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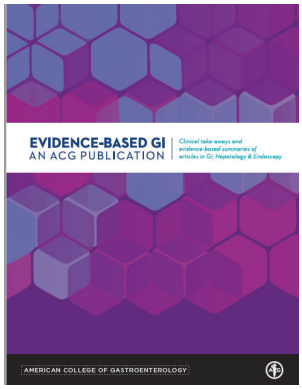

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EDITOR'S NOTE

January 2025 Announcement: New Co-Editor-in-Chiefs

Joseph C. Anderson, MD, FACG

Paul Y. Kwo, MD, FACG

With this issue of *Evidence-Based GI: An ACG Publication,* Joseph C. Anderson, MD, FACG and Paul Y. Kwo, MD, FACG, take over as co-Editor-in-Chiefs as the founding editor, Philip Schoenfeld, MD, MSEd, MScEpi, FACG completes his term. Dr Schoenfeld launched EBGI in October 2021, with a straightforward goal: to provide structured abstracts on the best clinical GI, hepatology, and endoscopy research published in US- and non-US-based general medicine journals using evidence-based methods. Each abstract is paired with editorial commentary on how physicians can apply this research to their practice. Since the inaugural issue, EBGI has covered 147 articles published in 17 medical journals, including 25 articles from the ACG's own flagship journal, *The American Journal of Gastroenterology.* This coverage has allowed our readers access to GI-related information covered in top tiered journals such as *New England Journal of Medicine, Lancet,* and *Annals of Internal Medicine.* Each month an electronic table of contents is sent to all ACG members worldwide, and the podcasts are accessed through popular platforms such as Spotify and iTunes—but are also available directly through the gi.org website. The ACG will soon be offering podcasts through YouTube in 2025. In Dr Schoenfeld's last year as Editor-in-Chief, he worked with the EBGI Social Media Ambassadors to develop slides for journal clubs based on the EBGI summaries. These slides can be downloaded from the website and used freely for educational purposes. Drs Anderson and Kwo will continue these popular features and thank Dr Schoenfeld for his work to establish the publication.

About the Editors

Dr Paul Kwo is currently the Director of Hepatology and Professor of Medicine at Stanford University School of Medicine. Dr. Kwo was Professor of Medicine at Indiana University and the Medical Director of Liver Transplantation where he distinguished himself in the field of viral hepatitis and served as the principal investigator for multiple seminal trials that established the efficacy of direct acting antiviral agents for the treatment of both non-transplant and post-transplant hepatitis C hepatitis C infection. His clinical and research interests are in novel therapeutic approaches to treat viral hepatitis including hepatitis B and C elimination and other chronic liver diseases. He has served on the editorial boards of multiple journals including *Hepatology*, *Hepatology Communications*, and the *Journal of Clinical Gastroenterology*. He also is an Associate Editor for Clinical and Molecular Hepatology as well serving as co-Editor-in-Chief for Current Hepatology reports. He has served on numerous ACG committees including the Education Committee, International Relations Committee, and was the Chair of the ACG Credentials Committee. He is a director of the ACG Hepatology Circle, as well as the ACG Hepatology School and served on the ACG Board of Trustees from 2016 to 2022.

Dr Joseph C Anderson is a full-time gastroenterologist at the White River Junction VAMC, Professor of Medicine at the Geisel School of Medicine at Dartmouth University, and an Associate Professor of Medicine at the University of Connecticut School of Medicine. His research focuses on colorectal cancer screening, and he is a member of the US Multi-Society Task Force on Colorectal Cancer. Dr Anderson serves on the editorial boards of *The American Journal of Gastroenterology, GIE, Endoscopy,* and *CGH*, and is an Associate Editor at *Journal of Clinical Gastroenterology.* Dr Anderson has served on numerous ACG committees including the Practice Parameters Committee, Research Committee, Educational Affairs, Practice Management, and was Chair of the Professionalism Committee. He also has served as an ACG Governor for New Hampshire.

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Tofacitinib in Acute Severe Ulcerative Colitis (TACOS): A Randomized Controlled Trial

Dr Ellen Axenfeld
Guest Contributor

Elie Al Kazzi
Associate Editor

Ellen Axenfeld, MD[1] and Elie S. Al Kazzi, MD, MPH[2]

[1]*Clinical Instructor, Division of Gastroenterology & Hepatology, New York University Langone Health, New York, NY*

[2]*Assistant Professor of Medicine, New York University*

This summary reviews Singh A, Goyal MK, Midha V, et al. Tofacitinib in acute severe ulcerative colitis (TACOS): A randomized controlled trial. Am J Gastroenterol 2024; 119 (7), 1365-1372.

Correspondence to Elie S. Al Kazzi, MD, MPH, Associate Editor Email: EBGI@gi.org

Keywords: Ulcerative colitis, infliximab, steroids, salvage therapy

STRUCTURED ABSTRACT

Question: Among adult patients with acute severe ulcerative colitis (UC), is the addition of tofacitinib to steroids more effective than steroids alone for treatment responsiveness?

Design: Prospective, double-blind (converted to open-label on day 7), placebo-controlled randomized trial (RCT) followed for 90 days.

Setting: This study was conducted at a single tertiary care center in India.

Patients: Patient included in the study were adult (18-years old and over) patients admitted to the hospital with acute severe ulcerative colitis (ASUC),

defined by the Truelove and Witts severity criteria. Excluded patients were those who had received intravenous corticosteroids or tofacitinib within 4 weeks before hospitalization, those with active infection e.g. *Clostridioides difficile* or cytomegalovirus, those with toxic megacolon, or those that were pregnant.

Interventions: Participants received hydrocortisone 100 mg every 6 hours plus tofactinib 10 mg 3 times daily for 7 days vs hydrocortisone plus placebo.

Outcomes: The primary outcome was the proportion of patients who responded to treatment, defined as a decline in the Lichtiger index by >3 points and an absolute score <10 for 2 consecutive days without the need for rescue therapy) by day 7. Secondary outcome included cumulative probability of patients requiring initiation of infliximab or undergoing colectomy after discharge within 90 days of randomization.

Data Analysis: Analyses were performed based on an intention-to-treat analysis. Descriptive analysis was done on patients' characteristics and outcomes. The Kaplan-Meier survival analysis was used to evaluate the cumulative probability of need for rescue therapy.

Funding: Funding was provided by the Research and Development Center of Dayanand Medical College and Hospital in Ludhiana, India. The funding source did not have a role in data collection, data analysis, data interpretation, or writing of the report.

Results: Among 150 patients hospitalized for ASUC during the study period, 104 participants were randomized (median age 37.5, 59% male, median disease duration of 2 years) to receive either tofacitinib (n=53) or placebo (n=51) in addition to standard of care steroid.

The primary outcome was met in 44 of 53 (83.01%) patients receiving tofacitinib vs 30 of 51 (58.82%) patients receiving placebo (odds ratio [OR] 3.42, 95% confidence interval [CI] 1.37–8.48, $P = 0.007$).

Rescue therapy by day 7 was required in 6 of 53 (11.32%) patients in the tofacitinib arm vs 16 of 51 (31.37%) patients receiving placebo (OR 0.27, 95% CI

0.09–0.78, $P = 0.01$). One patient in the tofacitinib arm and 3 patients in the placebo arm required colectomy between days 7 and 90 (after failure of infliximab rescue therapy). One patient in the tofacitinib arm developed hemorrhagic venous infarct in the left temporal lobe and dural venous sinus thrombosis.

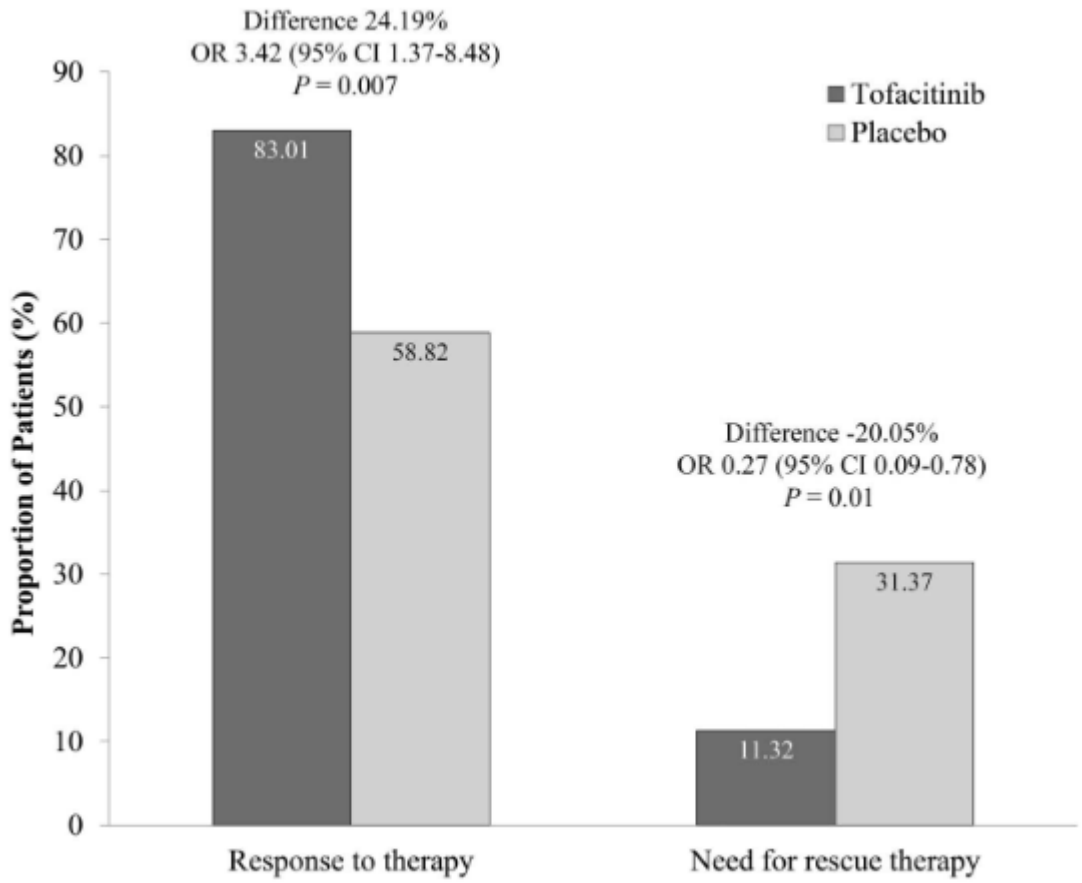

Figure 1. Efficacy outcomes at day 7. Rate of response to treatment by day 7 (primary outcome) and the percentage of patients requiring rescue treatment by day 7. CI, confidence interval; OR, odds ratio.

COMMENTARY

Why Is This Important?

Despite recent advancements in the treatment of UC, ASUC remains a severe complication affecting up to 25% of patients with UC.[1] Intravenous steroids continue to be the standard of care for initial treatment of ASUC, however up to 30%-40% of patients require a second line of therapy, or "rescue therapy".[2] Randomized controlled trials (RCTs) of infliximab and cyclosporine have shown equivalent efficacy as medical rescue therapies in ASUC, while non-randomized studies have suggested that infliximab has a better treatment response and reduced risk of colectomy.[3] Although the rates of urgent colectomy have decreased in the era of infliximab and cyclosporine, this remains a

prominent issue affecting up to 30% of patients with ASUC.[4]

This data underscores the need for advancements to improve responsiveness to medical therapy in ASUC. Prior to the TACOS trial, retrospective studies were published suggesting the effectiveness of Janus-kinase inhibitors (JAKi) for the treatment of ASUC. Berinstein et al, found that concomitant tofacitinib and intravenous corticosteroids may be an effective induction strategy in biologic-experienced patients hospitalized with ASUC.[5] To date, this is the first prospective, placebo-controlled RCT to evaluate the effectivity of a JAKi in the treatment of ASUC.

Key Study Findings

The primary outcome, defined as response to treatment by day 7, was achieved in 44 of 53 (83.01%) patients receiving tofacitinib vs 30 of 51 (58.82%) patients receiving placebo OR 3.42, 95% CI 1.37–8.48, $P = 0.007$)

The need for rescue therapy by day 7 was seen in 6 of 53 (11.32%) patients in the tofacitinib arm when compared with 16 of 51 (31.37%) patients receiving placebo (OR 0.27, 95% CI 0.09–0.78, $P = 0.01$). Five patients in the tofacitinib arm and 11 patients in the placebo arm received infliximab as rescue therapy, while 1 patient in the tofacitinib arm and 5 patients in the placebo arm underwent colectomy. In the open-label phase of the study (after unblinding at day 7 and until day 90), 1 patient in the tofacitinib arm and 3 in the placebo arm required initiation of infliximab. Furthermore, 1 patient in the tofacitinib arm and 3 patients in the placebo arm, who did not respond to the initial medical rescue therapy with infliximab, required colectomy between days 7 and 9. None of the patients received cyclosporine as rescue therapy.

The rates of both medical (infliximab) and surgical rescue therapy (colectomy) were lower in the patients receiving tofacitinib at days 7, 30, and 90. The cumulative probability of need for rescue therapy at day 90 was 0.13 in patients who received tofacitinib vs 0.38 in patients receiving placebo (log-rank $P = 0.003$).

The median CRP at day 7 was 5.17 (2.97–11.54) mg/L in the tofacitinib arm vs 6.18 (2.15–12.80) mg/L in the placebo arm. The total duration of hospital stay was shorter in the tofacitinib arm (9.69 ± 2.84 days) compared with that in the placebo arm (11.01 ± 5.99 days) though statistical significance could not be demonstrated ($P = 0.15$).

On subgroup analysis, in the tofacitinib arm, of the 26 patients who were on oral corticosteroids at the time of hospitalization, 5 (19.23%) patients required rescue therapy. On the contrary, 13 (56.52%) of the 23 patients in the placebo arm, who were on oral corticosteroids at the time of hospitalization, re-

quired rescue therapy. Similarly, in patients with previous exposure to thiopurines, the use of rescue therapy was lower in the tofacitinib arm (1/8, 12.5%) compared with that in the placebo arm (6/6, 100%).

Caution

This study is inherently limited by being a single-study center in India with a population that may not represent and therefore may not be generalizable to the UC patient demographics in the United States. The study period of 90 days may also be too short to evaluate important outcomes such as rates of colectomy. This study also used tofacitinib as a first line therapy prior to the use of an anti-tumor necrosis factor which is prohibited in the US due to FDA regulations. Outside of legal regulations, the lack of availability of generic formulation as was used in this study make this treatment strategy cost prohibitive in many hospitals worldwide. Finally, recent studies of comparative effectiveness including network meta-analyses have concluded that upadacitinib is more effective than tofacitinib in the treatment of UC.[6, 7]

My Practice

Our institution's practice strategy for ASUC begins with a similar approach. Patients are identified as presenting with ASUC and initiated on intravenous steroids (methylprednisolone 60 mg/day) with simultaneous stool infection testing. If patients are not responding adequately after approximately 48–72 hours of intravenous steroids based on clinical assessment or biochemical markers such as CRP, rescue therapy is pursued. Cyclosporine has largely fallen out of favor. In infliximab-naïve patients, infliximab 10 mg/kg is our standard of care for rescue therapy. If there is an inadequate response to infliximab, we would consider the use of upadacitinib as second-line rescue therapy.

For Future Research

The TACOS trial represents a proof-of-concept study showing the effectiveness of JAKi in the treatment of ASUC. Unknowns that remain are (1) the effectiveness of upadacitinib vs placebo as rescue therapy in ASUC and (2) the positioning strategy of JAKi vs anti-TNF as first-line rescue therapy, which would most ideally be evaluated in a head-to-head RCT.

Conflict of Interest

Dr. Ellen Axenfeld and Dr. Elie Al kazzi report no potential conflicts of interest related to this study.

Abbreviations

ASUC, acute severe ulcerative colitis; CI, confidence interval; FDA, Food and Drug Administration; OR, odds ratio; RCT, randomized controlled trial; TNF, tumor necrosis factor; UC, ulcerative colitis; US, United States

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Hot Take: Can We Lengthen Surveillance Intervals After EMR With Margin Thermal Ablation?

CRC SCREENING

Dr Margaret J. Zhou

Margaret J. Zhou, MD, MS

Clinical Assistant Professor of Medicine, Division of Gastroenterology & Hepatology, Stanford University, Stanford, CA

This summary reviews O'Sullivan T, Mandarino FV, Gauci JL, et al. Impact of margin thermal ablation after endoscopic mucosal resection of large (≥20 mm) non-pedunculated colonic polyps on long-term recurrence. Gut. 2024 Dec 10;74(1):67-74.

Correspondence to Margaret Zhou, MD, MS. Associate Editor. Email: EBGI@gi.org

Keywords: colon cancer screening, endoscopic mucosal resection, colonoscopy, margin thermal ablation

STRUCTURED ABSTRACT

Question: Does margin thermal ablation (MTA) after endoscopic mucosal resection (EMR) reduce the incidence of recurrence at the second surveillance colonoscopy (SC2) compared to EMR alone?

Design: Retrospective cohort study.

Setting: Four academic endoscopy centers in Australia.

Patients: Patients in the Australian Colonic Endoscopic (ACE) Resection Database with a large non-pedunculated colonic polyp (LNPCP) removed with EMR by a study investigator (gastroenterologist with advanced training in endoscopic resection) or senior interventional endoscopy fellow under supervision.

Interventions: LNPCPs treated with EMR + MTA from a prior randomized controlled trial (RCT) from July 2013-November 2022 were compared with a historical control arm of LNPCPs treated with EMR alone from January 2012-May 2016. Intravenous sedation with fentanyl, midazolam and propofol was used. EMR was performed using a standard technique including submucosal injection with succinylated gelatin, indigocarmine and epinephrine, with standardized electrocautery settings for snare polypectomy (Endocut effect 3, ERBE) and MTA (Soft Coag: 80W, Effect 4; ERBE).

Patients who underwent successful resection without submucosal invasive cancer underwent SC1 6 months after index resection. Resection scars were examined with high-definition white light (HDWL) and narrow band imaging (NBI). Biopsies were taken from bland scars at the endoscopist's discretion. If no recurrence was detected, SC2 was performed 12 months after SC1.

Outcomes: The primary outcome was recurrence at SC2 in patients without recurrence at SC1. Secondary outcomes included compliance with SC2, mean surveillance interval at SC2, and recurrence at SC1.

Data Analysis: Chi-square tests were used for categorical variables and Mann-Whitney U tests for continuous variables. Multivariable analysis was not possible due to the rare number of outcomes.

Funding: None reported.

Results: Of 1,152 patients who underwent EMR + MTA, 472 underwent SC2 at a mean interval of 23.2 months from index resection. Of 591 patients treated with EMR alone, 260 completed SC2 at a mean interval of 24.4 months from index. Baseline LNPCP characteristics of patients who underwent SC2 were similar between the EMR + MTA vs EMR arms overall. Of the SC2 cohort of 732 patients, mean polyp size was 35 mm, 175 (24%) lesions were the ascending colon, 146 (20%) were in the transverse colon, 410 (56%) were flat (Paris 0-IIa/IIb or 0-IIc), and 490 (67%) were tubulovillous adenomas. Polyps in the EMR + MTA vs EMR group were more often granular (73% vs 56%; P <0.001) and showed high-grade dysplasia (25% vs 15%; P = 0.003). There was 1 (0.2%; 95% confidence interval [CI] 0-1.2%) recurrence at SC2 in the EMR + MTA arm compared to 9 (3.5%; 95% CI 1.6-6.5%) recurrences at SC2 in the EMR arm (P <0.001; relative risk reduction 94%) (Figure 1). Further analysis on missing SC2 data using best-worse

analysis or worst-best analysis found lower recurrence after EMR + MTA vs EMR (0.2% vs 3.5%; 1.1% vs 2.6%, respectively). Recurrence at SC1 after EMR + MTA was 3.4% (29 of 854 patients) vs 19.7% after EMR alone (93 of 473 patients) (Figure 1).

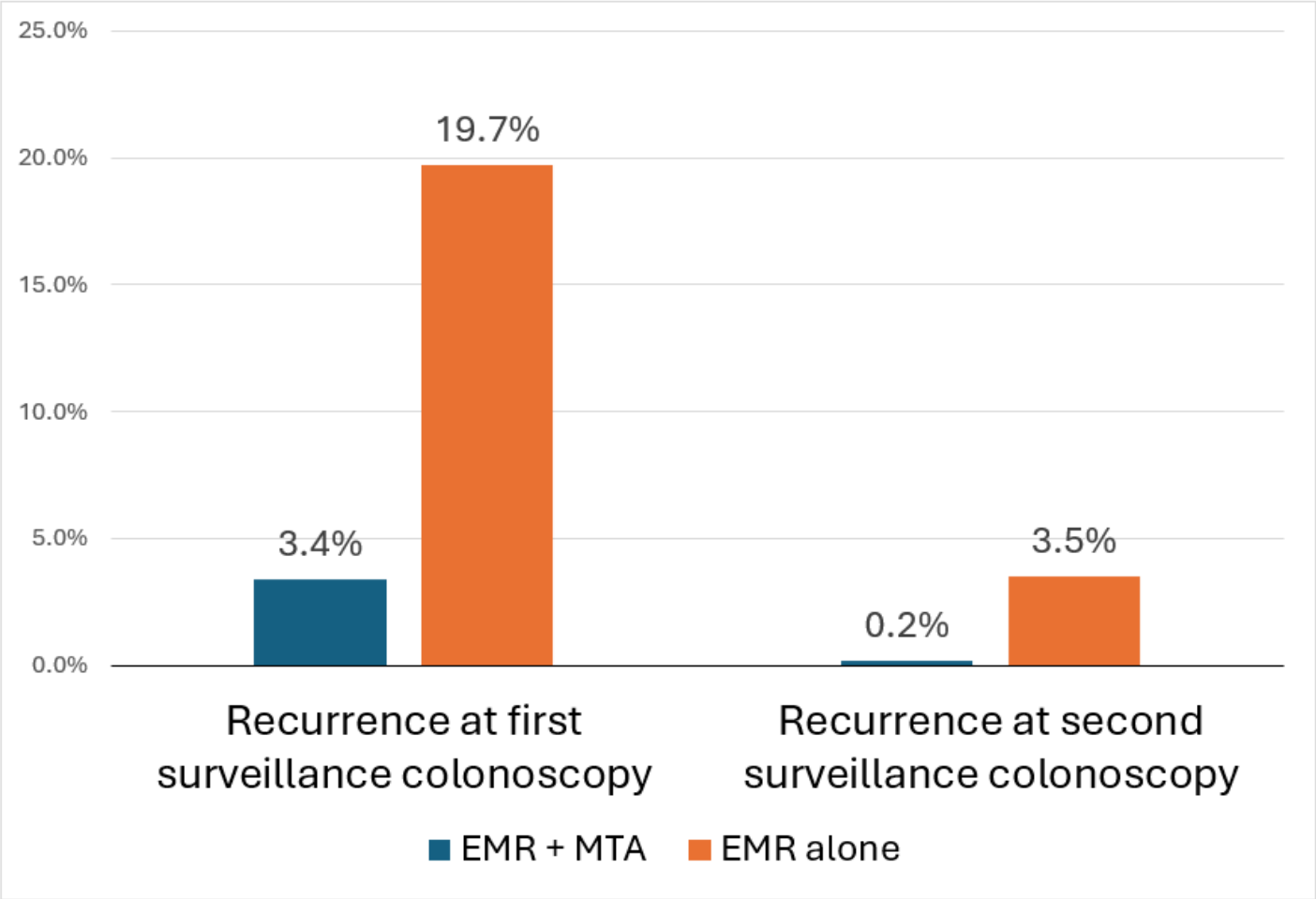

Figure 1. Recurrence rates at first and second surveillance colonoscopies.

EMR, endoscopic mucosal resection; MTA, margin thermal ablation.

COMMENTARY

Why Is This important?

EMR + MTA has been adopted as the standard EMR technique. Multiple studies have demonstrated dramatically improved recurrence rates at 6 months with EMR + MTA vs EMR alone, with the prior RCT by this study's authors showing recurrence of 5% with EMR + MTA vs 21% with EMR alone.[1] This current study provides needed data about the durability of EMR outcomes with MTA.

Recent guidelines from 2020 recommend SC1 at 6 months after index resection in patients who undergo piecemeal EMR and SC2 at 1 year after SC1

if there is no recurrence at SC1, as was done in this study.[2] These guidelines likely incorporate historic EMR outcomes where there was concern for potential delayed recurrence with EMR alone, with a prior longitudinal study demonstrating recurrence at 16 months from index resection of 4%.[3] However, outcomes after EMR + MTA are much improved, with a meta-analysis showing recurrence after EMR + MTA at SC1 of ~6%, ranging from 3%-12%.[4-6,7]

Surveillance colonoscopy after endoscopic resection can be a burden for patients and health care systems, and strategies to optimize surveillance intervals are needed. Identifying patients in whom surveillance intervals can be tailored and potentially lengthened may improve colonoscopy adherence and quality of life for patients as well as health care expenditures.

Key Study Findings

Recurrence at second surveillance colonoscopy at 2 years from index resection for adenomatous LNPCPs treated with EMR + MTA was significantly lower compared with those treated EMR alone (0.2% vs 3.5%; P <0.001, relative risk reduction 94%).

Caution

Given the low recurrence rate at SC2 after EMR + MTA, the study authors raise the question of whether the interval for SC2 can be lengthened to 3-5 years after SC1. However, they raise several important caveats. This study was performed at an expert center, and the study's EMR outcomes may not be generalizable to other centers. Endoscopists conducted high-quality exams to ensure detection of synchronous neoplasia, and the study excluded patients with synchronous neoplasia. Importantly, this study did not specify the proportion of EMRs performed en bloc vs piecemeal, which may impact outcomes since piecemeal resection is associated with a higher recurrence rate. In addition, argon plasma coagulation is sometimes used in practice instead of snare tip soft coagulation; while evidence for this is less robust than STSC, this is likely an effective alternative.

Adherence to surveillance in this study was sub-optimal, which may reflect real-world practice. Only 57% and 76% of patients eligible for SC2 completed colonoscopy in the EMR + MTA and EMR arms, respectively. Each arm had a high proportion of patients who did not undergo SC2 due to patient refusal, inappropriate surveillance recommendation, and loss to follow-up. To address this, the authors compared characteristics between patients with missing SC2 vs. those who completed SC2 and found no significant difference in morphology, granularity, size, location, or presence of dysplasia.

Lastly, it should be noted that there is ongoing discussion about the optimal resection technique for LNPCPs with

endoscopic submucosal dissection (ESD) vs EMR. The recent RCT comparing ESD vs EMR (with MTA) for LNPCPs >25 mm found recurrence at 6 months in 0.6% of ESDs vs 5.1% of EMRs and a higher rate of adverse events with ESD vs EMR (35.7% vs 24.7%).[7] While ESD likely improves recurrence and may allow for increased surveillance intervals, EMR remains a cornerstone of LNPCP resection and is much more widely available in most countries.

My Practice

For LNPCPs ≥20 mm treated with EMR + MTA, I adhere to current surveillance guidelines recommending SC1 at 6 months. I perform MTA in all large EMRs of adenomatous lesions using snare tip soft coagulation (Soft Coag: 80W, ERBE). For patients without recurrence at SC1, I do recommend SC2 at 12 months after SC1. However, some patients have difficulty adhering to frequent colonoscopies and in practice, SC2 sometimes occurs >12 months after SC1. With the results of this study, I feel more comfortable potentially prolonging SC2 to 18 months from SC1 with patients who may not be able to adhere to SC2 if their polyp had low risk features and there is no recurrence on SC1. Importantly, on the initial colonoscopy, I perform a careful inspection with HDWL and NBI to identify any features of submucosal invasion using the Paris and the Japan NBI Exert Team (JNET) classification systems. If there are any high-risk features of superficial submucosal invasion (Paris 0-IIc morphology, JNET 2B, increasing size, non-granular morphology) and I do not think I can resect the lesion en bloc, I have a low threshold to refer for ESD given the availability of ESD at my institution. I completed an advanced endoscopy fellowship which included training in EMR and am currently pursuing additional training to perform ESD.

For Future Research

Future studies to identify predictors of recurrence after EMR are needed to risk-stratify LNPCPs that may be higher risk for recurrence and warrant closer surveillance.

Conflicts of Interest

Dr Zhou has no reported conflicts of interest.

Abbreviations

ACE, Australian Colonic Endoscopic; EMR, endoscopic mucosal resection; LNPCP, large non-pedunculated colonic polyp; MTA, margin thermal ablation; RCT, randomized controlled trial; SC1, first screening colonoscopy; SC2, second surveillance colonoscopy.

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Double-Blind Multicenter Randomized Clinical Trial Comparing Glucagon Vs Placebo in the Resolution of Alimentary Esophageal Impaction

Christopher Vélez, MD

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This summary reviews de Benito Sanz M, Tejedor-Tejada J, Mangas-Sanjuan C et al. Double-blind multicenter randomized clinical trial comparing glucagon vs placebo in the resolution of alimentary esophageal impaction. Am J Gastroenterol. 2024 Jan 1;119(1):87-96.

Correspondence to Christopher Velez, MD. Associate Editor. Email: EBGI@gi.org

Keywords: glucagon, food impaction

STRUCTURED ABSTRACT

Question: Glucagon has been recommended for medical management of uncomplicated esophageal impaction in order to spare emergent gastroscopy. This recommendation has not been subject to a substantive randomized controlled trial (RCT).

Design: Multicenter, blinded, placebo-controlled RCT.

Setting: Four centers involving 17 endoscopists in Spain.

Patients: Adult patients who were admitted for emergent care for suspected esophageal foreign body impaction (EFBI) while a participating endoscopist

was on call were recruited. An EFBI clinical diagnosis was made if symptoms such as acute onset dysphagia, retrosternal or pharyngeal foreign body sensation, profuse salivation, or intolerance of *per os* intake were present after the last meal. Exclusion criteria included non-food EFBI or having been administered either glucagon or carbonated beverage prior to randomization. Additional participation was excluded for those who were pregnant, with a prior history of esophageal stricture and/or a manometrically-defined disorder of esophageal motility. Participants after randomization were excluded from primary analysis if the wait for gastroscopy exceeded 120-minutes (5 glucagon, 3 placebo).

Interventions/Exposure: After presentation in the emergency department for suspected EFBI, participants were interviewed. After discussion and agreement between the emergency department staff and the on-call endoscopist, patients were randomized to either receiving 1 mg of glucagon or the equivalent volume of saline. Randomization occurred in a stratified fashion, via a computer-generated random sequence. While the on-call endoscopist and study participant were masked as to what agent the participant received, emergency department staff were aware. After enrollment, no further interventions aside from urgent gastroscopy were permitted. All underwent gastroscopy even if there was a sensation of symptom relief, which would be analogous to consensus standard of care. It was at the endoscopists' discretion what maneuvers were to be taken to clinically address EFBI. A standardized telephone interview occurring 7-10-days after gastroscopy was performed, including administration of a variety patient reported outcome measures. The primary outcome was resolution of the EFBI identified on gastroscopy (performed for clinical intent).

Outcome: The primary outcome was resolution of the EFBI identified on gastroscopy (performed for clinical intent). Secondary outcomes included gastroscopy procedure length, the number and type of maneuvers, relevant endoscopic findings, and adverse events.

Data Analysis: Data was captured using the Spanish Digestive Endoscopy Society (ES: Sociedad Española de Endoscopia Digestiva) data capture tool. For the primary aim, the differences in EFBI resolution were assessed, with intention-to-treat and per protocol analysis. Secondary aims were analyzed by chi-squared test.

Funding: Spanish Society of Endoscopy "Beca Fundación SEED 2019" and the Gerencia Regional de Salud de Castilla y León, España (Regional Health

Administration of Castile-and-Leon, Spain).

Results: A total of 181 potential participants were screened, of whom 41 were excluded due to declining to participate, non-food-based EFBIs (for which glucagon usage would have been inappropriate), and 6 either had known prior strictures and/or esophageal motility disorders. A total of 72 subjects received glucagon and 68 were administered saline. There were no significant baseline differences between both groups, although prior history of Schatzki ring was more frequently found in the glucagon-administered group. Both groups had gastroscopy performed in slightly under 1-hour. Overall, 23.6% of glucagon subjects had EFBI resolution demonstrated on gastroscopy, compared to 20.6% of participants who had saline administered. Adverse events were distributed similarly across both groups, including some degree of pain, residual dysphagia, and mucosal tears.

COMMENTARY

Why Is This Important?

I think this article is of wide interest to the College's readership for one simple reason: we have all been there! We have all received a phone call overnight with a request for urgent endoscopy for EFBI and have not necessarily known how the consult request will play out. If it is early enough in the evening, do we rush into the hospital to address the EFBI when there are more resources that can be called upon if a complication occurs? Do we wait to see if glucagon will work? How do we translate urgency on the part of our emergency colleagues?

For decades, endoscopists on call have used glucagon to address some of this uncertainty. It has been thought that glucagon relaxes gastrointestinal smooth muscle and can induce lower esophageal sphincter relaxation[1,2]. Clinically, I have forgone gastroscopy in patients who can clearly delineate a significant/near-complete improvement of symptoms or who can drink water again. Yet, while glucagon has had this role in EFBI management since at least the 1970s, it has not been subjected to the rigors of our investigative discipline – a randomized control trial.

This study has an elegant design, and it is surprising that our profession has not generated it previously. These authors from Spain are to be commended for one of the most robust randomized trials on the use of glucagon in EFBI. This manuscript calls us to question the faith we place in glucagon being a tool we reach for when woken up from deep slumber at 3 AM.

Key Study Findings

Glucagon is no more effective than placebo at resolving EFBI. That being

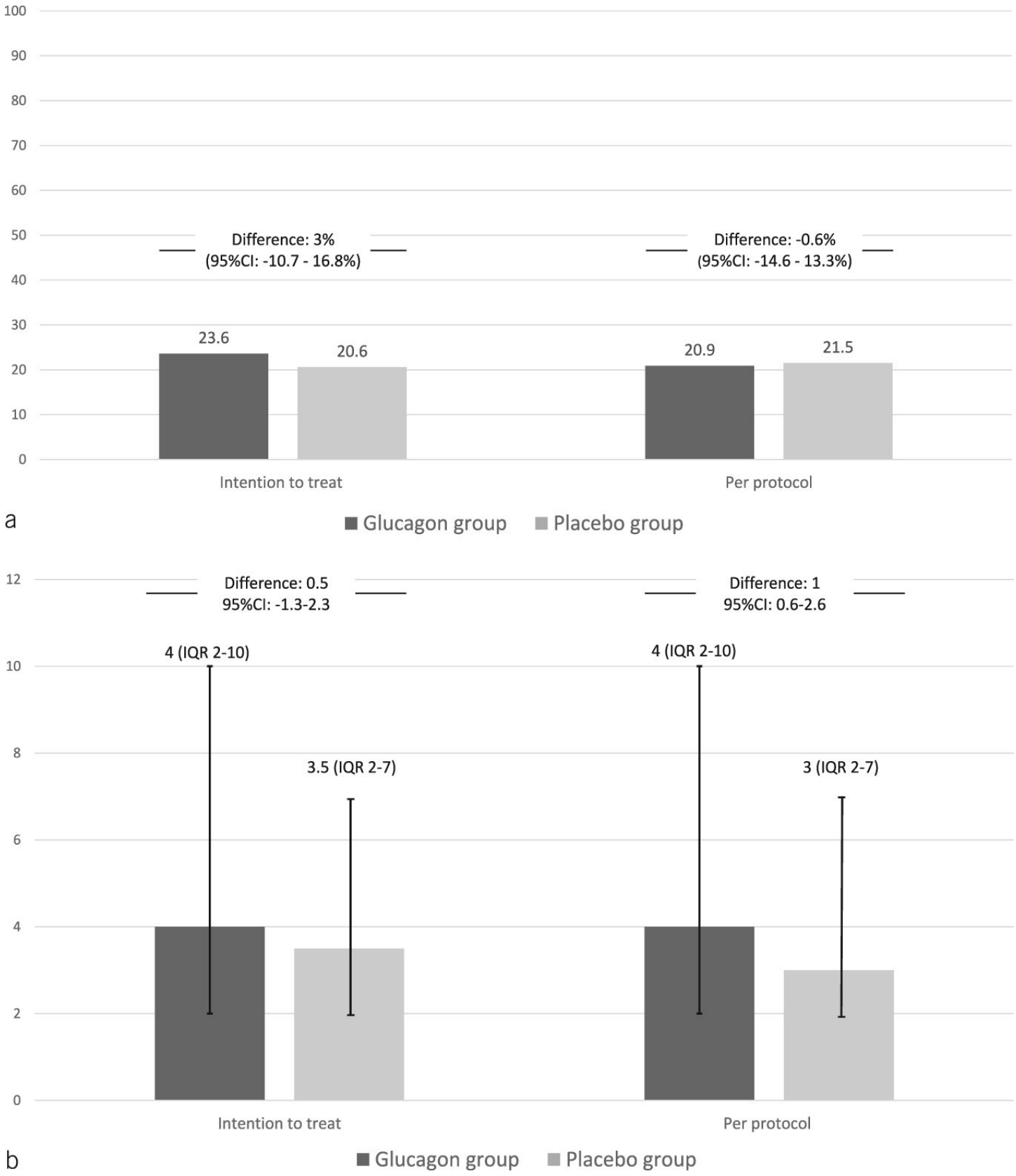

Figure 1. (a) Proportion of resolved esophageal impactions in the glucagon and placebo group (intention-to-treat and per-protocol analysis). (**b**) Duration of upper endoscopy in minutes in the glucagon and placebo group (intention-to-treat and per-protocol analysis). CI, confidence interval; IQR, interquartile range.

said, there does not appear to be any difference in adverse outcomes associated with its use.

It is less likely that glucagon administration is causing harm. It may be delaying inevitable endoscopies, which could lengthen the amount of time patients are spending in emergency departments.

Caution

While this study is a good one, I am not necessarily going to recommend to the emergency department that they chuck their vials of glucagon quite yet. The endoscopy centers represented in this study appear to be exceedingly efficient, with the participants undergoing endoscopy within an hour of either glucagon or placebo administration. Additionally, patients who had an interval of placebo vs glucagon administration greater than 120-minutes were excluded. I wonder if a longer period occurred between glucagon administration and endoscopy, that glucagon would fare better. I do not think that for the average consultation practice around the world that an endoscopy would occur this quickly.

My Practice

This trial has made me consider changing my threshold as it relates to gastroscopy for EFBI. In the daylight, I might be less likely to trial glucagon and potentially waste precious time if a complication occurred during foreign body removal. Overnight, I may still consider a trial of glucagon, as I would like to try to defer a gastroscopy if the patient feels amelioration. I always worry about procedural complications (particularly management of a perforation) when performing a gastroscopy that could wait for the first case of the day. While our colleagues in other service lines do not often appreciate the gastroenterologist's concern for complications, it is infinitely better to wait when rescue is more readily available. That said, this trial makes me question whether glucagon can continue to help serve this role.

While not directly related to my practice surrounding EFBIs, I would be remiss to not offer 3 pearls that the fellows I work with are probably tired of me repeating: (1) one must distinguish acute dysphagia – i.e. impaction – from chronic dysphagia; (2) biopsy the uninvolved portions of the esophagus to identify eosinophilic esophagitis; and (3) recurring dysphagia occurring in the setting of an acute impaction should prompt evaluation for missed stricture or esophageal dysmotility (particularly achalasia).

For fellows reading this article, I have seen nearly missed cases of food impaction that were registered by the primary emergency or medicine departments as "dysphagia" during consultation. Clarify the time course, make sure you are not missing an EFBI as this can then go on to progress to more emergent disease complications. Regarding biopsies, food impactions can be one of the first

signs of eosinophilic esophagitis[3]. In my motility consultation clinic, I have made diagnoses of eosinophilic esophagitis after multiple presentations for EFBI, that could have been avoided had the patient undergone food elimination, proton pump inhibition, swallowed steroids, or dupilumab treatment. In my mind, there must be a very high bar prior to deciding not to biopsy portions of the esophagus not involved in the food impaction. Finally, endoscopists can easily miss strictures that may explain symptoms, but are wider than our gastroscopes' diameters (generally 9-10 mm). Additionally, we do not do enough manometry to identify achalasia that can present as food impacted in the esophagus.

For Future Research

That it took over 50 years from the time that glucagon efficacy in EFBI management has been posited to this trial being performed, I do not imagine further work will be attempted to address the utility of glucagon in management of EFBI. I surmise that some endoscopists will abandon glucagon based on this study, others will still employ it. We must remember that while randomized clinical trials are the gold standard of our field, only the endoscopist can integrate relevant clinical facts and come up with the best resolution at that time.

Conflict of Interest

Dr. Vélez reports no relevant conflicts.

Abbreviations

FBI, foreign body impaction; RCT, randomized controlled trial.

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EVIDENCE-BASED GI
AN ACG PUBLICATION

Redefining Risks in CDH1 Hereditary Diffuse Gastric Cancer

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STOMACH

This summary reviews Ryan CE, Fasaye G, Gallanis AF, et al. Germline CDH1 variants and lifetime cancer risk. JAMA. 2024;332(9):722–729.

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Keywords: CDH1, Hereditary diffuse gastric cancer

STRUCTURED ABSTRACT

Question: What is the lifetime cumulative risk of gastric cancer in those with a *CDH1* pathogenic variant?

Design: Multicenter observational cohort study.

Setting: Academic medical centers: National Cancer Institute and 5 university-based systems.

Patients: Families with a germline pathogenic/likely pathogenic (P/LP) *CDH1* variant.

Interventions: Exposure to a germline pathogenic *CDH1* variant.

Outcomes: Self-reported personal and family histories of advanced gastric cancer (≥pT1b, N1, or any M stage) and breast cancer.

Data Analysis: Cumulative lifetime cancer risk among *CDH1* carriers was estimated using specific hazard ratios (HRs) compared to non-carriers, estimated

using segregation analyses and maximum restricted likelihood methods.

Funding: Intramural Research Program of the National Institutes of Health, National Cancer Institute.

Results: Two hundred and thirteen kindreds (extended families) with *CDH1* P/LP variants, consisting of 7,232 individuals; 85% were White and 49% female. The average age at diagnosis of gastric cancer was 49 (interquartile range [IQR] 39-59), and breast cancer at age 51 (IQR 44-58). The cumulative risk of advanced gastric cancer was 10.3% by age 80 in male carriers, and 6.5% by age 80 in female carriers with a HR 3.5 (95% confidence interval [CI] 0.4-26.2). Among individuals with ≥3 first-degree relatives with gastric cancer, the estimated risk by age 80 was 38% (95% CI 25-64%). The cumulative risk of any gastric cancer (including stage 1A) at the time of prophylactic total gastrectomy was 19.1% (95% CI 11.5-35.9%) among males and 12.6% (95% CI 7.6-24.8%) among females. Whether signet ring cells were found on endoscopic biopsies did not make a significant difference in cumulative risk of any gastric cancer.

COMMENTARY

Why Is This Important?

Although autosomal dominant hereditary diffuse gastric cancer due to *CDH1* is relatively uncommon, the lifetime cumulative risks of diffuse gastric adenocarcinoma (aka linitis plastica) have been historically been estimated up to 70% for male and 83% for female patients, although these studies have been of small sample size or from high-risk families outside of the United States.[1-3] Therefore, guidelines have recommended a prophylactic total gastrectomy for all *CDH1* patients as early as 20 years old.[4] In addition to complications after surgery, this has devastating lifetime impacts on a person's nutritional and fertility status for someone who has nearly their whole life ahead of them. This study redefines that risk to a more realistic expectations and questions the role of prophylactic gastrectomy as a blanket recommendation.

Key Study Findings

The cumulative lifetime risk of advanced gastric cancer (>pT1a) was approximately 10% in male and 7% in female *CDH1* carriers. The cumulative lifetime risk of any gastric cancer including stage IA gastric cancer of 19% in males and 13% in females, and whether or not signet rings were found on endoscopic biopsy seemed to have minimal impact.

Having a strong family history (3 first-degree relatives with gastric cancer) portended a lifetime risk of 38%.

Caution

First, studies have shown that essentially all *CDH1* patients harbor an occult pT1aN0 (stage IA) gastric cancer that itself is regarded as clinically insignificant, but clearly this shows that only a subset of those progress to pT1b and beyond.[5] While this study helps redefine that prophylactic gastrectomy is unlikely the default answer for most *CDH1* patients, particularly without a concerning family history of diffuse gastric cancer, we still do not have an evidence-based approach to surveillance and risk stratification for those who are at risk of future advanced gastric cancer. Second, this study does still have ascertainment bias given its focus on academic medical centers and patients who had germline genetic testing for a personal/family history of cancer, although this is a common issue. Third, the ascertainment of cancer outcomes was based on patient self-report without confirmation of pathologic diagnoses.

My Practice

CDH1 patients represent one of the difficult clinical decision-making conundrums in hereditary gastrointestinal cancers. I discuss this data with patients regarding risks of advanced gastric cancer and often defer prophylactic gastrectomy at age 20 in the absence of a strong family history. However, I do find it useful to still have them meet with a surgical oncologist to discuss what a surgery would entail. I perform surveillance endoscopy every 6-12 months based on the Cambridge protocol depending on their family history of gastric cancer.[6] It is important to take your time with the endoscopy, particularly to look for mucosal abnormalities such as ulcerated lesions, although note that signet ring carcinoma on a random or targeted biopsy of "pale areas" has not been clearly shown to correlate with advanced gastric cancer. Surveillance endoscopies should preferentially be performed at tertiary referral centers by an endoscopist with specific expertise in hereditary digestive cancer, if available.

For Future Research

Current studies are examining both endoscopic and other clinical risk factors for pT1b or advanced gastric cancer in *CDH1* patients to help identify who should undergo gastrectomy and when. This may include specific endoscopic or patient characteristics, incorporation of artificial intelligence into our endoscopic exams, as well as biomarkers.

Conflict of Interest

Dr Yen has no reported conflicts of interest.

Abbreviations

CI, confidence interval; HR, hazard ratios; IQR, interquartile range; P/LP, pathogenic/likely pathogenic.

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