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Spatial Evolution of Histologic and Endoscopic Healing in Left and Right Colon in Patients with Ulcerative Colitis

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Abstract

Background and Aims: Despite increasing interest in histologic remission as a treatment target in ulcerative colitis (UC), the accuracy of histologic findings in left colon in detecting pancolonic histologic remission is unknown.

Methods: In a retrospective cohort study of patients with endoscopically active pancolitis undergoing treat-to-target interventions, we evaluated the diagnostic accuracy of left-sided (distal to splenic flexure) histologic and endoscopic findings on colonoscopy for detecting histologic and endoscopic healing elsewhere in the colon.

Results: Of 86 patients with moderate to severely active pancolitis who underwent two consecutive colonoscopies during treat-to-target interventions, 38% and 51% achieved histologic and endoscopic remission, respectively. Substantial agreement (kappa, 0.67; 95% confidence interval (CI), 0.51–0.83) was observed in histologic findings between left and right colon on follow-up colonoscopy. Histologic, and endoscopic, findings in left colon showed excellent accuracy in detecting pancolonic histologic remission (area under the curve (AUC), 0.96 [95% CI, 0.93–1.0]; misclassification rate, 5.9%), histologic normalization (AUC, 1.0, 0%), endoscopic improvement (AUC, 0.95 [0.96–1.0], 3.5%) and endoscopic remission (AUC, 0.98 [0.96–1.00], 5.8%), respectively.

Conclusions: In patients with active pancolitis undergoing treat-to-target interventions, histologic and endoscopic findings in the left colon on colonoscopy have excellent accuracy for detecting pancolonic histologic remission, histologic normalization, endoscopic improvement, and endoscopic remission. Flexible sigmoidoscopy may suffice for monitoring histologic and endoscopic activity in patients with pancolitis.

Keywords

Treat-to-target; STRIDE; IBD; Inflammatory Bowel Disease

INTRODUCTION

Patients with ulcerative colitis (UC) who achieve endoscopic and histologic remission have significantly lower risk of relapse compared with patients who have mild endoscopic activity (Mayo endoscopy score [MES] 1), or persistent histologic activity despite endoscopic remission (ER; MES 0)[1–3]. Hence, there is increasing interest in histologic remission as an aspirational treatment endpoint in patients with UC. However, optimal modality for evaluating achievement of histologic remission in patients undergoing treat-to-target interventions is unknown. There is limited data on spatial evolution of histologic and endoscopic disease activity, in patients with active UC being treated to a target of endoscopic improvement (EI; MES 0 or 1). In a phase 2 study of etrolizumab in moderately to severely active UC, Colombel and colleagues observed a high level of agreement between endoscopic disease activity in the right and left colon.[4] However, they did not analyze evolution of histologic activity; moreover, their analysis was limited to a short-term induction trial.

To identify optimal modality, and assess whether histologic examination in the left colon may inform pancolonic histologic activity in patients with active pancolitis undergoing treat-to-target interventions, we conducted a retrospective cohort study to assess baseline concordance and spatial evolution of histologic activity between the right (proximal to splenic flexure) and left colon (distal to splenic flexure).

METHODS

Patients

In this retrospective cohort study, approved by the Institutional Review Board (IRB# 191127), we included patients with historically known endoscopic and histologically active pan-colonic UC (either active or in remission at cohort entry) who underwent two consecutive colonoscopies during routine practice between 2012–2019. In patients with moderate to severely active UC at the index colonoscopy, a treat-to-target strategy was implemented with a goal of achieving resolution of symptoms and EI, with iterative endoscopic evaluation to assess for therapeutic response. In patients with mild endoscopic activity or ER, consecutive colonoscopies were performed either for dysplasia surveillance or monitoring disease activity. Patients with Crohn's disease, no prior documented pancolitis, or those who underwent only flexible sigmoidoscopy for interval evaluation were excluded.

Routine clinical practice

All patients with IBD at UCSD are treated by a team of gastroenterologists and nurse practitioners trained in IBD, in accordance with evidence-based guidelines. Patients with endoscopically active UC (MES≥2) are treated-to-target of EI consisting of serial endoscopic evaluation after treatment modification, followed by stepwise treatment intensification, and then interval re-evaluation. Patients with active symptoms despite initial therapy may undergo treatment optimization based on patient-reported outcomes and/or elevated serum or stool biomarkers of inflammation, without confirmation on endoscopy, given high predictive value of a combination of active symptoms (rectal bleeding score 2 or 3 and stool frequency score 2 or 3) with elevated fecal calprotectin > 250μg/g[5]. All endoscopic procedures are performed by IBD-trained gastroenterologists, and two of four endoscopists serve as central readers for clinical trials. For disease activity assessment, typically four biopsies are obtained from the worst affected area of the right and left colon. If performed for dysplasia surveillance, then 8 biopsies each are obtained from the cecum/ascending, transverse, descending, and rectosigmoid colon, respectively. One of 5 pathologists blinded to all clinical information reviewed slides, and a single gastroenterologist (SJ) blinded to other clinical data at the time of review, performed histologic classification (described below). For patients with biopsies from multiple bowel segments, the segment with the most severe disease was used as the default choice in the analysis in order to provide the most conservative estimate. For biopsies taken within a segment, the biopsy with the most severe activity for each feature was scored.

Data abstraction and Definitions

A single reviewer abstracted relevant data using a standardized format. *Clinically active disease* was defined as a rectal bleeding (RBS >0) and 3–4 stools above normal (stool frequency score [SFS], 2 to 3); endoscopic moderate to severely active disease was defined as MES≥2. *Symptomatic remission* was defined as resolution of rectal bleeding (RBS 0) and near-normalization of stool frequency (SFS 0 or 1), with absence of corticosteroids. *Baseline disease severity* was classified as mild (low-risk of disease-related complications like colectomy) if patients were treated with 5-aminosalicylates therapy (5-ASA), and as moderate-to-severe (high-risk of disease-related complications like colectomy) if patients required anti-metabolites (thiopurines, methotrexate), biologic agents or janus kinase (JAK) inhibitors. Endoscopic remission/mild disease was defined as MES≤1, *endoscopic remission* as MES 0 and *mild endoscopic activity* as MES 1. *Histologic remission* was defined as either complete mucosal normalization or chronic architectural changes in the absence of neutrophilic infiltrate in the mucosa. *Histologic normalization* was defined as the absence of any acute infiltrate and the absence of any chronic architectural changes. *Histologic activity* was defined as architectural changes with superimposed acute infiltrate characterized as mild (neutrophilic cryptitis), moderate (neutrophilic cryptitis and neutrophilic crypt abscesses), or severe (presence of ulcer), similar to the established Geboes's score, and as previously utilized in published UC studies.[1, 6, 7] In a prior study of 38 patients from this cohort (58% with histologic remission based on our pragmatic definition), we observed a very strong correlation between our definition, and histologic remission defined by the Geboes' score (correlation coefficient, 0.85; 95% CI, 0.73–0.92).

Concordance of histologic (and endoscopic) activity

Concordance of histologic healing in right and left colon was examined in patients with active disease (MES≥2) treated-to-target of EI. Histologic findings were spatially *concordant* if findings in right and left colon were the same (histologic remission in right *and* left colon, or histologic activity in right *and* left colon), otherwise were considered spatially *discordant*. Similarly, concordance of EI in right and left colon was examined in a subset of patients with endoscopically active disease (MES≥2) at baseline who were treated-to-target of EI. Endoscopic findings were spatially *concordant* if findings in right and left colon were the same (either ER/mild disease in right *and* left colon, or endoscopic activity in right *and* left colon), otherwise were considered spatially *discordant*.

Outcomes and statistical analysis

We evaluated the spatial evolution of histologic activity in right and left colon among patients with endoscopic disease (MES≥2) who were treated to a target of EI. For this analysis, we evaluated (1) degree of spatial discordance on follow up colonoscopy between the right and left colon, presented as the weighted kappa statistic, (2) diagnostic accuracy of the left colon evaluation in detecting pancolonic disease activity status presented as area under the receiver operating curve (AUROC), sensitivity, specificity, and misclassification rate ([false positive + false negative]/total population). Similar analyses were performed to evaluate spatial evolution of endoscopic activity in right and left colon among patients

with endoscopically active disease (MES≥2) who were treated-to-target of EI. The weighted kappa statistic was interpreted based upon conventional criteria.[8]

We also explored factors associated with spatial discordance of histologic and endoscopic activity on follow up colonoscopy in patients with concordant activity at baseline, through univariate logistic regression. Due to small sample size, multivariable analyses were not performed. All statistical analyses were performed using RStudio (Version 1.1.456, Boston, MA). The "pROC" package was used for ROC construction and AUROC calculation.

RESULTS

We identified 135 patients with UC with history of pancolitis on endoscopy and biopsies, who underwent at least 2 consecutive colonoscopies. Of these, 86 patients had clinically and endoscopically active (MES≥2) disease at baseline colonoscopy, who underwent iterative treat-to-target interventions towards symptomatic remission and EI; colonoscopy was repeated within 1y in 53 (62%) patients. The remaining 49 patients were in ER/mild disease (MES≤1) at baseline, and on follow-up colonoscopy, 33 remained in ER/mild disease, and 16 developed endoscopic relapse (MES≥2) [Supp Fig 1].

Spatial evolution of histologic and endoscopic activity in patients with active disease at baseline, undergoing treat-to-target interventions

Baseline characteristics of 86 patients with clinically and endoscopically active disease at baseline is shown in Supplementary Table 1; one patient did not have histology at follow-up. Of these, 61 patients (71.8%) had histologic activity throughout the colon; the baseline distribution of histologic and endoscopic activity is shown in Supplementary Table 2.

Spatial evolution of histologic activity with treat-to-target interventions—Of 85 patients with active disease at baseline, 32 patients (37.6%) achieved histologic remission throughout the colon, with treat-to-target interventions; distribution of residual histologic activity per segment shown in Fig 1. None of the patients with exclusive left-sided histologic healing were receiving topical therapy and one patient had primary sclerosing cholangitis (PSC). Post-treatment histologic remission rates were higher in the right colon [Fig 2a-c]. Substantial agreement was observed for histologic remission between the right and left colon (kappa, 0.67; 95% CI, 0.51–0.83). Left-sided histologic findings on follow-up colonoscopy had excellent accuracy in detecting histologic remission throughout the colon, with AUC 0.96 (95% CI, 0.93–1.00), sensitivity 1.0 (95% CI, 0.87–1.00), specificity 0.91 (95% CI, 0.79–0.97), positive predictive value (PPV) 0.86 (95% CI, 0.70–0.95) and negative predictive value (NPV) 1.0 (95% CI, 0.91–1.00). [Fig 3a]. Rate of misclassification if only left-sided histologic findings were considered was 5.9%.

In examining a more stringent definition of histologic normalization, of 85 patients treated towards a target of EI, 7 patients (8.2%) achieved complete histologic normalization throughout the colon, with the distribution of residual non-normalized histology per segment given in [Fig 1]. Moderate agreement was observed for histologic normalization between the right and left colon (kappa, 0.41; 95% CI, 0.19–0.63). Left-sided findings of colonoscopy with biopsy had perfect accuracy in predicting the development of histologic normalization,

with an AUC of 1.0 [Fig 3b]. Sensitivity of left sided findings of colonoscopy with biopsy for detecting complete histologic normalization throughout the colon was 1.0 (95% CI, 0.56–1.0), with a specificity of 1.0 (95% CI, 0.94–1.00), PPV of 1.0 (95% CI, 0.56–1.00), NPV of 1.0 (95% CI, 0.94–1.00) and a misclassification rate of 0%.

In a subgroup analysis of patients with concordant histologic activity at baseline (71 patients) treated to target of EI, moderate agreement was observed for histologic remission between the right and left colon on follow-up colonoscopy (kappa, 0.55; 95% CI, 0.36–0.75) [Supplemental Table 3]. Left-sided histologic findings had excellent accuracy in detecting histologic remission throughout the colon (AUC, 0.97; 95% CI, 0.94–1.00).

Spatial evolution of endoscopic activity with treat-to-target interventions—Of 86 patients with active disease at baseline, 44 patients (51.2%) achieved EI throughout the colon with treat-to-target interventions; distribution of residual endoscopic activity per segment shown in Fig 1. Post-treatment endoscopic improvement rates were higher in the right colon [Fig 4]. Moderate agreement was observed for EI between the right and left colon (kappa, 0.58; 95% CI, 0.42–0.76). Left-sided endoscopic findings had excellent accuracy in detecting EI throughout the colon, with AUC 0.98 (95% CI, 0.96–1.00), sensitivity 1.0 (95% CI, 0.90–1.00), specificity 0.93 (95% CI, 0.79–0.98), PPV 0.94 (95% CI, 0.81–0.98) and NPV 1.0 (95% CI, 0.88–1.00) [Fig 3c]. Rate of misclassification if only left-sided endoscopic findings were considered was 3.5%. Similar observations were made when using a more stringent definition of ER (Supplementary appendix, Fig 3d).

Analysis of the subset of patients with concordant endoscopic activity at baseline (54 patients) treated towards a target of EI, substantial agreement was observed for the spatial evolution of EI between the right and left colon on follow-up colonoscopy (kappa, 0.66; 95% CI, 0.47–0.86) [Supplementary Table 3]. Left-sided findings of colonoscopy with biopsy had excellent accuracy in predicting the development of EI throughout the colon, with an AUC of 0.98 (95% CI, 0.95–1.00).

Predictors of spatial discordance on follow-up colonoscopy

On univariate analysis, we found that patients who had a longer interval between the index and follow-up colonoscopy had higher odds of achieving histologic concordance on follow up colonoscopy (OR, 1.07; 95% CI, 1.01–1.14). Due to small sample size, multivariable analyses were not performed. Similarly, on univariate analysis, patients who had a longer interval between the index and follow-up colonoscopy had higher odds of achieving endoscopic concordance on follow-up colonoscopy (OR, 1.07; 95% CI, 1.01–1.14).

DISCUSSION

In a well-characterized cohort of patients with UC evaluated with consecutive colonoscopies, we evaluated the spatial evolution of histologic, and endoscopic activity, between the right and left colon, and made several important observations. First, in patients with active UC managed using a treat to EI paradigm, evaluation of the left colon had excellent accuracy for detection of right-sided endoscopic and histologic disease

activity. If only flexible sigmoidoscopy had been performed, <6% patients would have been misclassified as having achieved EI and histologic remission, even though disease was active in the right colon. Second, both histologic and endoscopic disease activity tended to resolve consistently in the right colon relative to left-sided disease. Among patients with spatially concordant histologic and endoscopic disease activity in right and left colon, only 5% developed right-sided discordance on follow up that would have been misclassified by flexible sigmoidoscopy with biopsy. Third, patients who had longer intervals between consecutive colonoscopies are more likely to have spatial concordance in histologic and endoscopic disease, suggesting that longer intervals between procedures may allow time for uniform pancolonic mucosal healing.

Although treat-to-target strategies in UC currently focus on achieving EI, this area is potentially moving towards more stringent endpoints of endoscopic and histologic remission. However, assessment of these endpoints requires performance of endoscopy. Given the practicality of flexible sigmoidoscopy in clinical settings, if the diagnostic accuracy of sigmoidoscopy for assessment of both endoscopic and histologic disease activity was similar to colonoscopy, the former would be preferred. Similarly, for clinical trials where typically a minimum of 3 procedures are performed within a 52-week period, sigmoidoscopy would be a more tolerable option. Our findings demonstrate that left-sided colonoscopic evaluation had excellent accuracy for the detection of pancolonic histologic remission (AUC 0.96, misclassification rate 5.9%), histologic normalization (AUC 1.0, misclassification rate 0%), endoscopic improvement (AUC 0.95, misclassification rate 3.5%) and endoscopic remission (AUC 0.98, misclassification rate of 5.8%) provide strong evidence that flexible sigmoidoscopy is adequate for assessment of disease activity in most patients with active UC.

Our findings are also relevant to understanding the pathogenesis of UC. Although UC is conventionally characterized by contiguous inflammation involving the colon, starting from the anal verge to varying degrees proximally, a small subset of patients with UC may have atypical patterns of inflammation, such as the presence of a cecal patch, exclusive right-sided inflammation, relative sparing of the rectum, or segmental inflammation.[9] Rates of right-sided inflammation have been estimated at 3–4% in retrospective cohorts.[10, 11] However, to date, there has been very limited assessment of the spatial resolution of endoscopically/histologically defined inflammation following therapy. While Colombel and colleagues previously observed agreement between findings of rectosigmoid evaluation and full colonoscopy in the context of an induction trial, comparing concordance between rectosigmoidoscopy vs. full colonoscopy may artificially conflate agreement since full colonoscopy also includes rectosigmoid evaluation[4]. Moreover, the investigators presented data per video endoscopic evaluation, which makes interpretation of concordance rates at the patient level problematic. In contrast, we performed patient-level analyses that evaluated the pattern of resolution of EI under current treat-to-target paradigms. In contrast to findings from Colombel, who reported PPV 0.77 for rectosigmoidoscopy for evaluation of EI, we observed PPV 0.94. Timing of assessment may be responsible for part of this difference – while they examined discordant patterns of EI over 10 weeks, we assessed patients over 6–12 months, in a real-world practice setting. Importantly we also observed substantial agreement between the right and left colon for histologic outcomes, with left-

sided colonoscopic evaluation demonstrating positive predictive values of 0.81 and 1.00 in detecting pancolonic histologic remission and normalization.

Patients were more likely to achieve endoscopic improvement and histologic remission in the right colon, with evidence of persistent disease in the left colon. It is noteworthy that all patients in the cohort had pancolonic disease confirmed on endoscopy and histology, and a very small fraction of patients received topical therapy. Similarly, Christensen and colleagues found that histologic normalization tended to occur in the right colon before it occured in the left, and approximately 30% of patients who achieved right- sided remission had persistent microscopic inflammation in the left colon,[12] compared to the 18% estimated based upon our cohort. They also observed that only 1% of patients demonstrated residual *right* sided activity if the left colon normalized; in our cohort, using a similar definition of histologic normalization, we did not identify any patients with residual right-sided histologic activity if the left colon normalized. These findings support that isolated histologic activity in the right colon is rare, if the left colon has histologically normalized. Collectively, these findings provide reassurance that flexible sigmoidoscopy with biopsy, is an adequate surrogate for colonoscopic evaluation of histologic disease activity in clinical trials and practice.

Given that there was a small number of cases in which flexible sigmoidoscopy misclassified patients with persistent right sided disease as patients with pancolonic remission, a full colonoscopy may be warranted in patients with clinical and/or biochemical (elevated fecal calprotectin) evidence of active UC with normal flexible sigmoidoscopy, or patients with prior evidence of, or historically at higher risk of distal colonic sparing, such as pediatric patients or those with PSC.

Our study has important strengths and limitations. By focusing on patients with documented pancolonic inflammation, we avoided misclassification attributed to patients with only distal colitis. All endoscopies were performed by IBD-focused gastroenterologists. Histologic scoring was performed by a single pathologist blinded to clinical information using a pragmatic definition of histologic remission previously validated against the Geboes' score, with a very strong correlation[1] (r=0.85, CI [0.73–0.92]). While Geboes score and other his-tologic indices have proven utility in clinical trials, our definition of defining histologic remission as the absence of neutrophils from the lamina propria and epithelium may be more generalizable to routine clinical practice.

There are some limitations to our analyses. Due to the retrospective nature of our study, individual practitioners determined which patients underwent consecutive colonoscopies, potentially biasing towards patients deemed to be at higher risk of discordance. However, such a selection bias would result in even lower discordance estimates than were observed. The median interval between colonoscopies was wider than anticipated (12 months), also potentially introducing selection bias. Patients with good response to therapy at time of index colonoscopy, for instance, may have delayed their subsequent colonoscopy. However, serial colonoscopies are not commonly performed in the evaluation of ulcerative colitis patients undergoing T2T interventions, and these data therefore allow for the ascertainment of histologic and endoscopic healing throughout the colon longitudinally. The study sample

size was relatively small and limited evaluation of factors associated with the development of spatial discordance. Finally, we were unable to compare longer-term clinical outcomes in patients achieving segmental histologic remission relative to those with pancolonic histologic remission, which was beyond the scope of this study.

In conclusion, we observed that in patients with active UC treated towards a target of EI, evaluation of the left colon accurately classifies pancolonic histologic remission and EI, as well as the more stringent endpoints of histologic normalization and endoscopic remission. These findings suggest that flexible sigmoidoscopy would suffice for histologic and endoscopic monitoring in current treat-to-target treatment paradigms, as well as in advanced phase clinical trials for regulatory approval. Future prospective comparison of flexible sigmoidoscopy with colonoscopic monitoring in patients with UC is warranted to confirm these findings.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Disclosures:

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Abbreviations:

5-ASA	5-aminosalicylate
AUC	area under the curve
AUROC	area under the receiver operating characteristic
CI	confidence interval
ER	endoscopic remission
IBD	inflammatory bowel disease
IRB	institutional review board
IQR	interquartile range
JAK	Janus kinase
MES	mayo endoscopy score
NPV	negative predictive value
PSC	primary sclerosing cholangitis

RBS	rectal bleeding score
SFS	stool frequency score
UC	ulcerative colitis
UCSD	University of California, San Diego

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		Right Colon	
		MES≤1	**MES ≥ 2**
Left Colon	**MES≤1**	44 (51%)	3 (4%)
	MES ≥ 2	14 (16%)	25 (29%)
		MES 0	**MES > 0**
	MES 0	21 (24%)	5 (6%)
	MES > 0	24 (28%)	36 (42%)
		Histologic Remission	**Histologic Activity**
	Histologic Remission	32 (38%)	5 (6%)
	Histologic Activity	9 (11%)	39 (46%)
		Histologic Normalization	**Non-normalized histology**
	Histologic Normalization	7 (8%)	0 (0%)
	Non-normalized histology	15 (18%)	63 (74%)

MES= Mayo endoscopic score

Fig 1 -

Classification of endoscopic and histologic remission on follow up colonoscopy among patients with endoscopic moderately to severely active UC who underwent treat-to-target interventions.

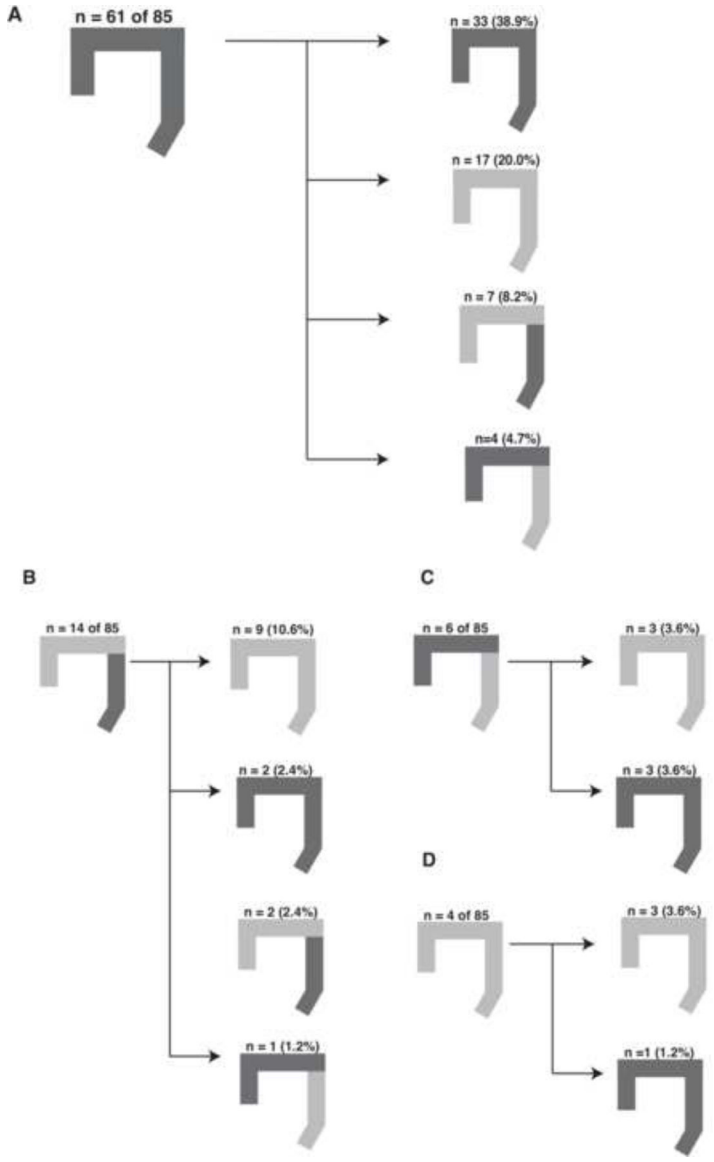

Fig 2 -

Spatial pattern of histologic remission (light grey) in UC patients with histologic activity (dark grey) who underwent treat-to-EI attempts (n=85) with baseline **(A)** pancolonically active histology (n=61) **(B)** exclusively left-sided histologic activity (n=14) **(C)** exclusively right-sided histologic activity (n=6) **(D)** pancolonic histologic remission (n=4).

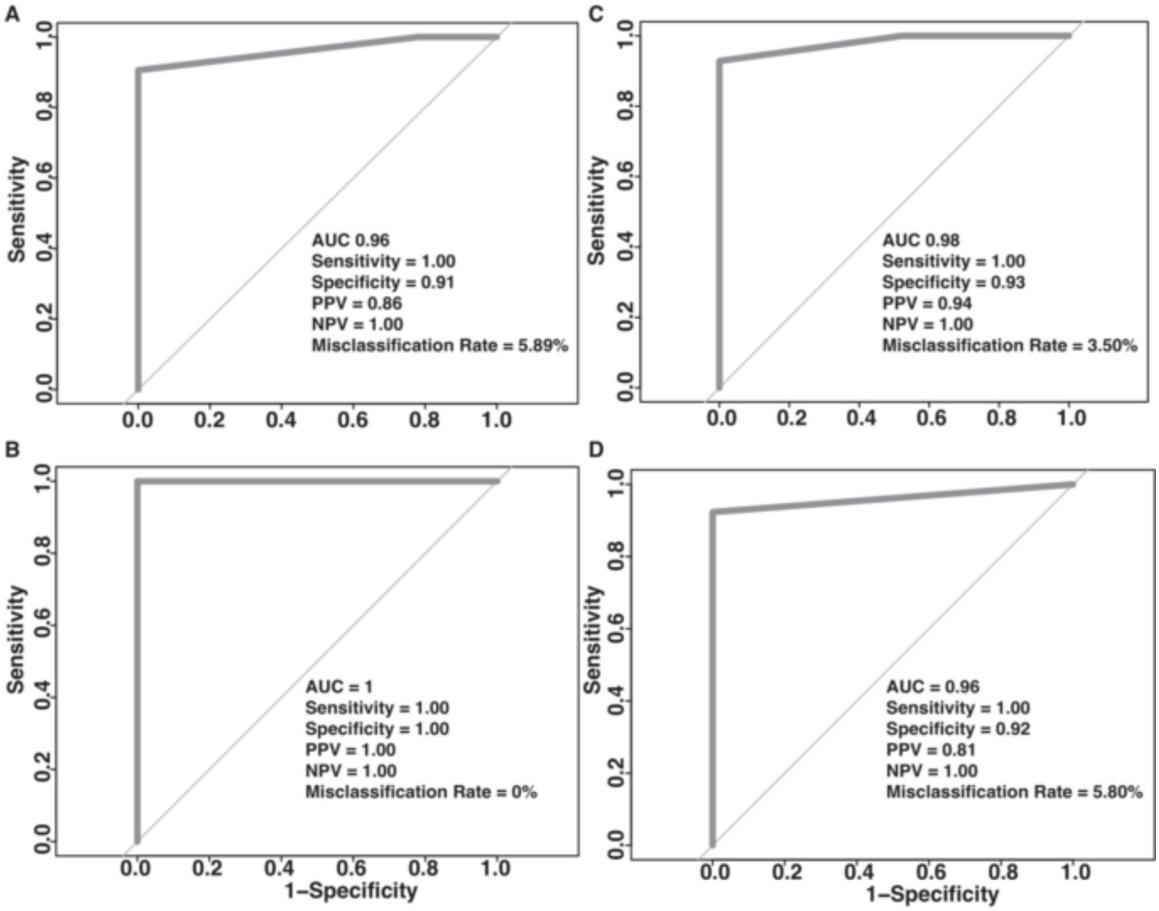

Fig 3 -

Following treat-to-EI interventions, accuracy of left-sided endoscopy in predicting (A) histologic remission anywhere in colon (AUC=0.96) (**B)** histologic normalization anywhere in colon (AUC=1.00) **(C)** endoscopic remission anywhere in colon (AUC=0.98) **(D)** complete endoscopic healing anywhere in colon (AUC=0.96).

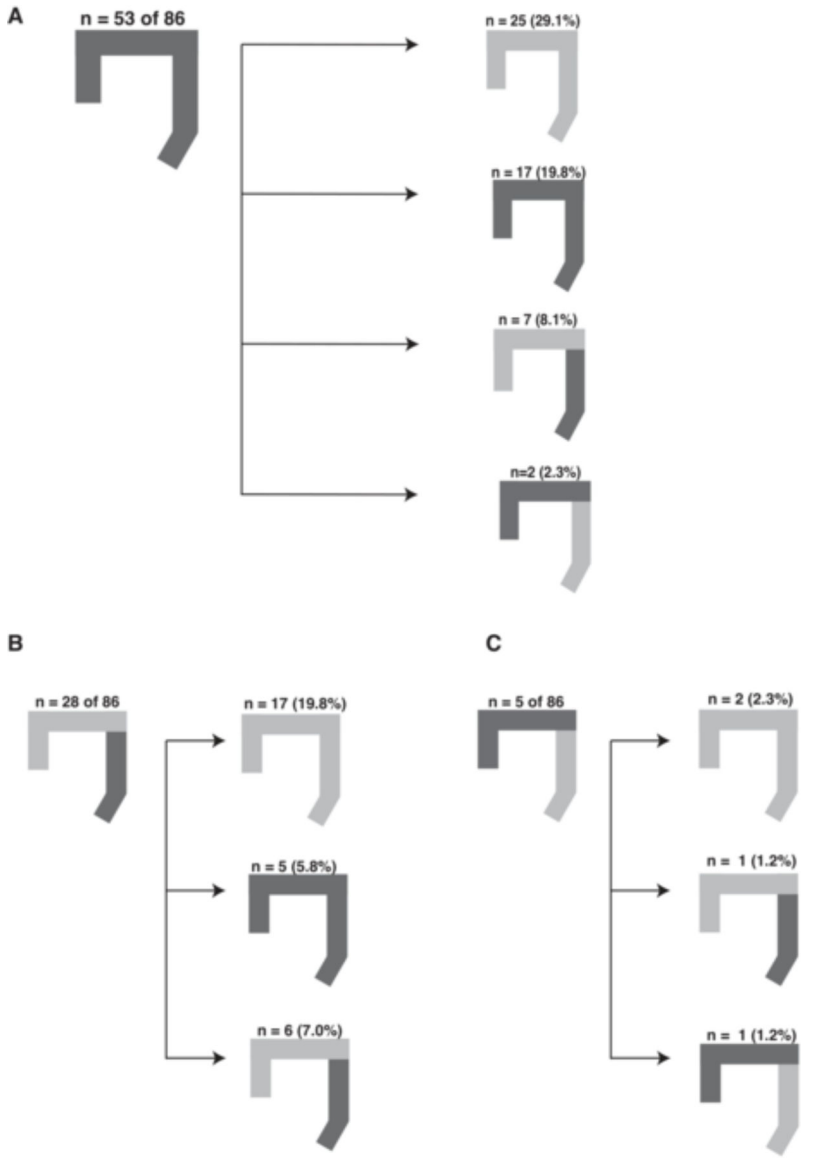

Fig 4 -

Spatial pattern of endoscopic improvement (light grey) in UC patients with endoscopic moderately to severely active endoscopic disease (dark grey) who underwent treat-to-EI attempts (n=86) with baseline **(A)** pancolonic endoscopic activity (n=53) **(B)** exclusively left-sided endoscopic activity (n=26) **(C)** exclusively right-sided endoscopic activity (n=5)