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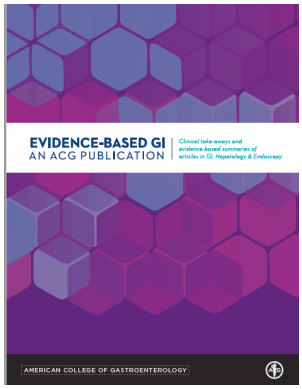

The American College of Gastroenterology (ACG) is an international organization with more than 14,000 physician members representing some 85 countries. The College's vision is to be the pre-eminent professional organization that champions the evolving needs of clinicians in the delivery of high-quality, evidence-based and compassionate health care to advance world-class care for patients with gastrointestinal disorders through excellence, innovation, and advocacy in the areas of scientific investigation, education, prevention, and treatment. *Evidence-Based GI* is a member publication of the American College of Gastroenterology.

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EDITORIAL

In Case You Missed It: A New EBGI Series

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Philip Schoenfeld, MD, MSEd, MSc (Epi)
Editor-in-Chief

Welcome to a new series, *In Case You Missed It*, which will summarize landmark randomized controlled trials (RCTs) from the past 3-5 years that impact clinical practice guidelines. Consistent with our mission at Evidence-Based GI, summaries will focus on RCTs published in non-GI journals (e.g., *New England Journal of Medicine, JAMA, Annals of Internal Medicine*, etc.) and provide structured abstracts about study design and results.

As I noted in my introductory editorial from October 2021, *Evidence-Based GI* is a work in progress where the content may change over time. This new series arose because our Associate Editors wanted to highlight seminal RCTs that changed recent clinical practice guidelines, regardless of whether or not they were published in the past 12 months. Emphasizing this research is worthwhile since compliance with clinical practice guidelines is often sub-optimal. For example, Dr. Swati Patel's summary of the ground-breaking PLCO study reminds us that average-risk individuals with 1-2 non-advanced adenomas have similar risk of colorectal cancer (CRC) as average-risk individuals with no adenomas.[1] This study, which was published in *JAMA* in 2018, was critical to the 2020 US Multi-Society Task Force on CRC recommendation that extended surveillance intervals from 5-10 years to 7-10 years among average-risk individuals with 1-2 non-advanced adenomas.[2] Yet, multiple studies show that

endoscopists frequently recommend intervals shorter than 5 years for these individuals.[3]

Although strong guideline recommendations should be applied to most patients, we also recognize that mindless application of RCT results to patient care is sub-optimal or even harmful. Thus, appropriate application of evidence-based medicine (EBM) recognizes the importance of the other "EBM": experience-based medicine. Therefore, these summaries provide standardized commentary, including sections such as "Caution," which discusses study limitations, as well as "My Practice," which describes how our Associate Editors combine evidence and experience to the treatment of individual patients.

We continue to make adjustments in format and presentation. Over the past 3 months, Joseph Sleiman, MD, our Associate Editor for Social Media, has expanded our outreach with weekly tweetorials. We're reaching out directly to GI fellows and GI fellowship program directors since Evidence-Based GI is a great resource for their journal clubs. I continue to welcome your comments and feedback and thanks for reading.

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COLORECTAL CANCER

In Case You Missed It

Wait 7-10 Years for Repeat Colonoscopy If You Only Find 1-2 Small Adenomas... It's Not Too Long!

Swati G. Patel, MD, MS

Associate Professor of Medicine, University of Colorado School of Medicine, Rocky Mountain Regional Veterans Affairs Medical Center, Aurora, Colorado

This summary reviews Click B, Pinsky PF, Hickey T, Doroudi M, Schoen, RE. Association of Colonoscopy Adenoma Findings with Long-Term Colorectal Cancer Incidence. JAMA 2018; 319(19): 2022-2031.

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STRUCTURED ABSTRACT

Question: Is the long-term risk of colorectal cancer (CRC) different between individuals with 1-2 non-advanced (<10mm) adenomas vs no adenomas?

Study Design: Multi-center, prospective cohort from the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Study. This study only examines PLCO patients randomized to receive flexible sigmoidoscopy and had a polyp or mass found and subsequently completed a colonoscopy.

Setting: Participants were recruited from 1993-2001 from 10 centers participating in PLCO.

Patients: Average-risk 55-74-year-olds who had a polyp or mass in the distal colon on flexible sigmoidoscopy, and then completed a follow up colonoscopy were included. Participants diagnosed with cancer at time of colonoscopy and those with no follow up time were excluded. Of the 15,935 participants included, 2,882 participants (18.1%) had an advanced adenoma, 5,068 participants (31.8%) had non-advanced adenomas, and 7,985 participants (50.1%) had no adenoma (i.e., hyperplastic polyp or no polyp found at colonoscopy). The median age was 64 (IQR: 61-68), 59.7% were men, 90.7% were White, and median follow up was 12.9 years (IQR: 9.8-15).

Exposure: Index colonoscopy with no adenoma, 1-2 non-advanced adenomas (< 10 mm) or advanced adenoma (adenoma ≥ 10 mm, with high-grade dysplasia or villous architecture).
Outcomes: Primary outcome was CRC incidence within 15 years of baseline colonoscopy. Secondary outcome was CRC mortality.
Results: Over a median 12.9 years of follow up, CRC incidence per 10,000-person years was 20.0, 9.1, and 7.5 in those with advanced adenomas, non-advanced adenomas, and no adenomas, respectively. Cumulative incidence of CRC over 15 years was 2.9%, 1.4%, and 1.2%, respectively, in those groups. Although those with advanced adenomas were significantly more likely to develop CRC (relative risk = 2.7; 95% CI: 6.7-11.5) compared to those with no adenoma, there was no significantly increased risk of CRC in those with non-advanced adenomas compared to those with no adenomas (RR = 1.2; 95% CI: 0.8-1.7) (Figure 1). The cumulative CRC incidence was similar between individuals with non-advanced adenomas and no adenomas at 5 years, 7 years, and 10 years from index colonoscopy (illustrated in Figure 2 of Click et al). The risk of CRC mortality was significantly increased in those with advanced adenomas (RR 2.6, 95% CI 1.2-5.7) compared to those with no adenomas. Again, those with non-advanced adenomas were not at increased risk of mortality compared to those with no adenomas (Figure 1).
Funding: National Cancer Institute.

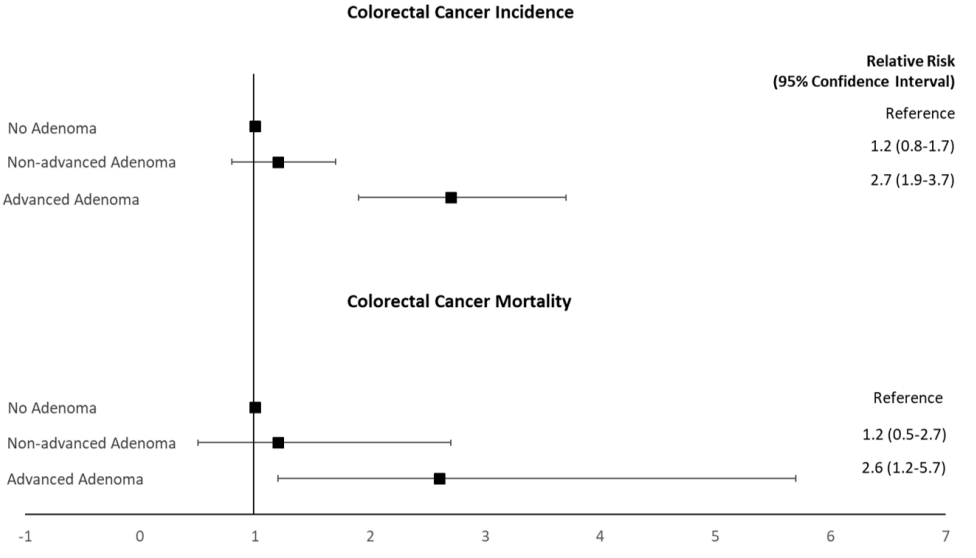

Figure 1. Relative Risk of CRC and CRC Mortality based on adenoma findings

COMMENTARY

Why Is This Important?

This research, along with 2 meta-analyses and European cohort studies, provide the foundation for the United States Multi-Society Task Force on Colorectal Cancer recommendation in 2020 to extend surveillance intervals to 7-10 years for average-risk individuals with 1-2 small or non-advanced adenomas on index screening colonoscopy.[1] The PLCO study was crucial because its large size (n = 15,935), prolonged follow-up (median 12.9 years), and comprehensive follow-up (93.8% compliance with annual study update on health) provided precise estimates of CRC incidence in the no adenoma and 1-2 small adenoma group.

Key Study Findings

Patients diagnosed with 1-2 non-advanced adenomas have the same long-term risk of colorectal cancer and death from colorectal cancer as those with no adenomas (Figure 1). Those with advanced adenomas have a 2.7-fold increased risk of developing CRC and a 2.6-fold increased risk of dying from CRC.

Caution

There was insufficient data to draw a conclusion about whether patients with three or more adenomas have an increased risk of CRC. This study was also conducted in an era before there was a strong commitment to colonoscopy quality (before split-dose bowel preparations, high-definition colonoscopes, adenoma detection monitoring, serrated lesion detection monitoring, endoscopic mucosal resection techniques). Most importantly, use of surveillance colonoscopy was only tracked for 21.9% of the study population, and surveillance colonoscopy was used more frequently in patients with 1-2 small adenomas (78.1%) vs individuals with no adenomas (69.9%). So, differences in use of surveillance colonoscopy could partly account for similarity of CRC incidence in these groups.

My Practice

This high-quality study, along with other recent meta-analyses and European cohort studies cited in the 2020 USMSTF on CRC Screening Guideline, I strongly support extending surveillance intervals for those with 1-2 small

tubular adenomas. If a patient has undergone a high-quality colonoscopy (adequate bowel preparation, complete to cecum, high-adenoma detection rate provider, complete polyp resection), I recommend 7-year surveillance for those with 1-2 small adenomas and additional risk factors (male sex, smokers, metabolic syndrome/diabetes, obesity, > age 60) and 10-year surveillance for those without additional risk factors and under age 60.

For Future Research

Validation that 1-2 small adenomas truly confer low risk of future CRC through a prospective randomized controlled trial of different surveillance intervals is currently underway (the FORTE trial, NCT05080673). We also still need studies to assess long-term CRC risk in patients with three or more small tubular adenomas and studies in the contemporary era of high-quality colonoscopy to validate whether intensive surveillance of advanced adenomas is still warranted.

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In Case You Missed It

It's (Usually) OK to Wait Until Morning to Scope that Patient with UGI Bleeding

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This article reviews Lau JYW, Yu Y, Tang RSY, et al. Timing of Endoscopy for Acute Upper Gastrointestinal Bleeding. N Engl J Med 2020; 382: 1299-308. doi: 10.1056/NEJMoa1912484

Correspondence to Philip Schoenfeld, Editor-in-Chief. Email: EBGI@gi.org

STRUCTURED ABSTRACT

Question: Is urgent esophagogastroduodenoscopy (EGD) (within 6 hours of GI evaluation) superior to early EGD (within 24 hours of GI evaluation) for reducing all-cause mortality or further GI bleeding in high-risk patients with melena or hematemesis?
Design: Single-center, randomized controlled trial.
Setting: Prince of Wales Hospital, Shatin, Hong Kong. Investigators from Institute of Digestive Diseases, Chinese University of Hong Kong.
Patients: Inpatients with overt acute upper gastrointestinal bleeding (UGI; hematemesis, melena, or both) and high risk for death and/or further bleeding based on a Glasgow-Blatchford bleeding score of 12-23 were randomized. The Glasgow-Blatchford bleeding score is based on heart rate, systolic blood pressure, hemoglobin, blood urea nitrogen, presentation with melena or syncope, and presence of cardiac failure and/or hepatic disease and risk stratifies patients on need for blood transfusion and endoscopic intervention. All patients received appropriate initial resuscitation with intravenous fluids and/or transfusion plus IV proton pump inhibitors with 80mg bolus plus 8mg/hour continuous infusion. Patients in hypotensive shock despite resuscitation were excluded.

Interventions/Exposure: Urgent EGD within 6 hours of GI consultation vs early EGD within 24 hours of GI consultation. In the early EGD group, patients who had their initial GI consultation between 8 AM and 11:59 PM underwent endoscopy the following morning.
Outcome: The primary endpoint was 30-day all-cause mortality rate. Secondary endpoints included persistent bleeding at conclusion of index endoscopy or recurrent bleeding (e.g., recurrent hematemesis, melena after normalization of stool color, new tachycardia or systolic hypotension, hgb drop of 2g/dl after hgb stabilizataion, etc), use of hemostatic interventions (e.g., hemoclips, contact thermocoagulation, band ligation for varices) during index endoscopy, duration of hospitalization and intensive care unit stay, blood transfusions, need for surgery or angiographic embolization, need for further endoscopic hemostatic treatment, and 30-day adverse event rate.
Data Analysis: Intention-to-treat analysis. Investigators achieved complete follow-up of patients with no missing data. Log-rank test used to compare time from randomization to death and/or further bleeding. Cox proportional hazards used to estimate hazard ratios.
Funding: The Health and Medical Fund of the Food and Health Bureau, Government of Hong Kong Special Administrative Region.
Results: There were 516 inpatients randomized (mean age: 70-71 years old; 63% male; average Glasgow-Blatchford bleeding score-13.7; 8.5% variceal bleed on index endoscopy; 61% peptic ulcer on index endoscopy). Due to a lag of approximately 8 hours between initial presentation with UGI bleeding (UGI) and GI consultation, this equated to patients getting EGD at means of 10 and 25 hours after presentation. *There was no advantage for urgent EGD vs early EGD for any primary or secondary endpoint* (Table 1), although endoscopic interventions were performed more commonly in the urgent-EGD group: 60.1% vs 48.4%; hazard ratio (HR)= 1.24 (95% confidence interval [CI]: 1.06-1.46). The study hypothesis was that urgent EGD would be beneficial. However, mortality rate and further bleeding rate were numerically lower in the early EGD group, although this was not a statistically significant difference.

Outcome (%)	Urgent EGD (n=258)	Early EGD (n= 258)	RR or Hazard Ratio (95% CI)
30-day all-cause mortality	8.9%	6.6%	1.35 (0.72-2.54)
Further Bleeding at 7 days	5.8%	5.4%	1.07 (0.53-2.17)
Further Bleeding at 30 days	10.9%	7.8%	1.46 (0.83-2.58)
Endoscopic hemostatic treatment at index endoscopy	60.1%	48.4%	1.24 (1.06-1.46)
Blood transfusion	89.5%	90.7%	0.99 (0.93-1.05)
Surgery or angiographic embolization	1.9%	1.2%	-
Median hospital duration	5 (4-9)	5 (3-8)	-

Table 1. 30-day all-cause mortality, further bleeding, and other secondary endpoints.
CI, confidence interval; EGD, esophagogastroduodenoscopy; RR, relative risk.

COMMENTARY

Why Is This Important?

Prior guidelines from the GI societies in the US, Europe, and Asia suggested that EGD within 12 hours should be considered in patients with UGI bleeding and hemodynamic instability at presentation in order to reduce mortality and further bleeding.[1] However, observational studies provide conflicting results about potential benefits of urgent EGD. Also, urgent EGD within 6 hours of presentation could be detrimental if adequate hemodynamic stabilization with IV fluids and stabilization of other chronic medical conditions hasn't been completed. Resolving this issue is crucial since acute UGI bleeding is the most common medical emergency faced by gastroenterologists. Thus, the landmark RCT conducted by Drs. Lau, Chan, Sung and their colleagues at the Chinese University of Hong Kong provides crucial data.

Their study results do not demonstrate any benefit for urgent EGD, especially among individuals with non-variceal UGI bleeding who can be stabilized hemodynamically. Primarily due to the results of this RCT, the 2021 ACG Clinical Guideline on Upper Gastrointestinal and Ulcer Bleeding[2] eliminated the suggestion from the 2012 ACG guideline that EGD within 12 hours "may be considered" in high-risk patients. Instead, the 2021 ACG guideline authors

emphasizes the importance of resuscitation with IV fluids and transfusion and stabilization of active co-morbid conditions before EGD is performed.

Key Study Findings

There was no advantage for urgent EGD vs early EGD for mortality or further UGI bleeding, which are the most important endpoints in this type of trial. Although endoscopic therapeutic interventions were performed more commonly in the urgent EGD group: 60.1% vs 48.4%; HR = 1.24 (95% CI: 1.06-1.46), this did not translate into a reduction in further UGI bleeding, which was numerically lower in the early EGD group.

Caution

This is a remarkably well-designed study with few limitations. Considering that about 8.5% (44/516) of study patients had esophageal or gastric varices and the natural history of acute esophageal variceal bleeding differs from peptic ulcer bleeding, these data may not be applicable to patients with a history of variceal bleeding or known cirrhotics. Also, this study excluded patients who had persistent "hypotensive shock" despite resuscitation attempts.

My Practice

My practice essentially mirrors the treatment of early EGD patients from this randomized controlled trial, which is also consistent with the conditional recommendation from the ACG Clinical Guideline on UGI and Ulcer Bleeding.[2] When a patient presents with melena or hematemesis plus tachycardia/systolic hypotension, then resuscitation with intravenous fluids and blood transfusion (threshold of hemoglobin < 7) to achieve hemodynamic stability is emphasized, regardless of time of day when I'm consulted. After hemodynamic stability is achieved, then EGD is performed within 24 hours of presentation. As per this RCT's "early-EGD" protocol, this usually means that EGD is performed around 8 AM on morning after presentation.

I'll perform EGD urgently if the patient doesn't become hemodynamically stable after appropriate resuscitation. If a patient has a history of esophageal variceal bleeding, then I may perform EGD sooner while still emphasizing cardiovascular resuscitation with intravenous fluids along with IV octreotide and IV ceftriaxone for presumed variceal bleed.

For Future Research

Data from well-designed randomized controlled trials about the efficacy of urgent endoscopy (within 6-12 hours) for patients with cirrhosis, past history of variceal bleeding, or persistent hypotensive shock despite resuscitation is lacking.

Conflict of Interest

Dr. Schoenfeld reports no conflicts of interest.

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ESOPHAGUS

In Case You Missed It

Low Grade Dysplasia in Barrett's Esophagus – Get Two Expert GI Pathologist Reviews and Repeat EGD After PPI Treatment

Shria Kumar, MD, MSCE[1] and Gary W. Falk, MD, MS[2]

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Shria Kumar, MD, MSCE
Associate Editor

Gary W. Falk, MD, MS
Contributing Writer

This article reviews: Vennalaganti P, Kanakadandi V, Goldblum JR, et al. Discordance Among Pathologists in the United States and Europe in Diagnosis of Low-Grade Dysplasia for Patients With Barrett's Esophagus. Gastroenterology 2017 Feb;152(3):564-570.e4.

Listen to thCorrespondence to Shria Kumar, MD, MSCE, Associate Editor. Email: EBGI@gi.org

STRUCTURED ABSTRACT

Question: How well do expert pathologists agree regarding the diagnosis of low-grade dysplasia (LGD) in Barrett's esophagus (BE)?

Design: First, 3 US-based expert pathologists discussed the diagnostic criteria for LGD, to distinguish inflammatory predominant vs dysplasia predominant LGD. Then, 7 experienced pathologists (4 from the US, 3 from Europe) reviewed pathology slides of patients with BE with varying degrees of dysplasia in a random and blinded fashion.

Setting: Seventy-nine randomly selected pathology slides were obtained from the Veterans Affairs Medical Center in Kansas City and the Cleveland Clinic Foundation.

Samples: Slides included 23 non-dysplastic BE, 22 LGD, and 34 high-grade dysplasia (HGD). Slides were selected in a manner to represent those normally seen in tertiary care centers. There was no accompanying clinical information, and no areas were marked. Slides were processed by standard protocols, similar to standard clinical care.

Interventions: The pathologists received slides in a random fashion, and were aware they were participating in a research study regarding dysplasia. Each

pathologist received a case report form to fill out per sample, which included the criteria for arriving at the diagnosis, the degree of weighting placed on each of the criteria, and the diagnosis: either non-dysplastic, LGD-dysplasia predominant, LGD-inflammation predominant, or HGD. Pathologists were also asked to indicate if they had "high confidence" in their diagnosis.

Outcomes: Inter-observer agreement was the primary outcome for the study. A second analysis was conducted to evaluate which histologic features influenced the final diagnosis.

Data Analysis: Inter-observer agreement was calculated and reported using the kappa statistic, κ. Table 1 depicts how the kappa statistic is interpreted. The second analysis was conducted via a multinomial logistic regression analysis, using histologic features as covariates and the grade of dysplasia as the outcome variable, with non-dysplastic BE as the reference category.

Results: Inter-observer agreement is depicted in Figure 1. The overall kappa value was moderate at 0.43 (95% CI, 0.42-0.48). LGD had the lowest level of agreement: 0.11 (95% CI, 0.004-0.15), followed by non-dysplastic BE: 0.22 (95% CI, 0.11-0.29), then HGD: 0.43 (95% CI, 0.36-0.46).

High-confidence in diagnosis improved inter-observer agreement somewhat to 0.57 (95% CI, 0.45-0.62. Notably, high confidence in diagnosis among the 3 European pathologists led to considerably higher inter-observer agreement 0.80 (95% CI, 0.74-0.97) compared to the 4 US pathologists: 0.63 (95% CI, 0.61-0.66). When stratified by degree of dysplasia, interobserver agreement was consistently higher among the European than the American pathologists.

In the logistic regression, the diagnosis of LGD was mainly associated with the presence of cytologic atypia, nuclear hyperchromasia, and nuclear crowding. HGD was associated with glandular crowding, cytological atypia, nuclear enlargement, and irregular nuclear contours. US based pathologists diagnosed inflammation predominant LGD, dysplasia predominant LGD, and HGD based on the presence of a median of 5, 6, and 7 criteria, respectively. European pathologists diagnosed inflammation predominant LGD, dysplasia predominant LGD, and HGD based on the presence of a median of 3, 4, and 5 criteria, respectively.

Funding: None.

Kappa statistic, κ	Interpretation
<0	Poor agreement
0.01 – 0.20	Slight agreement
0.21 – 0.40	Fair agreement
0.41 – 0.60	Moderate agreement
0.61 – 0.80	Substantial agreement
>0.80	Nearly perfect agreement

Table 1. How to interpret a Kappa statistic

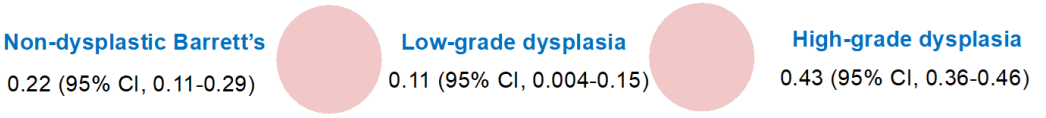

Figure 1: Inter-observer agreement between pathologists, by degree of dysplasia

COMMENTARY

Why Is This Important?

Endoscopic therapies for BE with dysplasia are a mainstay of BE treatment. At the same time, endoscopic eradication therapies are not indicated for non-dysplastic BE, so getting the diagnosis of dysplasia right is of paramount importance for treatment decisions. As endoscopic eradication therapy typically involves multiple endoscopies for ablation or endoscopic mucosal resection, and given the costs and risks associated with these procedures, accurate diagnosis of dysplasia is essential. An accurate diagnosis of the degree of dysplasia is also important in counseling patients for their risk of progression to esophageal adenocarcinoma. Multiple studies have found widely disparate rates of progression from LGD to cancer,[1,2] from <1%[3,4] to over 10%[5,6]. These wide ranges of progression rates make it difficult to both understand the natural history of LGD and offer patients appropriate risk estimates of progression.

It has been noted in particular that Barrett's esophagus patients in Europe with LGD have higher rates of progression than do patients in the US with LGD.[7] One hypothesis for these widely disparate rates is that LGD is difficult to diagnose, and there is not always pathologist consensus, due to the subjective nature of some LGD criteria, and the overlap between LGD and

inflammation and reactive changes. In fact, there is no clear gold standard for LGD, and there exist marked differences in LGD interpretation by pathologists in different geographic regions, and even academic vs. community based pathologists.[8] There are also some data to suggest that there may be overdiagnosis of LGD in the US, particularly among pathologists who are less among pathologists who are less experienced in BE,[9,10] and this overdiagnosis is accompanied a low risk of progression to HGD or esophageal adenocarcinoma. One study from the Netherlands demonstrated that expert review of histology specimens resulted in the downstaging of 73% of what were initially LGD specimens, to non-dysplastic BE.[11]

Recently, an updated ACG guideline on the Diagnosis and Management of Barrett's Esophagus was published.[12] It contains a strong recommendation to utilize endoscopic eradication therapy in patients with BE with HGD, but only a conditional recommendation for endoscopic eradication therapy in patients with BE with LGD. It further emphasizes that surveillance biopsy intervals are based on the degree of dysplasia. Importantly, although there is a low level of evidence in this arena, there is a strong recommendation to have dysplasia of any degree confirmed by a second pathologist with expertise in GI pathology. This underlines the notion that pathologic diagnosis is the cornerstone of esophageal adenocarcinoma prevention.

Key Study Findings

This is a well-designed study to evaluate the previously established observation that inter-observer agreement in LGD is poor, even among expert GI pathologists. The study demonstrates that LGD has the lowest inter-observer agreement for diagnosis, followed by non-dysplastic BE, and then HGD. Importantly, it demonstrates that European pathologists tend to have higher inter-observer agreement than their US counterparts. Lastly, it demonstrates that even with high confidence, inter-observer agreement regarding the degree of dysplasia is lacking.

Caution

Prior to having pathologists review slides, a consensus committee determined the criteria for LGD with predominantly inflammatory changes vs LGD with predominantly dysplastic changes. While inflammatory changes can muddle the diagnosis of LGD, it is not standard clinical practice to sub-divide LGD in

this manner, and pathologists had to elect one subtype of LGD. This may have led to a greater decrease in inter-observer agreement than would be normally seen in clinical practice. The selected slides also introduced some bias, and there was a high representation of HGD in the slides (43%). In routine clinical practice, non-dysplastic BE is the most common finding. Lastly, the pathologists were all experienced pathologists and were aware they were participating in a research study. This reduces the generalizability of the study findings – but with such low inter-observer agreement among experienced GI pathologists, the inter-observer agreement may be even lower, particularly among those not at high-volume BE centers.

My Practice

This study supports our own practice at our respective academic centers, where we ensure at least 2 expert GI pathologists review dysplasia diagnoses, particularly for LGD. After confirmation, patients with BE and LGD diagnoses are counseled carefully, taking into consideration personal risk factors, comorbidities, age, and overall health status. Repeat endoscopy is performed after 3 months of proton pump therapy (Figure 2 depicts our approach to patients with LGD who present to our practice). For patients with confirmed LGD, we recommend endoscopic eradication therapy to reduce the risk of progression to HGD or esophageal cancer, but also believe that endoscopic

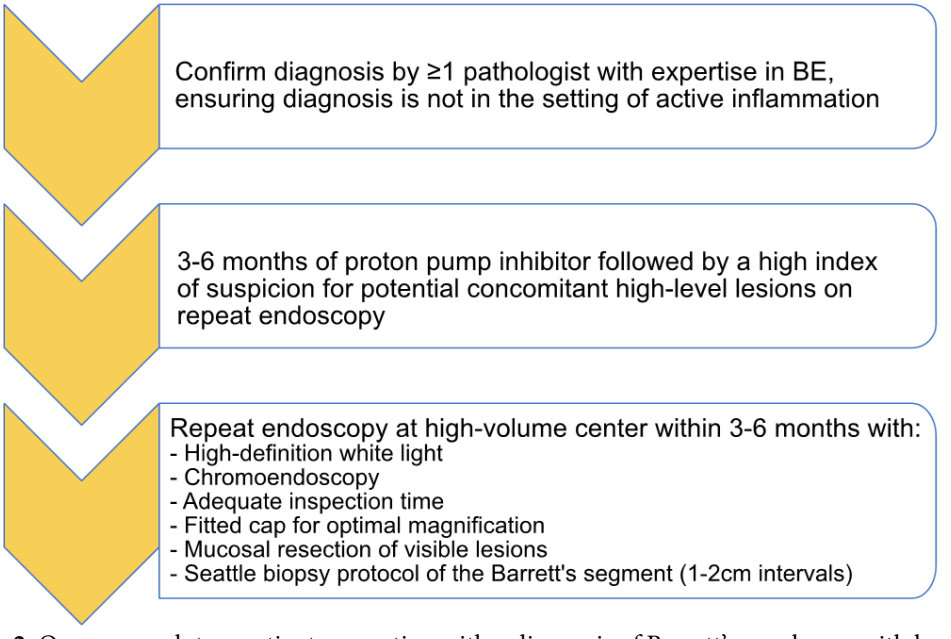

Figure 2: Our approach to a patient presenting with a diagnosis of Barrett's esophagus with low-grade dysplasia.

surveillance is an acceptable alternative.12 Overall, this study further supports our understanding of the literature, and backs a salient hypothesis for the widely variable rates of progression to HGD or esophageal cancer in persons with LGD, and reaffirms that the diagnosis of LGD is complex, but of paramount importance.

For Future Research

Newer methods of risk stratification for dysplasia management are on the horizon, and include assessment of p53 status,[13,14] a tissue systems pathology test (TissueCypher)[10], brushings with next generation sequencing (Barrett's Aneuploidy Decision),[15] and artificial intelligence.[16] At this time, however, accurate pathologic diagnosis remains the best risk-stratification tool we have. Effectively counseling patients and providing them with information so they can partake in shared decision making that is in line with their values requires accurate diagnosis, risk estimates, and considerations of the risks and benefits of therapy. In addition, conjunction, endoscopic examination and biopsy sampling can lessen the burden on pathologists for the diagnosis of dysplasia in BE. Future research should focus on bolstering accurate diagnosis of LGD, interrogating the differences between European and US pathologist diagnostic methods, developing tools for pathologists and gastroenterologists to provide optimal risk stratification, and dysplasia-guided therapies to minimize their risk of future cancer. The SURVENT Trial is a multi-center trial that will address many of these questions, and we look forward to its findings (A Multicenter Randomized Controlled Trial of Surveillance versus. Endoscopic Therapy for Barretts Esophagus with Low-grade Dysplasia, Project Number 1U34DK124174-01, www.clinicaltrials.gov).

Conflicts of Interest

G.W. Falk is a conclutant for Cernostics/Castle Biosciences, Lucid, Exact, Phathom, and CDX. S. Kumar has no conflicts of interest.

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EVIDENCE-BASED GI
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In Case You Missed It

Test and Treat *Helicobacter pylori* in First-Degree Relatives of Gastric Cancer Patients-Reduces Their Risk of Gastric Cancer

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This article reviews Choi IJ, Kim CG, Lee JY, et al. Family History of Gastric Cancer and Helicobacter Pylori Treatment. N Engl J Med 2020; 382: 427-36. doi: 10.1056/NEJMoa1909666

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STRUCTURED ABSTRACT

Question: Does *Helicobacter pylori* treatment reduce the risk of gastric cancer in individuals with a family history of gastric cancer?
Design: Single-center, randomized controlled trial.
Setting: National Cancer Center, South Korea.
Patients: Included patients were: (a) 40-65 years old; (b) first-degree relative with gastric cancer whose diagnosis was histologically confirmed by National Cancer Center; and (c) screening esophagogastroduodenoscopy (EGD) confirmed *H. pylori* infection by rapid urease test and wright-giemsa stain from gastric biopsies. Patients with a history of gastric cancer, peptic ulcer, and prior *H. pylori* eradication therapy were excluded.

Interventions/Exposure: Eligible patients were randomized to amoxicillin 1000 mg, clarithromycin 500mg, and lansoprazole 30 mg b.i.d. X 7 days vs placebo tablets. Patients then underwent

surveillance endoscopy every 2 years with directed biopsies of suspicious lesions to identify gastric adenomas or carcinomas. At first surveillance endoscopy, *H. pylori* status was checked with rapid urease test, but patients and physicians were blinded to results and patients were not re-treated if positive. At the final or close-out endoscopy, *H. pylori* status was again re-checked and salvage therapy provided if *H. pylori* infection was noted by rapid urease test.

Outcome: The primary endpoint was gastric cancer. Preferred secondary endpoints included development of gastric cancer based on *H. pylori* eradication status at surveillance EGD (accounting for patients with failed eradication treatment), gastric adenoma, and overall survival.

Data Analysis: Modified intention-to-treat analysis which excluded patients who never started *H. pylori* treatment/placebo or for whom no follow-up data was available. Kaplan-Meier analysis to assess primary and secondary endpoints. Log-rank test used to compare rates of gastric cancer. Cox proportional hazards used to estimate hazard ratios.

Results: Overall, 1,676 individuals were randomized (mean age: 49 years old; 49% male; 85%-86% with a single FDR with gastric cancer). Successful *H. pylori* eradication occurred in 70.1% of treated patients and 7.1% of placebo-treated patients at surveillance EGD. Median duration of follow-up for gastric cancer diagnosis was 9.2 years (IQR: 6.2-10.6; maximum 14.1). In the modified intention to treat analysis, placebo-treated patients were more likely to be diagnosed with gastric cancer vs antibiotic-treated patient: 2.7% vs 1.2%, P = 0.03; hazard ratio (HR)= 0.45; 95% confidence interval (CI): 0.21-0.94. *Individuals with persistent H. pylori infection were significantly more likely to develop gastric cancer vs individuals with successful eradication: 2.9% vs 0.8%; HR = 0.27; 95% CI: 0.10-0.70* (Figure 1). There were no significant differences in placebo-treated patients vs antibiotic-treated patients for overall mortality (2.0% vs 1.7%) or gastric adenoma (1.5% vs 1.7%).

Funding: National Cancer Center, South Korea

COMMENTARY

Why Is This Important?

The development of gastric cancer is most likely due to a complex interaction of genetic predisposition, environmental factors, and *H. pylori* infection. Having first-degree relatives of gastric cancer patients is associated

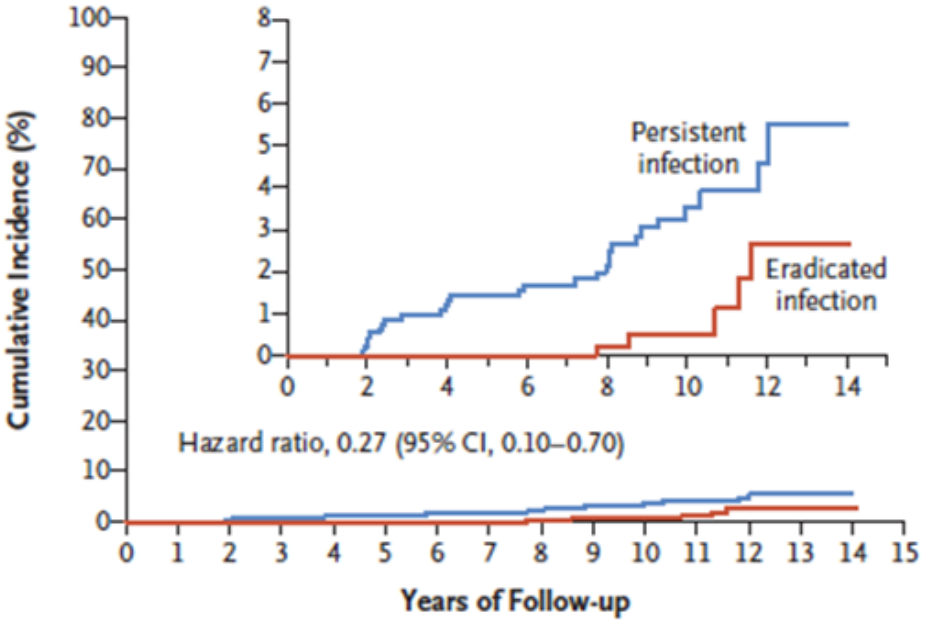

Figure 1: Cumulative Incidence of Gastric Cancer Based on H. pylori eradication status

with a 2-3 fold increase in the risk of gastric cancer, and first-degree relatives of gastric cancer are more likely to have *H. pylori* infection compared to controls. Partly based on these observations, the Houston[1] and Maastricht[2] Consensus Conference reports on *H .pylori* management recommend that first-degree relatives of gastric cancer patients should be tested for *H. pylori*. However, the 2017 ACG Clinical Guideline on Treatment of *H. pylori* Infection[3] is silent about testing and treating *H. pylori* in first-degree relatives of gastric cancer patients due to a paucity of evidence about its benefit. Given that gastric cancer is the one of the most common cancers worldwide, this question needs to be resolved, and the landmark RCT conducted by Choi and their colleagues at the Center for Gastric Cancer at the National Cancer Center in South Korea provides crucial data.

Key Study Findings

Successful eradication of H .pylori infection in first-degree relatives of gastric cancer patients decreased the risk of gastric cancer by more than 70%: HR= 0.27; 95% CI: 0.10-0.70.

Caution

This is another remarkably well-designed study. Since the authors used a placebo control, identified if patients had successful *H. pylori* eradication at surveillance EGD, enrolled a large study population that was evaluated for an extended period (median follow-up of 9.2 years), and had virtually complete data collection, this study provides a precise estimate of gastric cancer reduction after successful *H. pylori* eradication in this high-risk population. As noted by the study investigators, the use of placebo in this trial could raise concerns, but *H. pylori* testing and treatment was not covered in asymptomatic individuals when this study was conducted in South Korea. Also, the generalizability of these data to non-East Asian populations may be limited since the development of gastric cancer is a complex multi-step process which is influenced by genetics and environmental factors as well as exposure to *H. pylori*.

The 7-day clarithromycin-based triple therapy was sub-optimal as evidenced by only achieving successful *H. pylori* eradiction in 70.1% of study patients randomized to treatment. Given the risk of clarithromycin resistance in the US, clarithromycin-based therapies should be used with caution, if at all. Bismuth-based quadruple therapy and rifabutin-based triple therapy for 14 days are preferred.[4] Vonaprazam-based dual and triple therapies were also recently approved by the FDA.[5] Vonaprazam, a potassium-competitive acid blocker, produces earlier and more potent acid suppression than conventional proton pump inhibitors. In clarithromycin-resistant *H. pylori* strains, vonaprazam dual therapy is much more effective vs standard 14-days of clarithromycin-based triple therapy (70% vs 32%).[5]

My Practice

Although there may be important genetic and environmental differences in US patients compared to East Asian patients, the potential benefits of testing and treating first-degree relatives of gastric cancer patients seems to far outweigh potential risks. Therefore, when I make a new diagnosis of gastric cancer in my Veteran population, I advise family members to get tested for *H. pylori* and treated if positive.

As noted above, my preferred therapy is bismuth-based quadruple therapy and I don't recommend clarithromycin-based triple therapy routinely. In the near

future, I may use vonaprazam dual therapy (20 mg vonaprazam b.i.d. plus 1000mg amoxicillin tid for 14 days) depending on cost and availability. Currently, I'm limited by my formulary to only using rifabutin-based triple therapy for salvage therapy. It's also worth emphasizing the ACG Guideline recommendation that post-treatment testing should be performed routinely to ensure successful eradication. I prefer to do this with stool antigens for *H. pylori* and have the specimen collected at least 4 weeks after completing antibiotics and 2 weeks after discontinuing acid suppression therapy.

For Future Research

Prospective cohort data or retrospective case-control studies in US populations would be helpful. It would be unethical to perform a placebo-controlled trial in light of the data from Choi and colleagues.

Conflicts of Interest

Dr. Schoenfeld reports being an advisory board member and consultant for Phathom Pharmaceuticals.

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