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Original Article

The Impact of Rectal Stump Inflammation After Subtotal Colectomy on Pouch Outcomes in Ulcerative Colitis Patients

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Abstract

Background and Aims: Proctitis after subtotal colectomy with ileostomy for ulcerative colitis [UC] is common, but its impact on short- and long-term outcome after pouch surgery is unknown. The aim of this study was to determine the incidence of proctitis after subtotal colectomy and its impact on postoperative morbidity and pouchitis.

Methods: The distal margin of the rectal stump of all consecutive patients undergoing completion proctectomy and pouch procedure for UC, between 1999 and 2017, was revised and scored for active inflammation according to the validated Geboes score, and for diversion proctitis. Pathological findings were correlated to complications after pouch surgery and pouchitis [including therapy-refractory] using multivariate analyses.

Results: Out of 204 included patients, 167 [82%] had active inflammation in the rectal stump and diversion colitis was found in 170 specimens [83%]. Overall postoperative complications and anastomotic leakage rates were not significantly different between patients with and without active inflammation in the rectal stump [34.7% vs 32.4%, $p = 0.79$, and 10.2% vs 5.4%, $p = 0.54$, respectively]. Active inflammation of the rectal stump was significantly associated with the development of pouchitis [54.3% vs 25.5%, $p$log = 0.02], as well as with therapy refractory pouchitis [14% vs 0%, $p$log = 0.05]. Following multivariate analysis, active inflammation was an independent predictor for the development of pouchitis. Diversion proctitis showed no association with these outcome parameters.

Conclusions: Active inflammation in the rectal stump after subtotal colectomy occurs in 80% of UC patients and is a predictor for the development of pouchitis and therapy-refractory pouchitis.

Key Words: Ileal pouch-anal anastomosis surgery, proctitis, pouchitis

1. Introduction

Despite improvements in medical treatment strategies, a colectomy is still required in up to 20% of ulcerative colitis [UC] patients.[1,2] For these patients, subtotal colectomy with ileostomy, followed by completion proctectomy and reconstruction with ileal pouch-anal anastomosis [IPAA], is the treatment of choice.[3] In the era of extensive treatment with biologics, it is preferred to perform the IPAA some months after the subtotal colectomy [modified two- and

three-stage IPAA] to enable patients to recover and wean off drugs.[4,5] Proctitis in the rectal stump after subtotal colectomy is common. It is unclear how often proctitis occurs, what the origin of the proctitis is, and what the consequences are for early- and long-term results after pouch surgery. It is suggested that patients with active inflammation in the rectal stump are at increased risk for anastomotic leakage during IPAA surgery.[6] In addition, it has been speculated that patients with persistent active inflammation in the rectal stump, despite subtotal colectomy, have a different prognostic phenotype of UC and are at higher risk of pouchitis when compared with patients with no [diversion] proctitis[7,8]—specially since pouchitis is hardly ever seen in patients undergoing pouch procedure for familial adenomatous polyposis coli [FAP].[9]

The aim of this study was to determine the incidence of active inflammation and diversion proctitis in the rectal stump after a subtotal colectomy in UC patients, and to correlate these pathological findings to short- and long-term outcomes.

2. Materials and Methods

2.1. Patients

All consecutive UC patients who underwent a subtotal colectomy with end ileostomy, followed by a completion proctectomy with pouch procedure with or without a defunctioning ileostomy [modified stage two- or three-stage procedure], between January 1999 and October 2017 at the Amsterdam UMC, Amsterdam, the Netherlands, were included from a prospectively maintained database. Patients: with Crohn's disease, colorectal dysplasia, or carcinoma requiring total mesenteric excision; younger than 18 years; or who underwent a proctocolectomy and pouch procedure in one stage, and of whom the pathological resection specimen was not available or of too low quality to reassess microscopic examination; were excluded.[10] This study was granted a waiver from the medical ethics committee. Reporting of the data adheres to the STROBE Statement.[11]

2.2. Histological features

The primary endpoint was the number of patients with active inflammation in the rectal stump according to the validated Geboes grading system. For clinical relevance the distal margin of the rectal stump was scored, as UC generally starts distally with more pronounced inflammation.[12] After pouch surgery, the specimen was handled by the pathologist according to standard operating procedures, which included collection of the distal resection margin of the rectal stump in paraffin blocks. All haematoxylin and eosin [H&E]-stained slides of the distal margin were revised by a dedicated pathologist and two researchers blinded to clinical outcome. In case of interobserver variation, consensus was established by re-evaluation of the slides using a multiheaded microscope.

The Geboes score [GS] consists of grades 0 to 5: 0] structural [architectural changes]; 1] chronic inflammatory infiltrate; 2A] eosinophils in lamina propria; 2B] neutrophils in lamina propria; 3] neutrophils in epithelium [cryptitis]; 4] crypt destruction; and 5] erosions or ulcerations. A higher score indicates more severe histological inflammation [see Supplementary Table 1, available as Supplementary data at ECCO-JCC online].[13] Recently, a GS cut-off of > 3, compared with the original cut-off of >2, is suggested to be more clinically relevant in distinguishing between UC patients in histological remission or activity [also in the context of the Robarts Histopathology and Nancy Indexes].[14,15] Hence, active inflammation in the resection margin was defined as a GS of > 3. Within the GS 5.1–5.4 score, GS 5.1 and 5.2 were considered not applicable, as elements of active inflammation could not be reliably scored in an obliterated lumen.[16]

Diversion proctitis can also present as mucosal inflammation, but with different histopathological features allowing for discrimination of this entity from active inflammatory bowel disease. Diversion is defined as the occurrence of lymphoid follicular hyperplasia in the lamina propria.[17–20] Diversion proctitis is also scored in the distal margin. Consequently, patients could have pathological characteristics of both active and diversion proctitis in the same slide, which could result in overlapping groups.

2.3. Variables and outcomes

Patient and disease characteristics were collected from a prospectively maintained pouch database. Active inflammation in the rectal stump was correlated to postoperative complications and pouchitis.

Postoperative complications were defined as any deviation from the normal postoperative course within 90 days after IPAA

Table 1. Histological features in the distal margin of the rectal stump.

Inflammation

No active inflammation			Active inflammation						
GS 0	GS 1	GS 2		GS 3		GS 4		GS 5	
$n = 0$	$n = 0$	$n = 37$		$n = 14$		$n = 52$		$n = 101$	
		2.0	1 [0.5%]	3.0	0 [0.0%]	4.0	0 [0.0%]	5.0	0 [0.0%]
		2.1	3 [1.5%]	3.1	9 [4.4%]	4.1	5 [2.5%]	5.1	n.a.
		2.2	0 [0.0%]	3.2	5 [2.5%]	4.2	32 [15.7%]	5.2	n.a.
		2.3	33 [16.1%]	3.3	0 [0.0%]	4.3	15 [7.4%]	5.3	27 [13.2%]
								5.4	74 [36.3%]

Diversion proctitis $n = 170$ [83.3%]

No active inflammation	Active inflammation		
GS 2 and DP $n = 28/37$ [75.7%]	GS 3 and DP $n = 10/14$ [71.4%]	GS 4 and DP $n = 47/52$ [90.4%]	GS 5 and DP $n = 85/101$ [84.2%]

DP occurred in 76% and 85% of patients with non-actively and actively inflamed rectal stumps, respectively, kappa 0.10.

GS, Geboes score; DP, diversion proctitis.

creation. Complications were graded according to the Clavien-Dindo Classification, and included for analysis if the score was 2 or higher.[21] If a patient had more than one complication, only the most severe complication was graded. Anastomotic leakages were classified according to the required management as: Grade A, conservatively treated leakage [antibiotics]; Grade B, leakage requiring active therapeutic intervention [eg, percutaneous drainage], but manageable without re-laparotomy/re-laparoscopy; and Grade C, leakage requiring surgical intervention.[22]

Patients were classified as having pouchitis if they were given medical therapy in the presence of clinical findings and/or endoscopic findings compatible with the diagnosis of pouchitis. Patients were categorised into three groups: one episode of pouchitis; multiple episodes; or therapy-refractory pouchitis. Therapy-refractory pouchitis was scored when patients required maintenance therapy or immunosuppressive therapy. Patients who were discharged from the Amsterdam UMC, and had their follow-up at the gastroenterology department of the referring hospital, were contacted by post, mail, or phone to assess frequency, dates, and treatment of pouchitis. If necessary the treating physician was contacted. Inflammation restricted to the remaining cuff, based on endoscopy, was defined as cuffitis.

2.4. Statistical analyses

Differences in baseline characteristics and postoperative outcomes, between patients with and without active inflammation in the distal margin of the rectal stump, were assessed using a chi square test for categorical variables, or in case of low counts [<5], a Fisher's exact test; for numerical variables, the unpaired t test was used. For normally distributed variables, mean and standard deviation [SD] were reported; for non-normally distributed variables, median and interquartile range [IQR] were reported. A kappa test was used to assess the overlap between pathological features. Kaplan-Meier analysis was used to compare the 10-year pouchitis-free survival with log rank testing. Confounders for the development of pouchitis were based on risk factors described in previous literature.[23] Using Cox regression, independent factors associated with pouchitis were identified. Variables with a *p*-value of $p \leq 0.1$ in the univariable analyses were included in the multivariable model, after assessing multicollinearity; *p*-values and confidence intervals [CI] were calculated at a 95% confidence level. For statistical analyses, SPSS Statistics, version 24 [SPSS, Chicago, IL] was used.

3. Results

3.1. Patients and histopathological findings

Out of 398 UC patients who had previously undergone subtotal colectomy [STC] followed by completion proctectomy with pouch surgery between January 1999 and October 2017 at the Amsterdam UMC, 204 patients could be included. The main exclusion criterion was one- or two-stage procedures [*n* = 109], and 21 patients had missing or low-quality histological distal margin rectal stump sections [Figure 1]. There were 112 men [55%] and the median age was 38 years. A total of 34 patients [17%] had been using suppositories or enemas [mainly steroids] to treat the rectal stump after subtotal colectomy within the 12 weeks preceding pouch surgery. In 37 patients [18%], no microscopic active inflammation was found in the rectal stump, all graded as GS 2. Of the 167 patients [82%] with a microscopically inflamed distal margin, most patients had a GS of 5.3 or 5.4 [*n* = 101]. Diversion proctitis was demonstrated in 170 resection specimens [83%], and 142 patients [70%] had both active and diversion proctitis. Nine patients [4.4%] had no active inflammation and no diversion proctitis in the rectal stump [Table 1]. Looking at baseline characteristics, the percentage of patients using anti-inflammatory medication to treat the rectal stump [suppositories or enemas] after STC and before pouch surgery was 18% and 11% in the group with and without an microscopically inflamed rectal stump in the resection specimen after pouch surgery, respectively, *p* = 0.459 [Table 2].

3.2. Postoperative complications

Overall complications after pouch surgery did not differ between the two groups [Table 3, *p* = 0.790]. Seventeen patients [10%] with an actively inflamed rectum developed anastomotic leakage, which was not statistically significantly different from the two patients [5%] without rectal stump inflammation [Table 3, *p* = 0.536].

3.3. Pouchitis

The median follow-up period was 5 years [IQR 2–9]. The pouchitis follow-up was up to date for *n* = 175 [86%] of the patients. The 10-year pouchitis rate was 50%, and was significantly higher in the patient group with an inflamed rectal stump when compared with patients with a non-inflamed rectal stump [54% vs 26%, *p*log = 0.024, respectively; Table 3 and Figure 2a]. Therapy-refractory pouchitis did not occur in patients without active inflammation in the rectal stump, and was significantly more frequently seen in patients with
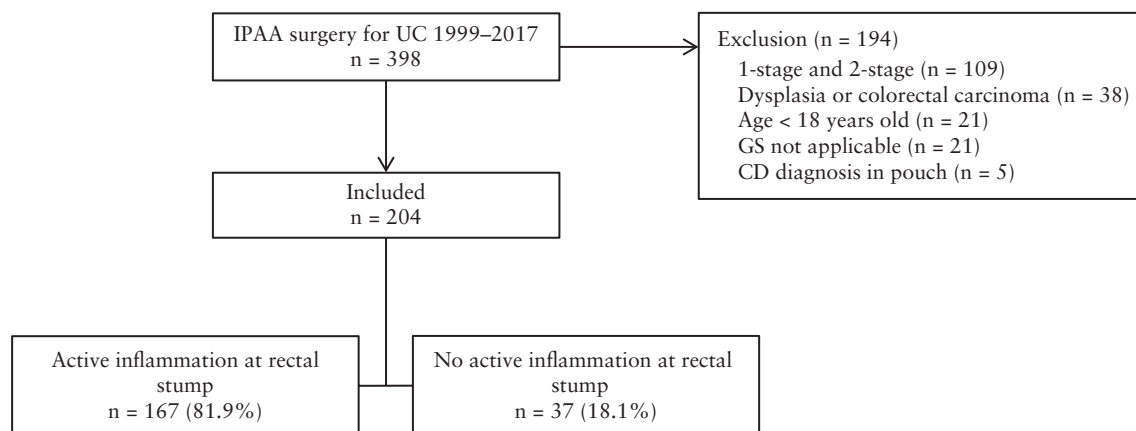

Figure 1. Study flowchart. IPAA, ileal pouch anal anastomosis; GS, Geboes score; CD, Crohn's disease.

Table 2. Baseline characteristics.

	Non-inflamed rectal stump *n* = 37 [18.1%]		Inflamed rectal stump *n* = 167 [81.9%]		*p*-value
Sex [M]	20	54.1	92	55.1	0.909
Age at IPAA surgery [years], mean SD	35.6	11.9	38.0	11.9	0.782
Time of IPAA surgery					0.461
1999–2010	12	32.4	65	38.9	
2010–2017	25	67.6	102	61.1	
Time between STC and IPAA [months], mean SD	23.9	35.7	19.8	26.3	0.100
BMI [kg/m²], mean SD	26.3	5.4	23.7	3.9	0.136
Diagnosis					0.498
UC	33	89.2	155	92.8	
IBDU	4	10.8	12	7.2	
PSC	2	5.4	3	1.8	0.224
ASA					>0.99
I-II	35	97.2	161	96.4	
III-IV-V	1	2.8	6	3.6	
Smoking					0.490
No	26	78.8	106	66.3	
Previously	3	9.1	41	25.6	
Yes	4	12.1	13	8.1	
Complications after STC	6	16.2	36	21.5	0.578
Unknown [STC other centre without clear rapport]	9	24.3	31	18.6	
UC left-sided	9	24.3	49	29.3	0.428
UC right-sided	3	8.1	5	3.0	
Pancolitis	11	29.7	57	34.1	
Toxic megacolon	7	18.9	25	15.0	
Unknown [preoperative scopy at other centre not received]	7	18.9	31	18.6	
Rectal stump therapy before IPAA [<12 weeks]	4	11.4	30	18.1	0.459
Steroid suppositories/enema useage	2	5.7	18	10.8	
Mesalazine suppositories/enema usage	2	5.7	12	7.2	
Systemic steroid useage before IPAA [<12 weeks, >20 mg/day]	0	0.0	12	7.2	0.132
Other systemic medication before IPAA <12 weeks]ᵃ					0.547
None	35	97.2	146	87.4	
Mesalazine	1	2.8	10	6.0	
Thioprine	0	0.0	4	2.4	
Anti-TNF	0	0.0	7	4.2	
Pouch procedure					0.467
Open	16	43.2	79	47.6	
Hand-assisted laparoscopic	10	27.0	53	31.9	
Total laparoscopic	11	29.7	34	20.5	
Stage of pouch procedure					0.716
Modified two-stage	31	83.8	133	79.6	
Three-stage	6	16.2	34	20.4	

ASA, American Society of Anesthesiologists; UC, ulcerative colitis; IBDU, inflammatory bowel disease unclassified; STC, subtotal colectomy; M, male; IPAA, ileal pouch-anal anastomosis; SD, standard deviation; BMI, body mass index; PSC, primary sclerosing cholangitis; TNF, tumour necrosis factor.

ᵃImmunosuppressive drug useage was defined as such when patients used steroids, immunomodulators (azathioprine [AZA], 6-mercaptopurine [6MP], and methotrexate [MTX]), or anti-tumour necrosis factor-alpha [anti-TNF] within 12 weeks preceding IPAA, considering the anti-TNF half-life.[24] In case of steroids, patients had to use more than 20 mg/day.[25]

active inflammation [14% vs 0%, *p*log = 0.054, Figure 2b]. For patients with or without diversion proctitis the 10-year pouchitis rates were comparable [53% vs 40%, *p* = 0.811]. Cuffitis was observed in 17 patients. All these patients had an actively inflamed rectal stump. The 10-year cuffitis rate was not significantly different between patients with and without an inflamed rectal stump [17% vs 0%, *p* = 0.074]. In patients with inflammatory bowel disease unclassified [IBDU] the pouchitis rate was 80.5%.

In univariate analyses, active inflammation in the rectal stump, IBDU diagnosis, and receiving systemic steroid within 3 months before pouch surgery, were associated with the development of pouchitis. As all 12 patients who used systemic steroids within 3 months before pouch surgery had an inflamed rectal stump, steroid useage was excluded from the multivariate model due to multicollinearity. In multivariate analysis, inflammation in the rectal stump (hazard ratio [HR] 2.6, 95% CI: 1.1–6.0, *p* = 0.025) and IBDU diagnosis [HR 2.5, 95% CI: 1.3–5.0, *p* = 0.006] remained significantly associated with the development of overall pouchitis [Table 4]. Thirteen patients needed permanent defunctioning, of whom nine had pouchitis; all nine also had

rectal stump inflammation. However, the incidence of therapy-refractory pouchitis and cuffitis was too low to perform multivariate analysis.

4. Discussion

This is the first study that systematically assessed inflammation in the rectal stump by a validated pathological scoring system, and correlated results to short- and long-term morbidity after pouch surgery. The study showed that the majority of patients [82%] had an actively inflamed rectal stump after subtotal colectomy, which was significantly associated with the development of pouchitis and therapy-refractory pouchitis. Active inflammation in the rectal stump was not significantly associated with overall postoperative complications or anastomotic leakage.

Table 3. Short- and long-term outcomes of patient with and without inflamed rectal stump.

	No inflamed rectal stump $n = 37$ [18.1%]		Inflamed rectal stump $n = 167$ [81.9%]		*p*-value
Overall complications	12	[32.4%]	58	[34.7%]	0.790
CD II	5	[13.5%]	25	[21.0%]	
CD III-IV	7	[18.9%]	33	[19.8%]	
Mortality	0	[0.0%]	0	[0.0%]	
Anastomotic leakage	2	[5.4%]	17	[10.2%]	0.536
Grade A	0	[0.0%]	0	[0.0%]	
Grade B	1	[2.7%]	1	[0.6%]	
Grade C	1	[2.7%]	16	[9.6%]	
10-year pouchitis	6	[25.5][a]	68	[54.3%] [a]	0.024[b]
1 episode	0		22		
Multiple episodes	6		46		
Therapy-refractory	0		17		

[a]Cumulative percentages.
[b]*p*log rank.

Table 4. Multivariate analyses.

Risk factors for 10-year pouchitis				
	Univariate [HR and CI]	*p* value	Multivariate [HR and CI]	*p* value
Clinical factors				
Female	0.914 [0.579–1.445]	0.701		
Diagnosis IBDU [ref: UC]	2.455 [1.258–4.788]	0.008	2.544 [1.304–4.963]	0.006
PSC	1.417 [0.445–4.512]	0.556		
Smoking [ref: no]		0.554		
Previously	1.322 [0.794–2.202			
Yes	1.178 [0.513–2.615]			
Complications after STC	0.980 [0.563–1.706]	0.944		
UC location [ref: right-sided]		0.958		
Left-sided	0.833 [0.288–2.413]			
Pancolitis	0.757 [0.262–2.189]			
Toxic megacolon	0.833 [0.268–2.585]			
Rectal stump therapy before IPAA	0.203 [0.660–2.191]	0.547		
Systemic steroid useage before IPAA	2.725 [1.352–5.492]	0.005	-	
Preoperative medication, any	1.001 [0.982–1.021]	0.891		
Anastomotic leakage	0.982 [0.450–2.141]	0.963		
Actively inflamed distal rectal stump	2.523 [1.094–5.815]	0.030	2.592 [1.124–5.978]	0.025
Diversion proctitis distal rectal stump	1.078 [0.581–2.002]	0.812		

UC, ulcerative colitis; IBDU, inflammatory bowel disease unclassified; STC, subtotal colectomy; IPAA, ileal pouch-anal anastomosis; PSC, primary sclerosing cholangitis; HR, hazard ratio; CI, confidence interval.

Previous studies suggested that it is difficult to differentiate between active inflammation and diversion colitis, as diversion colitis mimics or superimposes IBD changes.[26,27] Although discrimination might indeed be difficult endoscopically, microscopically the two pathological entities seem to present at different layers of the bowel wall. In this study, the entities were distinguished in the same H&E section. The occurrence of diversion proctitis [83%] is in accordance with previous series.[28] In contrast to active inflammation, diversion proctitis was not associated with any postoperative complication [including pouchitis]. Notably, this difference was not caused by a big variation in occurrence rates between diversion proctitis and active inflammation, since these rates were comparable. In accordance with these findings, no other studies have described an association between diversion proctitis and pouchitis, although it occurs very often after deviation for any kind of indication [eg, perforated diverticulitis, idiopathic obstipation, and incontinence]. Additionally, FAP patients are not known to develop pouchitis, although diversion proctitis occurs frequently in these patients. Large series have demonstrated that primary sclerosing cholangitisPSC is a risk factor for pouchitis.[29] In this study, the numbers of patients with PSC [*n* = 5] seemed too small to show a significant association between PSC and pouchitis.
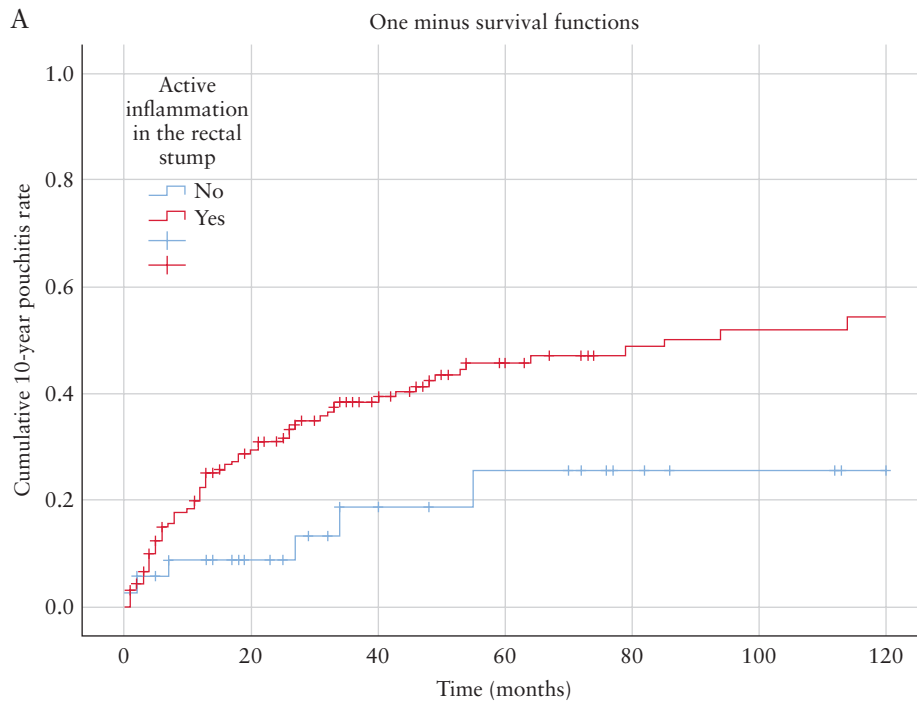
In this study, the total number of patients with anastomotic leakage was too small to demonstrate significant differences. Therefore despite not being significantly associated, an incidence twice as high in patients with active inflammation, compared with patients without active inflammation in the rectal stump, can still be a clinical relevant difference. It may become apparent in future studies. In univariate analyses, anastomotic leakage seemed not a predictor for pouchitis. However, insufficiently treated chronic anastomotic leakage can imitate pouchitis-like symptoms.[30]

These results of this study strengthen the hypothesis that patients with an actively inflamed rectal stump have a different prognostic phenotype of UC, with a higher risk for pouchitis—specially as an inflamed rectal stump was significantly associated with therapy-refractory pouchitis. In these patients with therapy-refractory
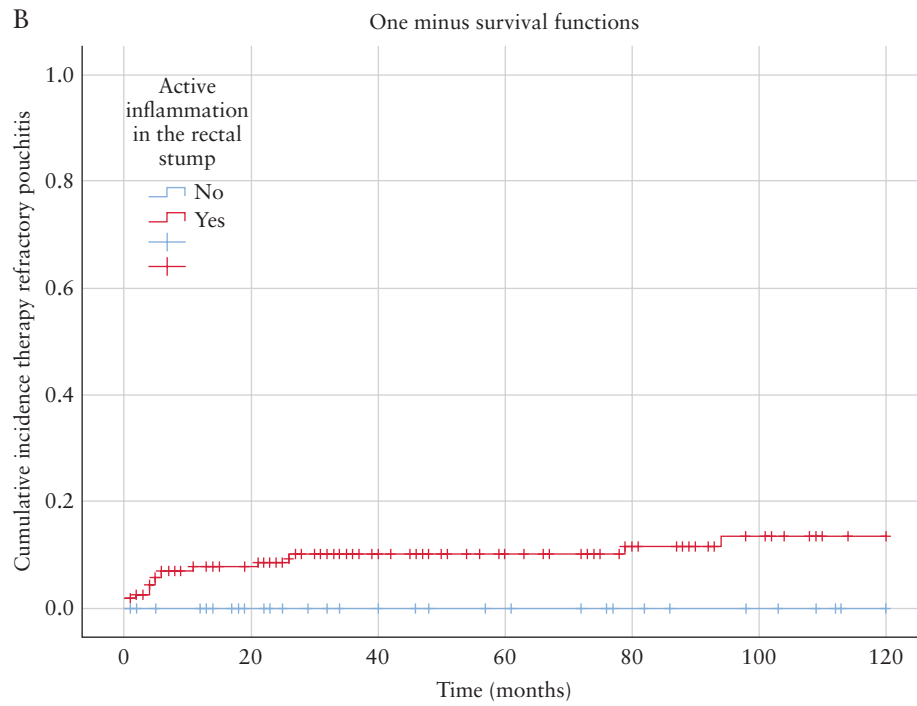
A

One minus survival functions

No. at risk	T = 0y	T = 5y	T = 10y
No	37	12	2
Yes	167	45	19

B

One minus survival functions

No. at risk	T = 0y	T = 5y	T = 10y
No	37	16	3
Yes	167	82	34

Figure 2. **[a]** Kaplan-Meier curve 10-year pouchitis rate in patients with inflamed and non-inflamed rectal stump. **[b]** Kaplan-Meier curve 10-year therapy-refractory pouchitis rate in patients with inflamed and non-inflamed rectal stump.

pouchitis, a different Crohn's like phenotype was considered, as their disease course was inexplicably severe. However, Crohn's disease could not be pathologically confirmed in these patients. Moreover, patients with postoperative pathologically confirmed Crohn's disease were excluded in this study. This pleads for the theory that different phenotypes can have different risk profiles. Furthermore, all 12 seriously ill patients, requiring systemic steroid useage within 3 months before IPAA surgery, had an inflamed rectal stump. Systemic steroid useage was significantly associated with pouchitis in univariate analyses, but was excluded for multivariate analyses because of this multicollinearity. It suggests that patients requiring systemic steroid have a more aggressive disease type. Furthermore, although not significantly different, a trend between proctitis and cuffitis was observed. It can be speculated that location of inflammation plays a role.

Therefore, it can be advised to prophylactically treat patients with a microscopically inflamed rectal stump, as these patients seem to have a higher risk profile. To facilitate this, pathological evaluation of the rectal stump should be implemented in daily clinical practice.

Ileorectal anastomosis [IRA] can be an alternative to IPAA in highly selected patients with a relatively spared rectum, good rectal compliance, and normal sphincter tone. Potential advantages of IRA are lower morbidity and preserved female fecundity. It could be considered to counsel patients without rectal stump inflammation for ileorectal anastomosis instead of an IPAA, following careful discussion with the patient regarding the increased risk of rectal cancer formation.[31] Last, patients with an inflamed rectal stump can be better informed and should be aware of their increased risk for pouchitis.

Limitations of this study are that pouchitis data were collected retrospectively and that no validated pouchitis score was used. This study emphasises the importance of pathological identification of active inflammation. Although pouchitis cannot be prevented, identifying high-risk patients is important for patient counselling. The follow-up of these patients may be intensified. However, since 80% of patients after an STC seemed to have active inflammation in the rectal stump, a first step for future studies could be to find a more specific marker for therapy-refractory pouchitis—specially as therapy-refractory pouchitis is an important reason for pouch failure.[32] Finally, for clinics performing ileorectal anastomosis, it could be hypothesised that the 20% of patients without active inflammation [regardless of diversion proctitis status] are the eligible patients for this procedure instead of an IPAA.

In conclusion, an actively inflamed rectal stump after STC is a risk factor for pouchitis. Identification of different prognostic UC phenotypes could improve patient counselling for IPAA surgery and pouchitis treatment.

Funding

Conflict of Interest

MD has served as adviser for Echo Pharma and Robarts Clinical Trials, reports non-financial support from Dr Falk Pharma, and received speaker fees from Janssen, Merck , Pfizer, Takeda, and Tillotts Pharma. CB has received consultancy fees and/or speaker's honoraria from AbbVie, Boehringer Ingelheim, and Takeda; she is part of the advisory board of Johnson & Johnson energy devices. WB has received a grant from Vifor, B. Braun, and Medtronic, and received speaker fees from Johnson & Johnson, Takeda, and AbbVie. The other authors declare having no conflict of interest.

Author Contributions

CB and WB conducted the study. KW, EvdD, LK, MD, CB, and WB collected and/or interpreted data. EvdD, KW, and CB drafted the manuscript. All authors approved the final draft submitted.

Supplementary Data

Supplementary data are available at *ECCO-JCC* online.

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