

# Long-Term Outcomes With Ileal Pouch-Anal Anastomosis and Crohn's Disease

## *Pouch Retention and Implications of Delayed Diagnosis*

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**Objective:** To assess long-term outcomes after ileal pouch-anal anastomosis (IPAA) in Crohn's disease (CD).

**Summary Background Data:** Although considered the procedure of choice in ulcerative colitis, performance of ileal pouch-anal anastomosis (IPAA) is controversial in CD.

**Methods:** CD patients were identified from a prospectively maintained IPAA database. Time-to-diagnosis and pouch retention rates were analyzed using Kaplan-Meier curves. Demographic, clinical, and pathologic factors associated with pouch retention were evaluated with log-rank test and Cox proportional hazards model.

**Results:** Two hundred and four CD patients (108 female, median age 33 years, and median follow-up 7.4 years) with primary IPAA were included. CD diagnosis was before IPAA (*intentional*) in 20(10%), from postoperative histopathology (*incidental*) in 97(47%) or made in a *delayed* fashion at median 36 months after IPAA in 87(43%). Overall 10-year pouch retention was 71%. On multivariate analysis, pouch loss was associated with delayed diagnosis ( $P = 0.03$ , hazard ratio [HR] 2.6 (95% confidence interval [CI] 1.1–6.5)), pouch-vaginal fistula ( $P = 0.01$ , HR 2.8 (95% CI 1.3–6.4)), and pelvic sepsis ( $P = 0.0001$ , HR 9.7(95% CI 3.4–27.3)). Patients with retained IPAA at follow-up had near-perfect/perfect continence (72%), rare/no urgency (68%) with median daily bowel movements 7 (range 2–20). Median overall quality of life, quality of health, level of energy, and happiness with surgery were 9, 9, 8, and 10 of 10, respectively.

**Conclusions:** For CD patients with IPAA, when the diagnosis is established preoperatively or immediately following surgery, pouch loss rates are low and functional results are favorable. Outcomes in patients with delayed diagnosis are worse but half retain their pouch at 10 years with good functional outcomes.

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Restorative proctocolectomy with ileal pouch-anal anastomosis (IPAA) is widely accepted as the surgical procedure of choice in mucosal ulcerative colitis (MUC) and some patients with familial adenomatous polyposis. In several small studies, creation of IPAA in the setting of Crohn's disease (CD) has been associated with severe problems, including impaired pouch function, need for long-term medical therapy, or pouch loss. Manifestations of CD in the pouch include inflammation in the afferent limb, pouch, or cuff; stricture; and fistula which can result in incontinence, obstruction, frequency, urgency, and impaired quality of life (QOL).<sup>1</sup> As a result of the perception of a poor long-term prognosis and a high risk of adverse outcomes, patients with Crohn's colitis have typically not been offered IPAA, and the role of IPAA as a treatment option for Crohn's colitis remains poorly defined.

Panis et al reported on IPAA in patients having isolated Crohn's colitis without anoperineal involvement<sup>2</sup> and demonstrated good results at long-term follow-up.<sup>3</sup> The implication of these results has remained controversial, however, because of the variability in pathologic criteria used for diagnosis of CD.<sup>4</sup> A proportion of these CD patients could have been reclassified as indeterminate colitis (IndC) at other centers, which has been associated with comparable outcomes to MUC after IPAA<sup>5</sup> and would be a major factor producing the excellent results reported by Panis et al.

In addition to CD patients in whom an *intentional* IPAA is created, another subset with apparent MUC or IndC undergoing IPAA will have their diagnosis revised to CD on the basis of postoperative histopathology (*incidental* IPAA creation with CD) immediately after completion proctectomy or proctocolectomy, as the preoperative distinction between CD and MUC can be difficult in 5% to 10% of cases.<sup>6,7</sup> A third group of IPAA patients will be diagnosed with CD months or years after their surgery on the basis of subsequent clinical course or histopathology (*delayed* diagnosis). Several centers, including our own, have reported on these 2 patient subgroups with mixed results,<sup>8–12</sup> and so there is still no clear guidance for surgeons faced with patients having IndC or Crohn's colitis who need colectomy but are reluctant to have a permanent ileostomy.

The objective of this study was to evaluate and update the long-term outcomes of a large group of CD patients with

primary IPAA performed at a large specialized referral center. We sought to understand long-term risk factors for pouch failure, natural history of CD of the pouch, functional outcomes, and QOL in these patients.

## METHODS

### Patients and Inclusion Criteria

The Cleveland Clinic Department of Colorectal Surgery prospectively maintained database of IPAA surgical patients was used to identify CD patients with IPAA creation between 1983 and July 2007. This database has institutional research board approval and is HIPAA-compliant. Database variables comprise patient demographics, duration and extent of disease, previous surgery, preoperative extraintestinal manifestations, preoperative extent of disease, preoperative clinical diagnosis, and preoperative histopathological diagnosis. Surgical procedure details, length of stay, postoperative histopathological diagnosis, postoperative complications, and postoperative outcomes are also included.

All patients with a diagnosis of CD and primary IPAA created at the Cleveland Clinic were included in this study. Patients referred after IPAA creation elsewhere or who had IPAA revision were excluded. For the entire study period, a diagnosis of IndC did not preclude IPAA.<sup>5,13</sup> In contrast, IPAA in patients with a clear diagnosis of CD was avoided during the initial study period. Over the past decade, our policy has been modified such that select patients who are highly motivated with a histopathological diagnosis of CD with isolated colon and rectal involvement without anoperineal or fistulous disease occasionally would be offered IPAA as a therapeutic treatment option.

### Protocol

All IPAA patients were followed annually using standardized protocols consisting of clinic visits where physical examination, pouch endoscopy, and pouch biopsy were performed, along with administration of functional status and QOL questionnaires.<sup>14</sup> Routine IPAA endoscopy included biopsies of the pouch body, afferent limb, and anal-transition zone. Additionally, QOL assessments were made prospectively using the previously validated Cleveland Clinic Global Quality of Life (CGQL) instrument with scores ranging from 0 to 10 for the various components of CGQL (0: worse, 10: best) and from 0 to 1 for CGQL (0: worse, 1: best).<sup>15,16</sup> Additional clinical outcomes and QOL assessments were made using medical charts, standardized mailed questionnaires, and telephone interviews where appropriate.

### Histopathological Diagnosis of Crohn's Disease

Pathology specimens from our institution, as well as outside pathology slides, were routinely reviewed at the Cleveland Clinic by gastrointestinal pathologists. Employing standards currently used at this institution and based on previous reports,<sup>17</sup> the diagnosis of CD was made based on the presence of nonnecrotizing granulomas or transmural lymphoid aggregates outside an area of deep ulceration, particularly in the presence of segmental lymphoid inflammation.

### Clinical Diagnosis of Crohn's Disease of the Pouch

The clinical diagnosis of CD of the pouch was classified as previously described by our group.<sup>1,18</sup> Because of the anatomic alterations from pouch formation, the Vienna<sup>19</sup> and Montreal<sup>20</sup> classifications do not directly apply to patients following IPAA. Patients with inflammatory CD of the pouch will have ulcerated lesions of the small bowel or afferent limb without diffuse pouchitis (excludes backwash pouchitis). These ulcers are persistent despite at least 4 weeks of antibiotic therapy. In patients with fibrostenotic CD of the pouch, examination of the pouch will reveal ulcerated strictures of the small bowel, afferent limb, pouch, or pouch inlet with concurrent ulcers or inflammation of the afferent limb, excluding nonsteroidal anti-inflammatory drug use. The third phenotype is fistulizing CD of the pouch defined by fistula development at interval time period following ileostomy takedown in the absence of surgically related local complications. Whereas most IPAA patients with clinical evidence of CD had disease confined to the pouch, a small number of patients developed CD in the more proximal areas of the small bowel.

### Definitions

We classified the diagnosis of CD with IPAA into 3 categories: preoperative diagnosis of CD if the diagnosis was made prior to restorative proctocolectomy (*intentional* pouch created with CD), diagnosis made immediately postoperatively from histopathological review of the surgical specimens following IPAA (*incidental* pouch created with CD), or diagnosis made in a *delayed* fashion remote to IPAA. Delayed diagnosis could be made by clinical features alone consistent with CD during follow-up or by confirmatory histopathology characteristic of CD, often in the presence of clinical features consistent with CD. In particular, a diagnosis of CD on the basis of clinical evaluation alone was made when clinical and/or radiologic features were felt to be consistent with CD, despite lack of histologic data, as judged and explicitly documented by an experienced gastroenterologist or colorectal surgeon. Patients with postoperative pouch problems (such as fistula) that might be indicative of CD without histopathological support, when occurring 3 months or earlier following ileostomy reversal, were not classified as having CD on this basis alone as it was typically not possible to determine the etiology of these complications and to distinguish between true CD manifestations and technical or postoperative complications.

Restorative proctocolectomy was categorized using standard definitions. A 1-stage procedure occurred when total proctocolectomy with IPAA was performed in a single procedure without a diverting stoma; a 2-stage procedure comprised total proctocolectomy with IPAA and loop ileostomy followed by ileostomy closure. Finally, a 3-stage procedure included subtotal colectomy followed by completion proctectomy with IPAA and loop ileostomy and then ileostomy closure. For the purpose of analysis, we considered a patient to have a pouch retained if at the time of follow-up the pouch was functioning in circuit. Conversely, those with diversion

or excision of their pouch were considered to have pouch failure.

**Statistical Analysis**

Statistics were performed using established methods. Statistical significance was accepted for  $P < 0.05$ . Unadjusted bivariate comparisons of continuous variables were performed using the Mann-Whitney rank sum test and comparisons of categorical variables using a  $\chi^2$  test. Time until diagnosis and pouch retention were analyzed using Kaplan-Meier curves. Clinicopathologic factors associated with

pouch retention were evaluated with log-rank test and Cox proportional hazards model to express hazard ratios (HR). Data are expressed as medians, with 95% confidence intervals (CI) included where appropriate.

**RESULTS**

Of the 2,834 patients with inflammatory bowel disease who underwent primary IPAA over the study period, 204 patients (7%) had a diagnosis of CD at the time of the study. As shown in Table 1, preoperative diagnosis with *intentional* pouch occurred in 20(10%), perioperative diagnosis with *incidental* pouch occurred in 97(47%), and *delayed* diagnosis occurred in 87 (43%) patients. The patients with delayed diagnosis had confirming histopathology in 32 (37%) or diagnosis on clinical evaluation alone in 55 (63%) at a median of 36 months after IPAA.

Table 2 summarizes the demographics, preoperative indications, and operative details for the cohort. Patients with *intentional* pouch were more likely to be female in comparison to those with *incidental* pouch or *delayed* CD diagnosis. In addition, patients with *delayed* CD diagnosis were significantly younger than patients with *incidental* pouch but not *intentional* pouch. Delayed CD diagnosis

**TABLE 1.** Diagnosis of Crohn's Disease in Patients With Restorative Proctocolectomy and Ileal Pouch-Anal Anastomosis

Total	204 (100%)
<i>Intentional</i> CD pouch: preoperative diagnosis	20 (10%)
<i>Incidental</i> CD pouch: perioperative diagnosis	97 (47%)
<i>Delayed</i> CD diagnosis	87 (43%)
Confirming histopathology	32 (37%)
Clinical diagnosis alone	55 (63%)

CD indicates Crohn's disease.

**TABLE 2.** Restorative Proctocolectomy and Ileal Pouch-Anal Anastomosis in 204 Patients With Crohn's Disease

	Total	Diagnosis of CD		
		<i>Intentional</i> CD Pouch	<i>Incidental</i> CD Pouch	<i>Delayed</i> CD Diagnosis
Total	204	20 (10%)	97 (47%)	87 (43%)
Female	108 (53%)	16 (80%)*†	45 (46%)*	47 (54%)†
Age (median, range) in years	33 (15–74)	30 (15–63)	36 (15–74)‡	29.5 (15–58)‡
Pre-IPAA diagnosis				
Ulcerative colitis	128 (63%)	—	61 (63%)	67 (77%)
Indeterminate colitis	56 (27%)	—	36 (37%)	20 (23%)
Crohn's disease	20 (10%)	20 (100%)	—	—
Length of pre-operative IBD history (median, range) in years	6.8 (0.2–33)	6.6 (0.2–33)	8.6 (0.2–32)‡	5.3 (0.3–30)‡
Indication for surgery				
Failed medical management	109 (53%)	7 (35%)	44 (45%)	58 (67%)
Medication dependency/toxicity	69 (32%)	10 (50%)	37 (38%)	22 (25%)
Dysplasia	16 (8%)	1 (5%)	11 (11%)	4 (5%)
Other	10 (5%)	2 (10%)	5 (5%)	3 (3%)
Operative treatment				
1-stage	2 (1%)	0 (0%)	0 (0%)	2 (2%)
2-stage	120 (59%)	12 (60%)	77 (79%)‡	31 (36%)‡
3-stage	82 (41%)	8 (40%)	20 (21%)	54 (62%)
Pouch type				
J-pouch	178 (88%)	19 (95%)	83 (86%)	76 (87%)
S-pouch	26 (13%)	1 (5%)	14 (14%)	11 (13%)
Anastomosis				
Stapled	156 (76%)	17 (85%)	72 (74%)	67 (77%)
Mucosectomy	48 (24%)	3 (15%)	25 (26%)	20 (23%)
Follow-up after IPAA (median, range) in years	7.4 (0.3–23)	5 (1–13)†§	9 (0.3–23)§	6 (0.3–22)†

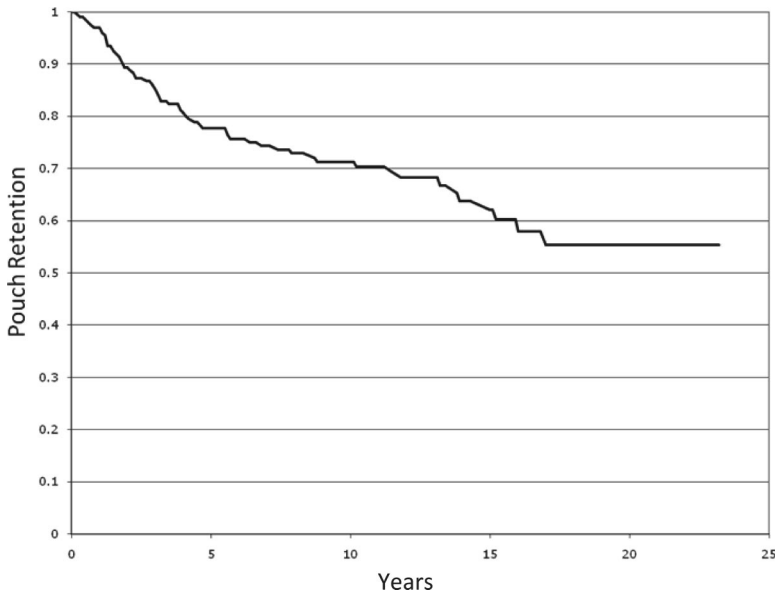
\* $P < 0.01$ , *intentional* CD pouch versus *incidental* CD pouch.

† $P < 0.05$ , *intentional* CD pouch versus *delayed* CD diagnosis.

‡ $P < 0.001$ , *delayed* CD diagnosis versus *incidental* CD pouch.

§ $P < 0.05$ , *intentional* CD pouch versus *incidental* CD pouch.

CD indicates Crohn's disease; IPAA, ileal pouch-anal anastomosis; IBD, inflammatory bowel disease.



**FIGURE 1.** Overall pouch retention in ileal pouch-anal anastomosis patients with Crohn's disease.

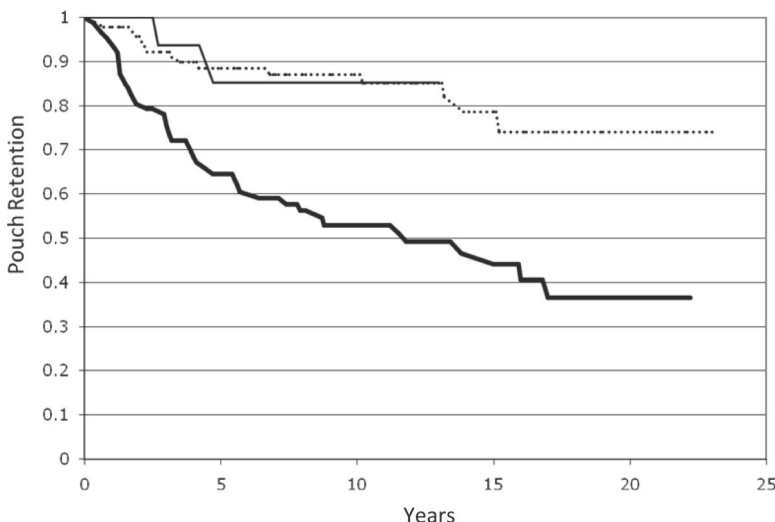
patients were more likely to have a 3-stage IPAA when compared with patients with *incidental* pouch ( $P < 0.001$ ) and, whereas not significant, also appeared more likely to have a 3-stage procedure when compared with patients with *intentional* pouch (62% versus 21%). Median follow-up for all patients was 7.4 (range 0.3–23) years and was significantly less in patients with *intentional* pouch.

Pouch retention for the entire cohort is depicted in Figure 1. Pouch retention rates were worse in patients with delayed diagnosis when compared with those with *intentional* or *incidental* pouch formation ( $P < 0.0001$ ), such that 10-year retention was 71% overall, 85% with intentional pouch formation, 87% with incidental pouch formation, and 53% with delayed diagnosis (Fig. 2).

On univariate analysis, younger patients (age <30 years), delayed CD diagnosis, history of mouth ulcers, history of anal fissure, 3-stage procedure, postoperative pouch-vaginal fistula, postoperative perianal fistula, and postoperative abdominopelvic

sepsis were associated with pouch loss (Table 3). Smoking status postoperatively, preoperative pathology, postoperative Infliximab or steroid use, preoperative nutritional status (albumin <3.0), and other extraintestinal manifestations were not associated with differences in pouch-retention rates. In addition, the rate of pouch loss was similar in patients with delayed diagnosis made with confirmatory histopathology or clinical factors alone. On multivariate analysis, pouch loss remained associated with delayed diagnosis ( $P = 0.03$ , HR 2.6 (95% CI: 1.1–6.5)), pouch-vaginal fistula ( $P = 0.01$ , HR 2.8 (95% CI: 1.3–6.4)), and abdominopelvic sepsis ( $P = 0.0001$ , HR 9.7 (95% CI: 3.4–27.3)) (Table 4).

At long-term follow-up, CD patients with IPAA often had disease sequelae (Table 5). The most frequent problems were pouchitis (54%); fistulous disease (35%, including pouch-vaginal fistula (24%, 26 of 108 females) and perianal fistula (25%)); and IPAA stricture (24%). These same problems were significantly more common in patients with a



**FIGURE 2.** Pouch retention of Crohn's disease. Patients with intentional CD pouch (solid thin line) and incidental CD pouch (dotted line) had significantly longer retention compared with those with delayed diagnosis (solid thick line) ( $P < 0.0001$ ).

**TABLE 3.** Restorative Proctocolectomy and Ileal Pouch-Anal Anastomosis in Crohn's Disease: Univariate Analysis of Factors Associated With Pouch Loss

Factor	Level	N	Failure/Total (%)	P	
Patient factors					
Gender	Male	96	29/96 (30%)	NS	
	Female	108	32/108 (30%)		
Age	<30 yr	77	32/77 (42%)	0.02	
	≥30 yr	127	29/127 (23%)		
CD diagnosis	Intentional pouch	20	2/20 (10%)	0.02*	
	Incidental pouch	97	15/97 (15%)		<0.0001 <sup>†</sup>
	Delayed diagnosis	87	44/87 (51%)		
Postoperative smoking status	Yes	39	15/39 (38%)	NS	
	No	165	46/165 (28%)		
Pre-operative albumin	<3.0	12	4/12 (33%)	NS	
	>3.0	182	56/182 (31%)		
Pre-operative diagnosis	IndC	56	16/56 (29%)	NS	
	MUC	128	42/128 (33%)		
Extra-intestinal manifestations					
Liver or bile duct involvement	Yes	12	5/12 (42%)	NS	
	No	185	55/185 (30%)		
Skin involvement	Yes	10	2/10 (20%)	NS	
	No	191	57/191 (30%)		
Mouth Ulcers	Yes	10	5/10 (50%)	0.05	
	No	182	51/182 (28%)		
Eye involvement	Yes	5	1/5 (20%)	NS	
	No	199	59/138 (43%)		
Bone or joint involvement	Yes	46	12/46 (26%)	NS	
	No	155	47/155 (30%)		
Intestinal disease					
Prior anal fissure	Yes	12	6/12 (50%)	0.04	
	No	192	50/192 (26%)		
Prior anal fistula	Yes	16	5/16 (31%)	NS	
	No	188	56/188 (30%)		
Prior stricture disease	Yes	12	2/12 (17%)	NS	
	No	185	53/185 (29%)		
Backwash Ileitis	Yes	11	3/11 (27%)	NS	
	No	149	45/149 (30%)		
	Not documented	6	3/6 (50%)		
Operative factors					
Procedure Stage	1-stage	2	1/2 (50%)	NS	
	2-stage	120	27/120 (23%)		0.009 <sup>‡</sup>
	3-stage	82	33/82 (43%)		
Pouch type	J-pouch	178	52/178 (29%)	NS	
	S-pouch	26	9/26 (35%)		
Anastomosis	Stapled	156	42/156 (27%)	NS	
	Mucosectomy	48	19/48 (40%)		
Postoperative medical treatments					
Postoperative steroids	Yes	37	16/37 (43%)	NS	
	No	168	43/168 (26%)		
Postoperative Infliximab	Yes	20	5/20 (25%)	NS	
	No	184	56/184 (30%)		
Postoperative outcomes					
Pouch-vaginal fistula	Yes	26	14/26 (54%)	0.02	
	No	82	18/82 (22%)		
Perianal fistula	Yes	52	28/52 (54%)	0.0002	
	No	152	33/152 (22%)		

(Continued)

TABLE 3. (Continued)

Factor	Level	N	Failure/Total (%)	P
Pouchitis	Yes	110	33/110 (30%)	NS
	No	94	28/94 (30%)	
IPAA stricture	Yes	48	16/48 (33%)	NS
	No	156	45/156 (29%)	
Afferent stricture	Yes	8	2/8 (25%)	NS
	No	196	59/137 (43%)	
Abdominopelvic sepsis	Yes	25	16/25 (64%)	<0.0001
	No	179	45/179 (25%)	
Obstruction	Yes	28	7/28 (25%)	NS
	No	176	54/176 (31%)	

\*Intentional pouch versus delayed diagnosis.

†Incidental pouch versus delayed diagnosis.

‡2-stage versus 3-stage.

CD indicates Crohn's disease; IPAA, ileal pouch-anal anastomosis; MUC, mucosal ulcerative colitis; IndC, indeterminate colitis; NS, not significant.

TABLE 4. Multivariate Analysis of Factors Associated With Pouch Loss

Factor	HR (95% CI)	P
Age <30 yr	1.3 (0.8–3.1)	0.26
Delayed CD diagnosis	2.6 (1.1–6.5)	0.03
Mouth ulcers	1.9 (0.7–3.8)	0.17
Prior anal fissure	1.5 (0.9–2.5)	0.13
3-stage IPAA	1.2 (0.8–1.8)	0.36
Postoperative pouch-vaginal fistula	2.8 (1.3–6.4)	0.01
Postoperative perianal fistula	1.3 (0.6–2.6)	0.56
Postoperative abdominopelvic sepsis	9.7 (3.4–27.3)	0.0001

HR indicates hazard ratio; CI, confidence interval; CD, Crohn's disease; IPAA, ileal pouch-anal anastomosis.

delayed diagnosis compared with those with *intentional* or *incidental* CD pouch: pouchitis (72% versus 40%,  $P < 0.0001$ ); fistulous disease (55% versus 19%,  $P < 0.0001$ ); pouch-vaginal fistula (38% versus 13%,  $P = 0.004$ ); perianal fistula (45% versus 11%,  $P < 0.0001$ ); and IPAA stricture (32% versus 17%,  $P = 0.01$ ). When a subgroup analysis of patients with a delayed diagnosis was performed, there were no differences in disease sequelae between patients with confirmatory histopathology and those diagnosed on the basis of clinical factors alone, nor were there significant differences in disease sequelae in patients with *intentional* or *incidental* pouch.

Table 6 summarizes the functional results at the time of follow-up in those patients with a retained, functioning pouch. Overall, 72% of patients reported near-perfect/perfect continence, 68% had no urgency or rare episodes of it, and median stool frequency was 7 bowel movements per day (range 2–20). Patients with *intentional* or *incidental* pouch were less likely than those with delayed diagnosis to have daytime seepage (27% versus 46%,  $P = 0.04$ ) or wear pads in the daytime (23% versus 51%,  $P = 0.002$ ) or nighttime (32% versus 57%,  $P = 0.009$ ). Median overall quality of life, quality of health, level of energy, and happiness with surgery were 9, 9, 8, and 10 of 10, respectively, and were similar in

patients with both *intentional* or *incidental* pouch and late diagnosis of CD.

## DISCUSSION

We report prospective outcomes for a cohort of 204 CD patients with IPAA from a single institution with a median follow-up of over 7 years. This study adds substantial numbers and long term follow-up to the literature of reported patients with CD and IPAA. Overall pouch retention, similar to several previous reports, was 55% at long-term follow-up (10-year retention, 71%).<sup>8–12</sup> On multivariate analysis, pouch loss was strongly associated with delayed CD diagnosis, pouch-vaginal fistula, and pelvic sepsis. As has been observed in patients referred to our institutional pouchitis clinic,<sup>1</sup> CD patients with postoperative fistulizing disease appear to be at greater risk for pouch loss. In particular, we observed that patients with perineal fistulizing disease, particularly pouch-vaginal fistula, after IPAA were at high risk for pouch failure. Whereas these results support the clear influence of the natural history and sequelae of CD on outcomes after IPAA in CD patients, technical factors which directly influence the rate of pelvic sepsis remain important determinants of the fate of the pouch.<sup>21</sup>

In previous small studies, differences in pouch failure rates have been observed after IPAA when CD is diagnosed from colectomy surgical specimens versus remotely at a later date.<sup>9,10,22</sup> Similarly, we found substantial differences in outcomes with IPAA patients having delayed CD diagnosis. The long-term evolution of CD in patients diagnosed immediately following surgery from histopathology appears to be less aggressive than in patients diagnosed later.<sup>23</sup> This is somewhat ironic, as cases where the diagnosis of CD and MUC is initially indistinguishable and CD is only diagnosed on final operative pathology typically have the most severe colonic inflammation at initial presentation.<sup>6,7</sup> Although somewhat a self-fulfilling observation, this study demonstrates higher rates of pouchitis, perineal fistula disease, and IPAA stricture in patients with delayed diagnosis and therefore often active clinical disease precipitating the diagnosis.

**TABLE 5.** Postoperative Outcomes In Patients With Intentional Or Incidental Pouch With Crohn's Disease Versus Delayed Diagnosis of Crohn's Disease

Outcome	Overall	Intentional or Incidental CD Pouch	Delayed CD Diagnosis	P
Pouch failure	61 (30%)	17 (15%)	44 (51%)	<0.0001
Any fistula	70 (35%)	22 (19%)	48 (55%)	<0.0001
Pouch vaginal fistula	26 (24%)	8 (13%)	18 (38%)	0.003
Perianal fistula	52 (25%)	13 (11%)	39 (45%)	<0.0001
Enterocutaneous fistula	4 (2%)	1 (1%)	3 (3%)	NS
Pouchitis	110 (54%)	47 (40%)	63 (72%)	<0.0001
IPAA stricture	48 (24%)	20 (17%)	28 (32%)	0.01
Afferent stricture	8 (4%)	4 (3%)	4 (5%)	NS
Abdominopelvic sepsis	25 (12%)	14 (12%)	11 (13%)	NS
Obstruction	28 (14%)	16 (14%)	12 (14%)	NS

CD indicates Crohn's disease; IPAA, ileal anal-pouch anastomosis; NS, not significant.

**TABLE 6.** Functional and Quality of Life Outcomes in Crohn's disease Patients With IPAA

	Overall	Intentional or Incidental CD Pouch	Delayed CD Diagnosis	P
Functional results				
Urgency (rarely/never)	68%	69%	65%	NS
Incontinence (rarely/never)	72%	71%	73%	NS
Seepage (Day)	32%	27%	46%	0.04
Seepage (Night)	48%	44%	57%	NS
Pads (Day)	31%	23%	51%	0.002
Pads (Night)	39%	32%	57%	0.009
Total bowel movements, median (range)	7 (2–20)	7 (2–20)	7 (4–20)	NS
Quality of life				
Quality of Life, median (range)	9 (4–10)	9 (4–10)	8 (4–10)	NS
Quality of Health, median (range)	9 (3–10)	9 (4–10)	9 (3–10)	NS
Level of Energy, median (range)	8 (2–10)	8 (2–10)	8 (2–10)	NS
Happiness with surgery, median (range)	10 (3–10)	10 (3–10)	9 (5–10)	NS

CD indicates Crohn's disease; IPAA, ileal anal-pouch anastomosis; NS, not significant.

Functional outcomes were also worse in some aspects, with increased need of pads both daytime and nighttime and greater daytime stool seepage in patients with delayed diagnosis. QOL, in contrast, was consistently good in those with their pouch in situ at follow-up.

Whereas the exact explanation for differences observed with delayed CD diagnosis remains unknown, we recognize that CD represents a spectrum of disease, ranging from mild to lethal in its course. Within the spectrum of Crohn's colitis, those patients with late appearing complications and manifestations of disease (*delayed* diagnosis) likely represent a group of patients who are predisposed to transition phenotypically to CD with small bowel involvement and more severe ongoing disease, resulting in greater pouch manifestations of CD. In contrast, Crohn's colitis patients selected preoperatively or discovered at the time of pouch creation in patients without anoperineal disease or small bowel involvement may represent a subset of patients with a predilection for disease in a colonic distribution alone. It may be possible that patients included in the delayed diagnosis group are those who have manifestations severe enough to be labeled as

having CD. On the contrary, it may be argued that those with subtle manifestations are likely to be missed and remain excluded from the study cohort. To avoid the risk of including patients with technical complications after IPAA being labeled as CD, we did not make a clinical diagnosis of CD within 3 months following ileostomy reversal. This is further corroborated by the observation that the proportion of patients with pelvic sepsis in the delayed diagnosis group was similar to that in the *intentional/incidental* group. In a follow-up study, we are examining clinical factors associated with the change in diagnosis to CD, whether *incidental* or *delayed*. Further developments that aid in a more conclusive diagnosis of CD and identify potential inciting environmental, genetic, or other pathophysiologic factors may resolve these questions and help identify and treat patients in a more tailored fashion.

Although the follow-up was relatively short when compared with the remainder of the cohort and patient number was small, patients with known Crohn's colitis who underwent IPAA (*intentional* pouch) had favorable results with respect to pouch retention and CD manifestations of the

pouch. Patients with *intentional* pouch tended to be younger, with relatively long preoperative disease duration (median 6.6 years), and more commonly female. Both in the past and present, our practice is to offer this procedure only to patients with Crohn's colitis, without anoperineal or small bowel involvement or the presence of other fistulizing disease, and with a relative long period of stable disease. Because of the small number of patients in this series and in the literature with *intentional* pouch creation, we do not currently have a fixed minimum amount of time between diagnosis and pouch creation but do view a stable disease course an important selection criteria.

As CD patients with rectal-sparing are more often offered subtotal colectomy with ileorectal anastomosis or segmental resection, IPAA has been offered primarily to CD patients with rectal involvement. The pouch retention rate at 10 years was 85% for intentional CD pouch. Our subgroup with either *intentional* pouch or *incidental* pouch had pouchitis, fistula, and IPAA stricture in 40%, 19%, and 17% respectively. These patients reported daytime seepage in 27%, nighttime seepage in 44%, 23% using daytime pads, and 32% using nighttime pads. In comparison, historical controls with MUC, IndC, and familial adenomatous polyposis patients with IPAA demonstrated 4% pouch loss, 16.8% pouchitis, 4.7% fistula (all types), 12% IPAA stricture, 18.8% with daytime seepage, 22.8% with nighttime seepage, 13.8% using daytime pads, and 20.0% using nighttime pads.<sup>24</sup> The functional results for *intentional* pouch patients, although relatively worse than these historical control patients with other indications for IPAA, compare favorably with the majority expressing their happiness with surgery as 10 out of 10. The additional, more subtle, message in these findings is that Crohn's colitis patients with an *intentional* pouch may be willing to accept worse than perfect functional outcome to avoid a permanent stoma, highlighting the need for patient education, understanding, and acceptance of these possible risks.

Whereas most literature on CD with IPAA has focused on comparing CD patients with MUC or IndC patients, Philips<sup>4</sup> has eloquently espoused that the most informative comparisons in CD with colonic distribution are between alternative operations, including permanent stoma or ileorectal anastomosis, to IPAA. Recurrence rates requiring further operative treatment of 25, 50, and 60% at 10-years for proctocolectomy with end ileostomy, total abdominal colectomy, and segmental colon resection respectively have been observed historically with isolated CD of the colon.<sup>25,26</sup> In one of the few reports that directly compared IPAA with other procedures in CD patients, Mylonakis et al<sup>22</sup> evaluated ileorectal anastomosis and IPAA in CD patients. Ileorectal anastomosis outcomes were superior to IPAA, including the need for rectal or pouch excision (8% versus 48% respectively) at 10 years follow-up. The authors note, however, that the 2 groups were distinctly different phenotypically, with ileorectal anastomosis patients having relative rectal-sparing disease in comparison to those undergoing IPAA. Additional useful follow-up studies would look at operative planning and outcomes in all patients with Crohn's colitis requiring colectomy or proctectomy. Trade-offs between different surgical

techniques for colonic CD, including IPAA, can be quite complex, making the need for studies with decision analysis techniques and direct comparisons of these procedures with larger numbers of patients helpful and necessary.

There are several limitations to this study. First, this is a cohort study of IPAA patients with CD that has only historical controls for comparison to MUC or IndC. Despite good pathology standards for our institution and experienced pathologists in inflammatory bowel disease, the diagnosis of CD remains partially subjective, particularly in patients where the diagnosis is based on clinical factors alone. Also, whereas we did not see differences in pouch loss with patients treated with steroids or Infliximab, it is difficult to adequately control for the effect of concurrent medications for CD of the pouch. Follow-up in patients with *intentionally* created CD pouch was shorter than other patient groups, and conclusions drawn from this group are limited because of the small patient numbers. However, our results do suggest comparable outcomes to patients with incidentally diagnosed CD in the immediate postoperative period. Despite these limitations, this study's strengths remain its large patient number, the standardized technique of diagnosis, and overall long period of follow-up with standardized protocols.

Ultimately, the results of this study can help counsel subgroups of CD patients in a more informed manner. Specifically, patients with known CD having isolated colonic distribution wishing to understand the risks of IPAA and those with presumed MUC or IndC who are found to have CD from their operative specimen can have a reasonable expectation of keeping their pouch with good functional results. In contrast, patients with a diagnosis of CD made remote from surgery can be told at the time of their diagnosis that they can anticipate a significantly higher risk of pouch loss and greater CD manifestations with concomitant morbidities. Despite this, approximately half of these patients will retain their pouch at over 10-years with acceptable functional results and favorable quality of life.

## CONCLUSION

Carefully selected patients with CD undergoing primary restorative proctocolectomy with ileal pouch-anal anastomosis have low pouch loss and favorable functional results. Patients with presumed ulcerative colitis or indeterminate colitis diagnosed with CD from operative histopathology can expect similar good results. Outcomes in patients with delayed diagnosis are worse but approximately half retain their pouch at 10 years with good functional outcome.

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