

Long-Term Outcomes in Indeterminate Colitis Patients Undergoing Ileal Pouch-Anal Anastomosis: Function, Quality of Life, and Complications

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Abstract

Introduction It is uncertain whether the outcomes of patients with indeterminate colitis (IC) undergoing ileal pouch-anal anastomosis (IPAA) deteriorate over time. The aim of this study was to determine the long-term pouch function, quality of life, complications, and incidence of Crohn's disease after IPAA for patients with IC compared to ulcerative colitis (UC).

Methods A case matched analysis was performed on patients undergoing IPAA for pathologically confirmed IC or UC, between 1985 and 2014. Patients were case matched for age ± 5 years, gender, date of surgery ± 3 years, type of anastomosis and presence of a diverting loop ileostomy. All patients were followed up for greater than six months.

Results 448 patients were case matched, the average age was 36.8 year old and 52.7 % of patients were male. Mean follow-up was 122.06 months (± 80.77 months). There were statistically and clinically comparable number of daytime bowel movements (5.7 v 5.5, $p = 0.45$), rates of incontinence (26.1 % v 18.3 %, $p = 0.09$) and nighttime seepage in patients (23.1 % v 28.4 %, $p = 0.28$) with IC and UC. Quality of life markers and patient restrictions were comparable between the two groups. Rates of pelvic sepsis (IC 8.5 %, UC 8.5 %, $p = 0.99$) and anastomotic leak (IC 3.1 %, UC 4.0 %, $p = 0.61$) were similar but fistula formation (IC 15.6 %, UC 8.0 %, $p = 0.01$) and IPAA Crohn's disease rates (IC 6.7 %, UC 2.7 %, $p = 0.04$) were significantly increased in IC patients. There was no statistically significant difference in pouch failure rates for IC and UC (5.8 % vs. 4.9 %, $p = 0.58$).

Conclusion Patients undergoing IPAA for IC have a higher risk of post-operative fistulae and development of Crohn's disease, but comparable morbidity, functional outcomes, quality of life scores and pouch failure rates when compared to UC patients. Long-term data confirms that IPAA is a good surgical option in patients with IC.

Keywords Indeterminate colitis · Ileal pouch-anal anastomosis · Restorative proctocolectomy · Outcomes · Quality of life

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Introduction

Proctocolectomy with ileal pouch-anal anastomosis has been established as the procedure of choice for ulcerative colitis (UC) patients who require surgical intervention. The diseased colon and rectum are removed and bowel continuity is restored, avoiding a permanent ileostomy and maximizing patient quality of life.¹

Since indeterminate colitis (IC) was first described by Price in 1978, it has presented a diagnostic and management dilemma. The diagnosis of IC is made in 5–20 % of colectomy specimens in patients with a preoperative diagnosis of UC and is based upon histopathological features of the surgical specimen.² Medical management for IC and UC is similar, but the surgical management for IC remains controversial. Previous studies have shown widely variable outcomes with pouch loss ranging between 0 and 27 % and development of subsequent Crohn's disease ranging between 6 and 15 %.^{3–12} This variability has in part been due to small study numbers, retrospective design, and the ambiguity associated with the diagnoses of both indeterminate colitis and Crohn's disease of the ileal pouch. It has led to an ongoing debate regarding the appropriateness of IPAA as a surgical option in IC patients. It remains unclear what the outcomes of patients with IC undergoing IPAA are and whether these deteriorate over time. A previous assessment of ileal pouch-anal anastomosis (IPAA) for IC in our institution indicated acceptable functional outcomes.⁶ However, as the risk of Crohn's disease of the ileal pouch might be cumulative over time, it is imperative to assess whether outcomes of IPAA for IC remain acceptable after long-term follow-up.

The aim of this study was to determine the long-term pouch function, quality of life, complications, incidence of Crohn's disease, and pouch loss after IPAA for patients with IC compared to UC.

Methods

A single-institution, prospectively maintained database of patients undergoing IPAA was used to identify IC patients with IPAA creation between 1985 and 2014. This database has the institutional research board approval and is HIPAA compliant. Database variables included in the study were patient demographics; preoperative clinical and histopathological diagnosis; preoperative perineal disease; operative details; post-operative complications, short term (<90 days after pouch creation) and long term (>90 days after pouch creation); post-operative bowel function; continence and seepage; post-operative diagnosis of Crohn's disease; and quality of life scores. Post-operative complications included septic complications (anastomotic leak, pelvic sepsis, and pouch related

fistula) and pouch failure as previously defined using specific criteria.¹

Patients with preoperative clinical features suggestive of Crohn's, including perianal sepsis, fistulae, or fissures, were excluded.

Patients were case matched with patients having a diagnosis of ulcerative colitis based on the following criteria: gender, age at time of surgery ± 5 years, surgery date ± 3 years, type of anastomosis, presence of diverting loop ileostomy, and length of follow-up ± 3 years.

All operations were performed at the Cleveland Clinic by fellowship-trained colorectal surgeons using a uniform technique as previously described.¹³

Patients were routinely followed up at 3 months and 1 year post-operatively, then annually. At each follow-up visit, a complete history and physical were performed and each patient was administered two validated questionnaires: the Cleveland Clinic Pouch Questionnaire and the Cleveland Global Quality of Life Instrument.^{1, 14} Follow-up data for the most recent patient visit was used for our analysis.

A diagnosis of UC/IC was made from the pathology specimen. Patients with preoperative clinical or radiological features of Crohn's disease were excluded.

Diagnosis of post-IPAA Crohn's disease was made by clinical features alone when clinical and/or radiological features were felt to be consistent with Crohn's disease, even without histological evidence, as judged and explicitly documented by an experienced gastroenterologist or colorectal surgeon. Clinical features were defined as ulcerated lesions of the small bowel or afferent limb without diffuse pouchitis present after 4 weeks of antibiotic therapy, ulcerated strictures of the small bowel, afferent limb, pouch, or pouch inlet associated with concurrent ulcers or inflammation of the afferent limb or development of a pouch fistula in the absence of a technical complication. These features must have been present for greater than 3 months after reversal of ileostomy to be determined Crohn's disease, as it was typically not possible to determine whether these early manifestations were secondary to Crohn's disease or technical complications.¹⁵

Pouch failure was defined as excision of the ileoanal pouch with permanent end ileostomy or not having the diverting loop ileostomy reversed, (indefinite stoma diversion).

Data and Statistical Analysis

Continuous measures were described as means, standard deviations, and percentiles. Categorical measures were summarized using frequencies and percentiles. Pearson's chi-square test or Fisher's exact test was used to assess the associations between colitis group and categorical measures. Comparisons with respect to the quantitative and ordinal variables were performed by Wilcoxon rank sum test (*W*) or Kruskal-Wallis test (*K*) for group comparisons. All tests were performed at a

significance level of 0.05. SAS 9.3 software (SAS Institute, Cary, NC) was used for all analyses.

Results

Case Matching

Two hundred twenty-four indeterminate colitis patients were case matched with ulcerative colitis patients as outlined above. Study groups were well matched for all the matching criteria (Table 1). In particular, the mean length of follow-up was 121 months for IC patients compared with 115 months for UC patients ($p = 0.69$). Over 97 % of patients in both groups underwent stapled anastomosis, and a diverting loop ileostomy was performed at the same time in almost 90 % of patients.

Post-Operative Complications

Short-term complications including anastomotic leak, pelvic abscess formation, and pelvic sepsis were no different between the two groups (Table 2). On the other hand, the long-term complications of fistula formation and development of Crohn's disease in the ileal pouch were both significantly increased in IC patients. However, the risk of pouch failure was not statistically different between IC patients and UC patients and did not exceed a 6 % rate (Table 3 and Fig. 1).

Pouch Function

There was no statistically significant or clinically meaningful difference in the number of daytime or nighttime bowel movements, rates of incontinence, and nighttime seepage in patients with IC compared to UC. Patients with both IC and UC had on average five bowel movements per day and two bowel movements at night after their IPAA procedure. Rates of

Table 1 Case matched variables for indeterminate colitis and ulcerative colitis patients undergoing IPAA

	Indeterminate colitis (n = 224)	Ulcerative colitis (n = 224)	p value
Male	118 (52.7 %)	118 (52.7 %)	0.99
Age (years)	36.8 ± 13.3	36.8 ± 13.0	0.95
Stapled anastomosis	218 (97.3 %)	218 (97.3 %)	0.99
Diverting loop ileostomy	195 (87.1 %)	200 (89.3 %)	0.47
Length of follow-up (months)	121 ± 84	115 ± 76	0.69

Table 2 Short-term post-operative complications in indeterminate colitis and ulcerative colitis patients undergoing IPAA

	Indeterminate colitis (n = 224) (%)	Ulcerative colitis (n = 224) (%)	p value
Anastomotic leak	7 (3.1)	9 (4.0)	0.61
Pelvic abscess	14 (6.2)	9 (4.0)	0.29
Pelvic sepsis	19 (8.5)	19 (8.5)	0.99

incontinence and pad usage at night time due to seepage were also similar between the two groups (Table 4).

Quality of Life Analysis

All quality of life scores except social restrictions were generally similar between the two groups. The average score for quality of life, health, and energy levels in both groups was 7 out of 10. Social restrictions were experienced by 22 % of IC patients vs. 14 % of UC patients, which was marginally significant with a p value of 0.05. Work, diet, and sexual restrictions were not statistically different. Most patients in both groups reported that they would undergo IPAA surgery again and would recommend this surgery to other people (Table 5).

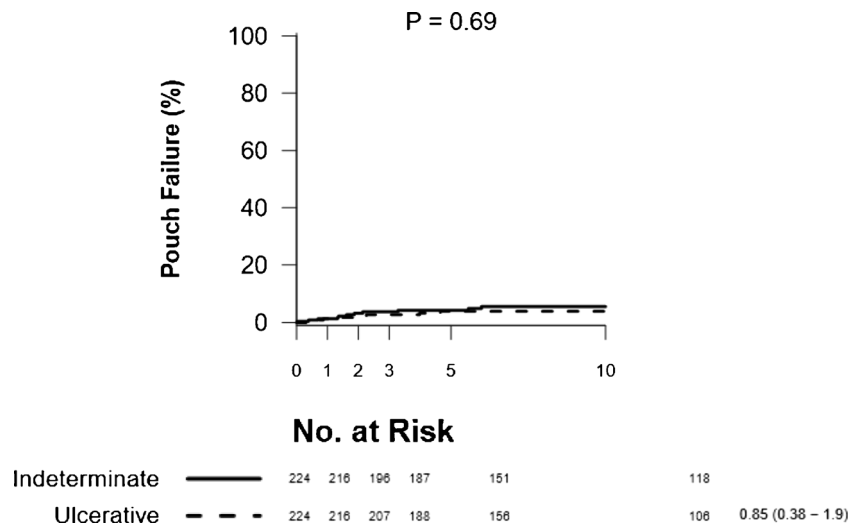
Discussion

The reluctance to perform an IPAA in patients with IC stems from the concern that these patients have a higher chance of being subsequently diagnosed with Crohn's disease and will therefore be subject to the increased complications of IPAA associated with Crohn's disease.^{4, 5, 16} We have shown that although patients with IC undergoing IPAA are associated with a higher risk of developing Crohn's disease, the actual pouch failure rates were not significantly higher than those among patients with UC. In addition, functional outcomes and quality of life parameters were similar between IC and UC patients. Our case match study design is unique among studies comparing IPAA for IC and UC and was selected to minimize selection bias in baseline patient characteristics,

Table 3 Long-term post-operative complications in indeterminate colitis and ulcerative colitis patients undergoing IPAA

	Indeterminate colitis (n = 224)	Ulcerative colitis (n = 224)	p value
Fistula	35 (15.6 %)	18 (8.0 %)	0.01
Crohn's disease of ileal pouch	15 (6.7 %)	6 (2.7 %)	0.04
Pouch failure	13 (5.8 %)	11 (4.9 %)	0.58
Happy to undergo IPAA again	94.8 %	94.5 %	0.90

Fig. 1 Kaplan–Meier curves demonstrating pouch failure rates for indeterminate colitis and ulcerative colitis patients undergoing IPAA



critical treatment-related variables and equalized the length of follow-up.

Previous retrospective, unmatched comparative studies have shown pouch failure rate for IC to be between 3.4 and 27 % and for UC to be between 2 and 11 % (Table 6), which is lower than or similar to many published series reporting on pouch loss among UC patients.^{4, 5, 7, 10} In our study, pouch loss was not significantly higher in IC patients, 5.6 % favorably compares to pouch failure rates that other studies have reported after IPAA for UC. This information is vital in the preoperative decision making and patient counseling. Our favorable results corroborate previous institutional findings of 3.4 and 3.5 % pouch failure rates for IC and UC, respectively, after a mean follow-up of 3.4 years after IPAA for IC vs. 5.5 years after IPAA for UC.⁶ We believe the relatively small increase in the pouch failure rates reported in the present study reflect a longer follow-up rate and did not reveal an unexpected spike in the onset of Crohn’s disease. A longer follow-up confirms IC as an appropriate indication for IPAA.

The findings of a significantly increased rate of Crohn’s disease of the pouch after IPAA for IC without a concurrent increase in the pouch failure rate when compared to UC counterparts is hardly surprising. In general, previous work from

our institution has indicated that IPAA associated with a diagnosis of Crohn’s disease is associated with an overall pouch retention rate of 71 % at 10 years and favorable functional results.¹⁵ This also included a subset of carefully selected patients undergoing IPAA with an established preoperative diagnosis of Crohn’s disease (intentional IPAA) so that IC patients should automatically fit the previously studied selection criteria for these Crohn’s patients (isolated colon and rectal disease without anoperineal or fistulous disease). In addition, development of a delayed diagnosis of Crohn’s disease of the ileal pouch does not inevitably result in pouch failure. Our institutional pouch survival rate after a mean follow-up of 7.9 years was 57 % and varied according to the phenotypical presentation of the ileal pouch Crohn’s disease, with penetrating disease being associated with the worst survival, but stricturing disease still compatible with long-term pouch salvage.¹⁷ Further studies might be able to clarify the specific presentations of delayed Crohn’s disease of the pouch among IC patients and their possible differences with patients originally diagnosed with UC.

Table 4 Pouch function in indeterminate colitis and ulcerative colitis patients undergoing IPAA

	Indeterminate colitis (n = 224)	Ulcerative colitis (n = 224)	p value
Number of daytime bowel movements	5.7 ± 2.9	5.5 ± 2.6	0.45
Number of nighttime bowel movements	2.2 ± 1.9	2.0 ± 1.6	0.34
Incontinence	26.1 %	18.3 %	0.09
Nighttime seepage	23.1 %	28.4 %	0.28

Table 5 Quality of life in indeterminate colitis and ulcerative colitis patients undergoing IPAA

	Indeterminate colitis (n = 224)	Ulcerative colitis (n = 224)	p = value
Quality of life	7.86 ± 1.74	7.90 ± 1.97	0.36
Quality of health	7.82 ± 1.73	7.73 ± 1.85	0.80
Level of energy	7.00 ± 2.13	7.60 ± 2.08	0.85
CGQL score	0.76 ± 0.17	0.76 ± 1.80	0.94
Social restrictions	21.7 %	14.4 %	0.05
Work restrictions	20.4 %	15.4 %	0.19
Diet restrictions	31.9 %	31.6 %	0.95
Sexual restrictions	24.2 %	18.9 %	0.19

Table 6 Selected series on outcomes of indeterminate colitis and ulcerative colitis following IPAA

Authors	Year	IC patients (n)	IC with Crohn's in pouch (%)	IC with pouch failure (%)	UC Patients (n)	UC with Crohn's in pouch (%)	UC with pouch failure (%)
Pezim	1989	25	8	8	489	NA	4
McIntyre	1995	71	11	19	1232	NA	8
Marcello	1997	42	13	12	499	3	2
Yu	2000	82	15	27	1437	2	11
Delaney	2001	115	6	3.4	1399	1.3	3.5
Rudolph	2002	35	NA	0	71	NA	6
Brown	2005	21	0	10	1135	NA	6
Murrell	2009	98	14	NA	236	11	NA

NA not applicable

Quality of life of patients undergoing IPAA regardless of their diagnosis is an important factor in choosing the correct surgical approach. IC patients undergoing IPAA have comparable quality of life indices to patients with UC. Social restrictions were more prevalent among patients with IC, but work, dietary, and sexual restrictions were not statistically different. Regardless of these restrictions, 95 % of patients in both groups would undergo IPAA again indicating the high level of patient satisfaction with this procedure.

Despite the case match design, our study remains limited by the constraints of a retrospective case series. Our database is prospectively maintained to overcome clinician and patient recall bias, which is particularly important for assessment of quality of life variables. In addition, the study population is derived from a specialist tertiary care center where surgery and pathology assessment were uniformly performed by experienced colorectal surgeons and pathologists. In the absence of large population-based studies on the topic of this specific study or even meta-analyses, our data might be less applicable to the wider surgical community.

The diagnosis of indeterminate colitis is a pathological diagnosis which may be suggested by colonoscopic biopsies, but cannot be confirmed until the surgical specimen is reviewed. Therefore, the diagnosis of indeterminate colitis may not have been made at the time of IPAA. In this instance, our paper provides valuable prognostic information rather than direct guidance in choosing the surgical intervention. If a possible diagnosis of Crohn's remains unclear at the time of surgery, a three-stage procedure could be considered. The pathology from the colon specimen can be used to confirm the diagnosis, and the decision as to whether to proceed with IPAA can be made with this knowledge. However, this data can be used to support the use of IPAA as a safe, durable surgical option in patients with IC.

The preoperative discussion with the patient regarding expected rates of short- and long-term complications, bowel function, and quality of life can be guided by this information and allow an evidence based decision to be made.

Conclusion

Patients undergoing IPAA for IC have a higher risk of post-operative fistulae and development of Crohn's disease, but comparable morbidity, functional outcomes, quality of life scores, and pouch failure rates when compared to UC patients. Long-term data confirms that IPAA is a good surgical option in patients with IC.

Author Contribution Jackson: Substantial contributions to the conception or design of the work; the acquisition, analysis, and interpretation of data for the work; drafting the work and revising it critically for important intellectual content; final approval of the version to be published; agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Stocchi: Substantial contributions to the conception or design of the work; the analysis and interpretation of data for the work; drafting the work and revising it critically for important intellectual content; final approval of the version to be published; agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Duraes: Substantial contributions to the conception or design of the work; the acquisition, analysis, and interpretation of data for the work; drafting the work; final approval of the version to be published; agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Remzi: Substantial contributions to the conception or design of the work; the acquisition of data, analysis, and interpretation of data for the work; revising the work critically for important intellectual content; final

approval of the version to be published; agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

- Fazio VW, Kiran RP, Remzi FH, Coffey JC, Heneghan HM, Kirat HT, Manilich E, Shen B, Martin ST. Ileal Pouch Anal Anastomosis: Analysis of Outcome and Quality of Life in 3707 Patients. *Ann Surg* 2013; 257:679–685
- Price AB. Overlap in the Spectrum of Non-Specific Inflammatory Bowel Disease—‘Colitis Indeterminate’. *Journal of Clinical Pathology* 1978; 31:567–577
- Koltun WA, Schoetz DJ, Roberts PL, Murray JJ, Collier JA, Veidenheimer MC. Indeterminate Colitis Predisposes to Perineal Complications After Ileal Pouch-Anal Anastomosis. *Dis Colon Rectum* 1991; 34:857–860
- McIntyre PB, Pemberton JH, Wolff BG, Dozois RR, Beart RW. Indeterminate Colitis Long-Term Outcome in Patients After Ileal Pouch-Anal Anastomosis. *Dis Colon Rectum* 1995; 38:51–54
- Sik Yu C, Pemberton JH, Larson D. Ileal Pouch-Anal Anastomosis in Patients with Indeterminate Colitis. *Dis Colon Rectum* 2000; 43:1487–1496
- Delaney CP, Remzi FH, Gramlich T, Dadvand B, Fazio VW. Equivalent Function, Quality of Life and Pouch Survival Rates After Ileal Pouch-Anal Anastomosis for Indeterminate Colitis and Ulcerative Colitis. *Ann Surg* 2002; 236:43–48
- Rudolph WG, Uthoff SM, McAuliffe TL, Goode ET, Petras RE, Galandiuk S. Indeterminate Colitis: The Real Story. *Dis Colon Rectum* 2002; 45:1528–1534
- Braveman JM, Schoetz DJ, Marcello PW, Roberts PL, Collier JA, Murray JJ, Rusin LC. The Fate of the Ileal Pouch in Patients Developing Crohn’s Disease. *Dis Colon Rectum* 2004; 47:1613–1619
- Pishori T, Dinnewitzer A, Zmora O, Oberwalder M, Hajjar L, Cotman K, Vernava AM, Efron J, Weiss EG, Noguera JJ, Wexner SD. Outcome of Patients with Indeterminate Colitis Undergoing a Double Stapled Ileal Pouch-Anal Anastomosis. *Dis Colon Rectum* 2004; 47:717–721
- Brown CJ, MacLean AR, Cohen Z, MacRae HM, O’Connor BI, McLeod RS. Crohn’s Disease and Indeterminate Colitis and the Ileal Pouch-Anal Anastomosis: Outcomes and Patterns of Failure. *Dis Colon Rectum* 2005; 48:1542–1549
- Tekkis PP, Heriot AG, Smith O, Smith JJ, Windsor ACJ, Nicholls RJ. Long-term Outcomes of Restorative Proctocolectomy for Crohn’s Disease and Indeterminate Colitis. *Colorectal Disease* 2005; 7:218–223
- Murrell ZA, Melmand GY, Ippoliti A, Vasiliauskas EA, Dubinsky M, Targan SR, Fleshner PR. A Prospective Evaluation of the Long-Term Outcome of Ileal Pouch-Anal Anastomosis in Patients with Inflammatory Bowel Disease-Unclassified and Indeterminate Colitis. *Dis Colon Rectum* 2009; 52:872–878
- Remzi FH, Fazio VW. Ileoanal pouch procedure for ulcerative colitis and familial adenomatous polyposis. Fischer JE, ed. *Mastery of Surgery*. Philadelphia, PA: Wolters Kluwer Health/Lippincott Williams & Wilkins; 2007:1475–1488
- Fazio VW, O’Riordain MG, Lavery IC, et al. Long-term Functional Outcome and Quality of Life after Stapled Restorative Proctocolectomy. *Ann Surg* 1999; 230:575–584
- Melton GB, Fazio VW, Kiran RP, He J, Lavery IC, Shen B, Achkar JP, Church JM, Remzi FH. Long-term Outcomes with Ileal Pouch-Anal Anastomosis and Crohn’s Disease. *Ann Surg* 2008; 248:608–616
- Marcello PW, Schoetz DJ, Roberts PL, Murray JJ, Collier JA, Rusin LC, Veidenheimer MC. Evolutionary Changes in the Pathologic Diagnosis after Ileoanal Pouch Procedure. *Dis Colon Rectum* 1997; 40:263–269
- Gu J, Remzi FH, Shen B, Vogel JD, Kiran RP. Operative Strategy Modifies Risk of Pouch-related Outcomes in Patients with Ulcerative Colitis on Preoperative Anti-Tumor Necrosis Factor- α Therapy. *Dis Colon Rectum* 2013; 56:1243–1252