from dysplasia to cancer, two randomized trials had stricter inclusion criteria, with consensus review by pathologists with experience in Barrett's esophagus,[25,38] than the inclusion criteria in an observational cohort study,[36] which reflects the diagnostic variability in routine practice. The highest rates of progression from nondysplastic Barrett's esophagus to cancer were seen in a dedicated registry of patients with Barrett's esophagus who underwent endoscopy with the use of enhanced imaging techniques.[37]

Although the absolute risks associated with Barrett's esophagus are low, one study showed a standardized incidence ratio, with respect to risk of progression to cancer, of 11.3 (95% CI, 8.8 to 14.4) among patients with Barrett's esophagus as compared with the general population.[32] Because the consequences of a symptomatic esophageal cancer are grave, continued endoscopic surveillance of Barrett's esophagus is an important consideration, even though high-grade evidence to support its efficacy at reducing adverse cancer outcomes is lacking.

A case–control trial involving a single health care provider in a community setting showed that surveillance within 3 years after a previous endoscopy checkup was not associated with a decreased risk of death from esophageal adenocarcinoma (adjusted odds ratio, 0.99; 95% CI, 0.36 to 2.75).[41] Patients with Barrett's esophagus who died from esophageal carcinoma were nearly as likely to have undergone surveillance (55.3%) as patients in the control group who had Barrett's esophagus and survived (60.4%).[41] On the other hand, a meta-analysis of 12 cohort studies showed lower mortality related to esophageal carcinoma and that related to any cause among patients with surveillance-detected esophageal carcinoma than among those with symptom-detected esophageal carcinoma (relative risk, 0.73 [95% CI, 0.57 to 0.94]; hazard ratio, 0.59 [95% CI, 0.45 to 0.76]).[42] Although surveillance was associated with detection of esophageal cancer at earlier stages, adjustment for lead-time bias and length-time bias substantially attenuated the observed benefits.[42]

The BOSS (Barrett's Oesophagus Surveillance vs. Endoscopy at Need Study) trial, which was a randomized trial involving 3453 patients that assessed surveillance endoscopy performed every 2 years as compared with endoscopy performed as needed, showed no substantial difference in cancer-detection rates or mortality between the two groups; of 40 patients in the surveillance group who received a diagnosis of esophageal adenocarcinoma, 22 died from their cancer.[35] The absolute rate of death from esophageal adenocarcinoma was 131 per 100,000 person-years — approximately 4.5 times the national average in the United Kingdom among persons 50 to 79 years of age.[43] Among 38 patients with available data on cancer stage who were undergoing surveillance, 20 (53%) had stage II or higher disease, meaning that they had missed the opportunity for endoscopic therapy. The varying quality of endoscopy was a concern in the BOSS trial as well as in other studies, which showed up to 10 to 20% risk of postendoscopy Barrett's neoplasia, defined as an esophageal adenocarcinoma diagnosis in the 12 months after patients underwent surveillance endoscopy for Barrett's esophagus.[44] In a systematic review and meta-analysis, neoplasia detected at or within 6 months after an index endoscopy accounted for substantially more cases of Barrett's neoplasia (high-grade dysplasia or cancer) than that detected before the next surveillance interval or 36 months after a negative endoscopy.[45] This finding is inversely correlated with rates of neoplasia detection, which suggests that how often an endoscopist or endoscopy center diagnoses dysplasia or cancer during surveillance could be a useful endoscopy quality indicator.[44]

Surveillance involves an endoscopic assessment for visible evidence of possible dysplasia and cancer coupled with systematic biopsies for microscopic changes (a biopsy sample of visible abnormal areas and four biopsy samples for every 2 cm of the segment with Barrett's esophagus are recommended) (Table 1). Additional tools currently under evaluation include wide-area transepithelial sampling with three-dimensional analysis (WATS 3D), which obtains a wide-area and deep cytologic sample of the mucosa during endoscopy that is analyzed with a three-dimensional reconstruction of the pathologic features with the use of artificial intelligence (AI).[46] Biomarkers are another approach to augment the histopathological diagnosis. The Tissue Systems Pathology Test (TSP-9 or TissueCypher) is commercially available and includes TP53 among the 15 protein features that are classified. A pooled analysis of

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Table 2. Progression of Barrett's Esophagus According to Study Type and Baseline Criteria for Inclusion.*

Study	Context	Follow-up	Baseline	End Points	Percent Progressed per Year†
		yr			
Population studies with case ascertainment dependent on real-world coding					
Hvid-Jensen et al.[32]	Danish pathological registry (11,028 patients)	Median, 5.2	Pathologic intestinal metaplasia	Esophageal adenocarcinoma	0.12
Krishnamoorthi et al.[33]	United Kingdom General Practice Research Database (9660 patients)	Mean, 4.8	Diagnostic code for Barrett's esophagus	Esophageal adenocarcinoma	0.223
Bhat et al.[34]	Northern Ireland Barrett's Esophagus Register (8522 patients)	Mean, 7	Nondysplastic disease or low-grade dysplasia	High-grade dysplasia or esophageal adenocarcinoma	0.38
Randomized trial comparing surveillance and endoscopy as needed in real world					
Old et al.[35]	Multicenter trial in the United Kingdom (3453 patients)	Median, 12.8	Nondysplastic disease or low-grade dysplasia	High-grade dysplasia or esophageal adenocarcinoma	0.164
Historical cohort study					
Wani et al.[36]	Multicenter, retrospective study in the United States (1204 patients)	Mean, 5.5	Nondysplastic Barrett's esophagus	High-grade dysplasia or esophageal adenocarcinoma	0.63
Contemporary, single-center, longitudinal study					
Honing et al.[37]	Involved endoscopists trained on enhanced imaging and biopsy review by expert pathologists (969 patients)	Median, 5.8	Nondysplastic Barrett's esophagus or low-grade dysplasia	High-grade dysplasia or esophageal adenocarcinoma	1.63
Retrospective analysis of randomized trial					
Duits et al.[38]	Patients screened for SURF trial (255 patients)	Median, 3.5	Low-grade dysplasia detected at baseline	High-grade dysplasia or esophageal adenocarcinoma	
Low-grade dysplasia confirmed by one pathologist					2.4
Low-grade dysplasia confirmed by two endoscopies					9.28

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Randomized trial of radiofrequency ablation efficacy					
Phoa et al.[39]‡	European multicenter trial (68 patients)	3	Low-grade dysplasia	High-grade dysplasia or esophageal adenocarcinoma	11.8
Shaheen et al.[25]‡	United States (43 patients)	1	Low- or high-grade dysplasia	Esophageal adenocarcinoma	9.3
Meta-analysis of four previously published studies					
Rastogi et al.[40]	Previously diagnosed high-grade dysplasia (236 patients)	Mean, 5.3	High-grade dysplasia	Esophageal adenocarcinoma	5.57

* SURF denotes Surveillance versus Radiofrequency Ablation.
† The percent progressed per year was calculated for each study by dividing the number of patients with a change from the baseline to the end point pathologic status by the years of follow-up and is expressed as a percentage. The baseline status and the end point status for each study are shown in separate columns. For randomized trials evaluating a therapy, the control group (i.e., sham treatment) was used to avoid confounding by treatment. The standardized percent progressed per year enables a comparison between different study designs and between progression from different dysplasia statuses at baseline.
‡ The data shown were extrapolated from the control group.

data from 552 patients showed that the test could predict progression to high-grade dysplasia or adenocarcinoma with an odds ratio of 6.0 (95% CI, 2.9 to 12.0) and high specificity (94%), although sensitivity was low (38%).[47]

A sensitive triage test could be an alternative approach to risk stratification and could improve the efficacy of surveillance by allowing the endoscopist to focus on higher-risk cases. One such test comprises the assessment of clinical risk factors (age, sex, and segment length) and cellular biomarkers (TP53 and atypia) tested on cells collected from a nonendoscopic device that uses a sponge-containing capsule to determine whether patients are at low, moderate, or high risk for dysplasia or cancer. The test was shown to have an area under the receiver operating characteristic curve of 91% (95% CI, 86 to 95) for high-grade dysplasia or cancer (sensitivity, 80% [95% CI, 66 to 91]; specificity, 87% [95% CI, 83 to 91]) in a prospective validation study.[48] When administered to 910 patients in a real-world implementation study, the test identified 138 patients (15.2%) at high risk for dysplasia or cancer who could be triaged immediately for endoscopy; any neoplasia (low- or high-grade dysplasia or cancer) was detected in 52 (37.7%) of these patients. The biomarker type and combination are highly predictive; among 27 patients who had both positive TP53 and cellular atypia, neoplasia occurred in 23 (85.2%; 95% CI, 65.4 to 95.1).[49] In contrast, 489 of the 910 patients (53.7%) were deemed to be at low risk according to the nonendoscopic test, and only 2 of these patients (0.4%) had high-grade dysplasia at follow-up (median, 35.9 months), with no cases of esophageal adenocarcinoma.[49]

Chemoprevention has been investigated as an alternative to surveillance and includes treatment with aspirin, statins, or antireflux medication. The strongest evidence is for PPIs, which were shown to reduce the risk of progression from Barrett's esophagus to neoplasia in a meta-analysis and in a randomized, controlled trial involving 2557 patients receiving either a low-dose PPI or a high-dose PPI (no placebo group was included).[50,51] In the randomized trial, the risk of death from any cause, cancer, or high-grade dysplasia was significantly lower among the patients receiving high-dose esomeprazole (40 mg twice daily) than among those receiving low-dose esomeprazole (20 mg once daily) at a me-

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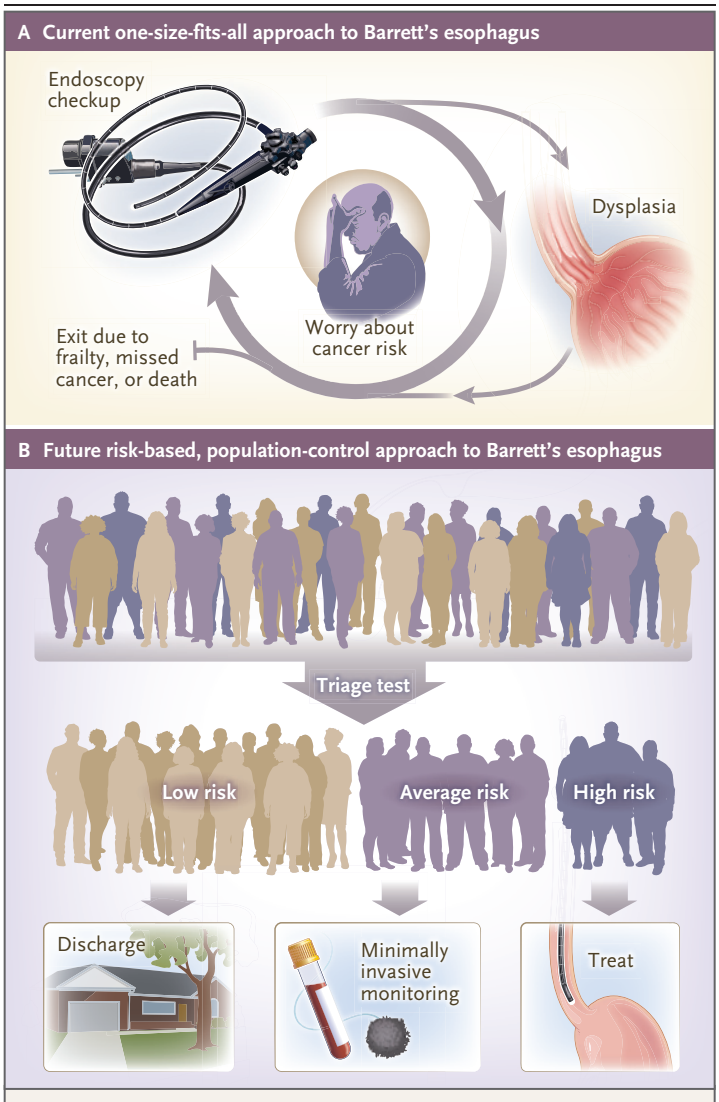

Figure 3. Current and Future Management of Barrett's Esophagus.

Panel A shows the current approach to managing Barrett's esophagus. The disease is diagnosed on a case-by-case basis, with patients entering a vicious circle of lifetime endoscopy checkups and treatment if dysplasia or early cancer is detected. Patients exit the circle if they become too frail for further checkups, have a missed cancer (i.e., an interval cancer diagnosed before the next cycle of surveillance) warranting systemic treatment, or die from another cause. Panel B shows a future risk-based, population-control approach to managing Barrett's esophagus. The population to be offered screening is enriched on the basis of risk factors. A triage test determines whether the patients in this population have a low, average, or high lifetime risk of cancer. The approach to management is tailored to each patient to minimize harm and maximize detection of dysplasia or stage I cancer.

dian of 8.9 years of follow-up (10.9% vs. 13.8%; P=0.04). At 8 years after randomization, 73% of the trial patients were still taking a high-dose PPI, although only 57% were still taking aspirin. A multinational and population-based cohort study did not show that antireflux surgery led to a lower risk of esophageal adenocarcinoma than antireflux medication.[52]

GUIDELINES

Societal guidelines recommend against screening for Barrett's esophagus in an unselected population. Patients with reflux and three additional risk factors (Table 1) are recommended to undergo a screening procedure (low-grade evidence)[53,54]; however, GERD is not a prerequisite (evidence not graded) for decision making with respect to screening according to the American Gastroenterological Association Clinical Practice Update.[55] The type of test can be endoscopy (reference standard, high-grade evidence) or a nonendoscopic cell-collection device (low-to-high-grade evidence, depending on the technology).[53,55]

Societal guidelines generally recommend surveillance once Barrett's esophagus is identified, and most societies recommend consideration of the segment length when the follow-up intervals are being determined, although the data on sojourn time are lacking (low-grade evidence).[53,54] Because of the low risk of progression associated with short segments, the value of surveillance is being questioned (low-grade evidence).[2,56]

Treatment is recommended for patients with confirmed dysplasia or cancer associated with Barrett's esophagus (high-grade evidence), including eradication of all the remaining epithelium affected by Barrett's esophagus after endoscopic resection (moderate-grade evidence). None of the societies recommend endoscopic therapy for nondysplastic Barrett's esophagus (very-low-grade evidence).[56]

AREAS OF UNCERTAINTY AND FUTURE RESEARCH

Research is warranted to understand germline predisposition and influences of ancestry on the risk of Barrett's esophagus and progression to cancer. With the advent of nonendoscopic cell-collection tools, a large randomized trial (ISRCTN Registry number, ISRCTN85044808) is assessing whether screening is warranted in a targeted population enriched for age, sex, and symptoms. Blood-based biomarkers could provide an alternative screening method that is even less invasive, although their sensitivity for early-stage disease

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KEY POINTS

BARRETT'S ESOPHAGUS

- Barrett's esophagus occurs in response to damage from acid and bile reflux and is associated with an increased risk of adenocarcinoma.
- No specific symptom is associated with Barrett's esophagus; therefore, most patients do not receive a diagnosis, or they present with symptoms of gastroesophageal reflux disease and other associated risk factors or complications.
- The diagnosis is based on endoscopic and histopathological features, including a visible columnar-cell–lined segment measuring at least 1 cm long that contains a mosaic of gastric and intestinal cells that must include goblet cells.
- Ongoing monitoring focuses on identifying and stopping malignant progression through early detection of lesions (such as high-grade dysplasia and early-stage cancer) for curative endoscopic therapy without the adverse effects associated with chemotherapy or esophagectomy.
- Participation in clinical trials to inform better case ascertainment and risk stratification should be encouraged.

needs to be prospectively evaluated in the target population.[57]

An ongoing European, multicenter, prospective cohort study (ClinicalTrials.gov number, NCT03222635) is evaluating an endoscopic, surgery-sparing approach for the surveillance of stage T1b disease with the use of an intense imaging regimen. The SURVENT (Surveillance vs. Endoscopic Therapy for Barrett's Esophagus with Low-Grade Dysplasia) randomized trial is under way to assess whether surveillance could be a safe alternative to ablative therapy in patients with low-grade dysplasia; risk stratification biomarkers are also being evaluated (NCT05753748).[58]

AI shows promise for assisting with endoscopic and pathological assessment of Barrett's esophagus. However, further studies are warranted to understand the performance of AI as compared with state-of-the-art imaging or tissue biomarkers.[59]

In the future, coupling an effective baseline screening method with risk stratification and an upfront decision to discharge or treat the patient could reduce population mortality while avoiding ongoing monitoring for most patients with Barrett's esophagus (Fig. 3). However, the efficacy of this approach needs to be proved in prospective trials. Potent risk stratification probably warrants an objective evaluation of the molecular status of the metaplastic epithelium. Given the socioeconomic disparities that lead to early-onset, aggressive disease coupled with barriers to screening and surveillance, an approach to diagnosis and prevention that is accessible is needed.

CONCLUSIONS AND RECOMMENDATIONS

Because the patient in the vignette has GERD and several other risk factors for Barrett's esophagus — such as male sex, older age, history of smoking, overweight, and heartburn — I would recommend a diagnostic test with either direct endoscopy or a nonendoscopic triage test, depending on the patient's preference and the resources available. His symptoms are interfering with his quality of life; therefore, a review of behaviors and medications would be useful to address causes of reflux that can be modified. Potent and continuous antireflux medication could ensure adequate control of symptoms; if medication is unsuccessful, then surgical antireflux options could be considered. If a diagnosis of Barrett's esophagus is made, a careful explanation of the disease should be given with a recommendation to undergo surveillance at intervals determined by the length of the affected segment (3 years for a segment of ≥3 cm and 5 years for a short segment of 1 to <3 cm) or treatment if dysplasia is identified and confirmed. Decision making should be based on the low lifetime risk for cancer and the effectiveness of treatment for early disease identified during surveillance. Apart from PPIs, there is no evidence that treatment with aspirin or statins will reduce the risk of cancer and obviate the need for monitoring.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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