Journal of Crohn's and Colitis (2014) 8, 662–670

Available online at www.sciencedirect.com

ScienceDirect

Outcomes after ileal pouch anal anastomosis in patients with primary sclerosing cholangitis☆

Michael Pavlides[a], Jon Cleland[a], Monira Rahman[a], Annabel Christian[b], Jennifer Doyle[b], Robert Gaunt[c], Simon Travis[a], Neil Mortensen[d], Roger Chapman[a,*]

[a] *Translational Gastroenterology Unit, University of Oxford, Oxford, UK*
[b] *Division of Medical Sciences, University of Oxford, Oxford, UK*
[c] *Department of Statistics, University of Oxford, Oxford, UK*
[d] *Nuffield Department of Surgery, University of Oxford, Oxford, UK*

Received 13 November 2013; received in revised form 11 December 2013; accepted 11 December 2013

KEYWORDS
Acute pouchitis;
Pouch dysfunction;
Quality of life;
Sexual function

Abstract

Background and aims: Outcomes after ileal pouch anal anastomosis (IPAA) are not well established in patients with primary sclerosing cholangitis (PSC). We conducted a comprehensive outcomes assessment in these patients.
Methods: A retrospective case note review of complications in all PSC-IPAA (n = 21) and matched ulcerative colitis patients with IPAA (UC-IPAA; n = 79) after surgery in Oxford (1983–2012) was conducted, and functional outcomes (Öresland score) were evaluated (2012). Quality of life [Cleveland Global Quality of Life Questionnaire, Short Form-36 (SF-36)], and sexual function were also assessed (2012) including patients with PSC-associated UC without IPAA (PSC-UC; n = 19). Sub-group analysis of patients with large duct (*ld*) PSC-IPAA (n = 17) was also performed.

Abbreviations: IPAA, ileal pouch anal anastomosis; PSC-IPAA, patients with PSC who have undergone IPAA; *ld*PSC-IPAA, patients with large duct PSC who have undergone IPAA; UC-IPAA, patients with UC and without PSC who have undergone IPAA; PSC-UC, patients with PSC and UC who have not undergone IPAA; CGQOL, Cleveland Global Quality of Life score; SF-36, Short Form 36; FSFI, Female Sexual Satisfaction Index; IIEF, International Index of Erectile Function; SF-36, summary scores; PF, physical functioning; RP, role limitation due to physical problems; BP, bodily pain; GH, general health; VT, vitality and energy; SF, social functioning; RE, role limitation due to emotional problems; MH, mental health; PCS, physical health summary score; MCS, mental health summary score.

☆ Conference presentations: Preliminary data of this work were presented at the European Crohn's and Colitis Organisation Annual Conference (2013, Vienna, Austria) and at the Falk Symposium 190 titled "Challenges in the Care of IBD in Patients of All Ages" (2013, London, UK) and Falk Symposium 191 titled "Liver Diseases in 2013: Advances in Pathogenesis and Treatment" (2013, London, UK).

* Corresponding author at: Translational Gastroenterology Unit, Nuffield Department of Medicine, John Radcliffe Hospital, Headley Way, Oxford, OX3 9DU, UK. Tel.: +44 1865 220618; fax: +44 1865 228763.
E-mail address: roger.chapman@ndm.ox.ac.uk (R. Chapman).

1873-9946/$ - see front matter
http://dx.doi.org/10.1016/j.crohns.2013.12.007

Results: The 1-, 5-, 10- and 20-year risk of acute pouchitis for PSC-IPAA was 10%, 19%, 31% and 65% respectively, compared to 3%, 10%, 14% and 28% in UC-IPAA (p = 0.03). More PSC-IPAA (36%) had poor nocturnal pouch function (vs 2% in UC-IPAA; p = 0.0016). There were no differences in surgical complications, quality of life or sexual function between the 3 main groups. *Ld*PSC-IPAA had poorer pouch function (Öresland score: 7.7 vs 5.4 in UC-IPAA; p = 0.02), and worse quality of life [SF-36 Physical: 42 vs 50.5 in UC-IPAA; 47.7 in PSC-UC; p = 0.03 and Mental Health summary scores: 41.6 vs 51.2 in UC-IPAA; 42.3 in PSC-UC; p = 0.04].
Conclusions: PSC-IPAA suffer more acute pouchitis and have worse functional outcomes than UC-IPAA. *Ld*PSC-IPAA also have poorer quality of life.

1. Introduction

Primary sclerosing cholangitis (PSC) is an immune mediated cholestatic disease characterised by inflammation and fibrosis of the bile ducts.[1] It is closely associated with inflammatory bowel disease, particularly ulcerative colitis (UC). The prevalence of UC in patients with PSC is as high as 75% in Northern European cohorts.[2] PSC incurs an increased risk of colon dysplasia and cancer[3] and the prevalence of PSC is higher in patients with UC undergoing colectomy when compared to those who do not need surgery.[2] Patients with PSC may need to undergo colectomy because of medically-refractory UC or to treat colonic dysplasia and neoplasia. The operation of choice for the management of UC in these patients is a restorative proctocolectomy with ileal pouch anal anastomosis (IPAA). This operation is safe and cures the patients of the intestinal manifestations of their disease.

Post-operative complications including pouchitis can occur, but on the whole, patients with UC undergoing IPAA have good outcomes and quality of life.[4] However, there are conflicting reports in the literature on the impact of PSC on post-operative functional outcomes.[2,5–8] Furthermore, there are limited data on the effect of PSC on the quality of life and sexual function in patients who undergo IPAA for UC.

The aim of this study was to investigate complications, functional outcomes, quality of life and sexual function in patients with PSC associated UC who have undergone IPAA.

2. Patients and methods

2.1. Definitions

2.1.1. Ulcerative colitis (UC)

The diagnosis of UC was based on recognised endoscopic, histological and clinical features.[9] The extent of the disease was described according to the Montreal classification (proctitis: disease limited to the rectum, left sided: disease distal to the splenic flexure and extensive: disease extends proximal to the splenic flexure).[10]

2.1.2. Primary sclerosing cholangitis (PSC)

The diagnosis of PSC was based on characteristic findings on cholangiography (ERCP or MRCP) and histological features on liver biopsy.[11] The presence of cholangiographic findings alone was enough to diagnose large duct PSC (*ld*PSC). Patients were considered to have small duct PSC if they had a normal cholangiogram but the clinical presentation, biochemistry and histology findings were compatible with PSC.

2.1.3. PSC-IPAA

These were patients who were diagnosed with PSC associated with UC and had undergone colectomy and IPAA. The diagnosis of PSC could have been made at any point during the follow-up period.

2.1.4. UC-IPAA

These were patients who were diagnosed with UC (but not PSC) and had undergone colectomy and IPAA.

2.1.5. PSC-UC

These were patients who were diagnosed with PSC and UC but had not undergone colectomy and IPAA.

2.1.6. Pouch dysfunction

This was defined as any episode of symptoms (including diarrhoea, blood in the stool, urgency, abdominal pain, fever) that raised clinical concerns and led to further investigations or treatments. Pouch dysfunction may be the result of many underlying pathologies including surgical complications (e.g. anastomotic stenosis, pouch related pelvic sepsis), Crohn's disease of the pouch, cuffitis (inflammation of the mucosa in the remaining rectal stump due to the underlying UC), irritable pouch syndrome and pouchitis.[12]

2.1.7. Acute pouchitis

This was defined as any episode of pouch dysfunction with endoscopic and histological evidence of acute pouchitis. The presence of any of mucosal oedema, granularity, friability, loss of vascular pattern, exudates and ulceration[13] was considered to be endoscopic evidence of acute pouchitis. Pouch biopsies were assessed according to the system reported by Shepherd et al. in 1987.[14] Briefly, this score evaluates the degree of acute (0–6) and chronic (0–6) inflammatory changes in the pouch mucosa. For the assessment of acute inflammation the extent of mucosal infiltration by neutrophils (0: none to 3: severe with crypt abscesses) and the degree of ulceration (0: none to 3: extensive) are evaluated and a total acute score of ≥ 4 is considered to be histological evidence of acute pouchitis.

2.2. Patient cohorts

PSC-IPAA who had surgery between 1983 and 2012 were identified. This group was matched to UC-IPAA who had

surgery in the same period. Patients who had their index colectomy and pouch surgery in a different centre, and were subsequently referred to Oxford, were not excluded. PSC-IPAA were also matched to PSC-UC for the quality of life and sexual function assessment (see below). All patients were identified from departmental records. Data for demographics, disease characteristics, technical surgical characteristics and outcomes (pouch dysfunction, episodes of acute pouchitis, surgical complications, pouch failure, pouch dysplasia or cancer, biologic therapies or immunomodulators for treating pouch dysfunction and all cause mortality) were collected by retrospective note review. No distinction was made between early and late surgical complications. Patients under the age of 18 and over the age of 80, as well as patients who could not read English were excluded.

2.3. Patient questionnaires

The Öresland score[15] and Cleveland Global Quality of Life Questionnaire (CGQOL)[16] were respectively used to establish self-reported pouch function and the impact of IPAA on the quality of life. Quality of life was also assessed by the Short Form 36 (SF-36)[17] questionnaire and sexual function by the Female Sexual Satisfaction Index (FSFI)[18] and the International Index of Erectile Function (IIEF).[19] Examples of all the questionnaires used are included in the Supplementary material. The questionnaires were mailed to the patients who returned their responses anonymously in the post. All patients provided written informed consent before completing the study questionnaires.

The Öresland score questionnaire asks patients to rate their pouch function with regard to 12 domains (number of daytime and nighttime stools, urgency, evacuation difficulties, daytime and nighttime soiling or seepage, peri-anal soreness, the need to wear a daytime or nighttime protective pad, dietary restrictions or need for medication to control pouch function and social handicap). Each domain is scored separately by giving a total score out of 15, with higher scores indicating poorer pouch function.

The CGQOL tool asks patients to rate 3 items (quality of life, quality of health and energy levels) on a scale of 0–10. The final scores are obtained by adding the individual scores and dividing by 30. Higher scores indicate better quality of life.

The SF-36 measures generic health related quality of life. It consists of 36 questions which measure 8 multi-item dimensions of health [physical functioning (PF; 10 items), role limitation due to physical problems (RP; 4 items), bodily pain (BP; 2 items), general health perception (GH; 5 items), energy and vitality (VT; 4 items), social functioning (SF; 2 items), role limitation due to emotional problems (RE; 3 items) and mental health (MH; 5 items)]. There is a further unscaled single item asking respondents about health change over the past year. For each dimension item scores are coded, summed and transformed onto a scale from 0 (worst possible health state measured by the questionnaire) to 100 (best possible health state). Two standardised summary scores can also be calculated, the physical component summary (PCS) and the mental component summary (MCS) scores.

The FSFI contains 19 questions that assess female sexual function over the last 4 weeks and yields scores in six areas: sexual desire, arousal, lubrication, orgasm, satisfaction and pain. The IIEF has 15 items that assessed male sexual function over the last 4 weeks and produces scores in five domains: erectile dysfunction, orgasmic function, sexual desire, intercourse satisfaction and overall satisfaction. Higher scores in both FSFI and IIEF indicate better sexual function.

The study was approved by a UK National Research Ethics Committee (Ref 10/H0106/16) and the Institutional Review Board.

2.4. Statistical analysis

Parametric data were expressed as mean and standard deviation (S.D.). Non-parametric variables were expressed as median and inter-quartile range (IQR). Fisher's exact test and χ^2 were used to determine associations between categorical variables. Numerical data were compared using Student's t-test and Mann Whitney (if not normally distributed). The Shapiro–Wilk's test was used to test for normality. For the analysis of data from 3 groups, the Kruskal–Wallis test with Dunn's post test correction was used. The occurrence of acute pouchitis was estimated as a function of time using the Kaplan–Meier method. The log-rank (Mantel–Cox) test was used to test for significance between the curves. Statistical significance was taken as $p < 0.05$ except for the analysis of the individual components of the Öresland score where the statistical significance was set at $p < 0.01$ to allow for multiple comparisons. The statistical analysis was carried out using the GraphPad Prism software (version 5, GraphPad Software, Inc.).

3. Results

Twenty-one PSC-IPAA who had surgery in the study period were identified. They were age and gender matched to 79 UC-IPAA and 19 PSC-UC. PSC-IPAA had higher rates of extensive colitis (86%) when compared to UC-IPAA (30%; p = 0.01) but otherwise the groups were appropriately matched (Table 1). The median (IQR) age at IPAA of PSC-IPAA was 39 (27–48) years and for UC-IPAA 37 (28–47) years. The median (IQR) follow-up period after IPAA formation was 11 (8–17) years for PSC-IPAA and 10 (7–18) years for UC-IPAA. Tables 1 and 2 show the clinical and surgical characteristics at baseline.

3.1. Pouch dysfunction

In the overall cohort (n = 100), pouch dysfunction occurred in 52% of patients. There was a strong trend towards more pouch dysfunction in PSC-IPAA (71%) than UC-IPAA (47%) (p = 0.053; Table 3).

3.2. Acute pouchitis

Acute pouchitis occurred in 24% of the overall cohort of patients (n = 100). PSC-IPAA had a higher cumulative risk of suffering acute pouchitis over time (Fig. 1). The 1-, 5-, 10- and 20-year risk of pouchitis for PSC-IPAA was 10%, 19%, 31% and 65% respectively, compared to 3%, 10%, 14% and 28% (p = 0.03) in UC-IPAA. There was no significant difference between treatments (immunomodulator or biologics) for acute pouchitis between the two groups (Table 3).

Table 1 Baseline clinical characteristics.

	PSC-IPAA n = 21 (%)	UC-IPAA n = 79 (%)	PSC-UC n = 19 (%)	p value *
Age at IPAA (years; IQR)	39 (27–48)	37 (28–47)		0.83
Male	15 (71%)	44 (56%)	16 (84%)	0.22 [a]
Marital status				
Single	6 (29%)	26 (33%)		0.83
Married/partner	14 (67%)	51 (65%)		
Separated/divorced	1 (5%)	2 (3%)		
Smoking status at IPAA				
Smoker	2 (10%)	11 (14%)		0.73
Non-smoker	19 (91%)	65 (82%)		
Extent of UC				
Extensive	18 (86%)	34 (43%)	16 (84%) [b]	**0.01** [c]
Left sided	1 (5%)	18 (23%)	1 (5%)	
Proctitis	0	13 (17%)	1 (5%)	
Indication for colectomy				
Active UC (ASC or medically refractory)	18 (86%)	76 (96%)		0.08
Dysplasia	2 (10%)	2 (3%)		
Cancer	1(5%) [d]	0		
Interval from UC diagnosis to IPAA (years; IQR)	7 (2.3–11.8)	3 (1–8.5)		0.09
Interval from UC diagnosis to PSC diagnosis (years; IQR)	4 (1.3–8)		6 (0–14.3)	0.76
EIMs	4 (19%)	9 (11%)	1 (5%)	0.40
Method of PSC diagnosis				
Biopsy alone (small duct PSC)	4 (19%)		4 (21%)	0.97
Biopsy and Cholangiogram (ERCP or MRCP)	10 (48%)		8 (42%)	
Cholangiogram alone (ERCP or MRCP)	7 (33%)		6 (32%)	

Data from some patients who had their initial surgery at other centres could not be obtained.
Abbreviations: PSC: primary sclerosing cholangitis, IPAA: ileal pouch anal anastomosis, IQR: inter-quartile range, UC: ulcerative colitis, ASC: acute severe colitis, EIMs: extra-intestinal manifestations, ERCP: endoscopic retrograde cholangio-pangreatography, MRCP: magnetic resonance cholangio-pangreatography.
* statistically significant values in bold.
[a] For PSC-IPAA vs UC-IPAA.
[b] Two patients described as having "right sided ulcerative colitis".
[c] Significant difference between PSC-IPAA and UC-IPAA only.
[d] The post operative histology showed a giant inflammatory polyp.

3.3. Surgical complications

In PSC-IPAA, pelvic abscess, fistulae and anastomotic strictures occurred respectively in 4.8%, 0% and 14% of patients compared to 11%, 13% and 18% in UC-IPAA. A loop ileostomy was needed for temporary relief of symptoms or due to complications in 4.8% of PSC-IPAA and 11% of UC-IPAA. The index pouch was excised in two (9.5%) PSC-IPAA with one going on to have a second pouch refashioned. In the UC-IPAA group, five (6.3%) patients needed excision of the index pouch with three going on to have a second pouch refashioned. One (4.8%) patient with PSC who has undergone IPAA and two (2.5%) patients with UC and without PSC who have undergone IPAA suffered pouch failure. There were no significant differences in surgical complications between the two patient groups (Table 3).

3.4. Mortality and cancer

There were no cases of pouch dysplasia or cancer in either the PSC-IPAA or the UC-IPAA group. Three PSC-IPAA died within the follow-up period (2 from cholangiocarcinoma, 1 from liver failure while awaiting liver transplantation). There were no deaths in UC-IPAA.

3.5. Functional outcomes

Questionnaires were sent to 150 patients and 85 (57%) returned some or all of their questionnaires (17/21 with PSC-IPAA; 49/79 with UC-IPAA and 19/50 with PSC-UC). PSC-IPAA and UC-IPAA had similar mean Öresland scores of 6.5 and 5.4 respectively (p = 0.16). However, when the individual components of the score were considered separately, PSC-IPAA were found to have more nighttime bowel movements (p = 0.0016; Table 4).

3.6. Quality of life

There was no significant difference in the quality of life of patients between the two IPAA groups when assessed by the CGQOL tool (median score was 0.73 for both PSC-IPAA and UC-IPAA). In the SF-36, the median physical health summary scores (PCS) were 46.6, 50.5 and 47.7 and the median mental health summary scores (MCS) were 45.6, 51.2 and 48.3

Table 2 Baseline surgical characteristics.

	PSC-IPAA [a] n = 21 (%)	UC-IPAA [a] n = 79 (%)	p value
Type of colectomy surgery			
Laparotomy	19 (91%)	57 (72%)	0.14
Laparoscopy	2 (10%)	20 (25%)	
Type of IPAA			
Hand sewn	4 (19%)	6 (7.6%)	0.11
Stapled	14 (68%)	66 (84%)	
Number of stages			
One	2 (10%)	5 (6%)	0.35
Two	11 (52%)	28 (35%)	
Three	8 (38%)	42 (53%)	
Construction of pouch at time of colectomy			
Yes	10 (22%)	22 (28%)	0.11
No	10 (55%)	55 (70%)	
Duration of stool diversion after IPAA (months; IQR)	6.5 (0–11)	5 (2–8.8)	0.60
Post IPAA follow-up (years; IQR)	11 (8–17)	10 (7–18)	0.60

The reference group of patients with primary sclerosing cholangitis and ulcerative colitis (PSC-UC) is not shown as it is not relevant.
Abbreviations: PSC-IPAA: patients with primary sclerosing cholangitis and ileal pouch anal anastomosis following colectomy for ulcerative colitis, UC-IPAA: patients with ileal pouch anal anastomosis following colectomy for ulcerative colitis, IPAA: ileal pouch anal anastomosis, IQR: inter-quartile range.
[a] Data from some patients who had their initial pouch surgery at other centres could not be obtained.

Table 3 Pouch related and surgical complications.

	PSC-IPAA n = 21 (%)	UC-IPAA n = 79 (%)	p value
Pouch dysfunction	15 (71%)	37 (47%)	0.053
Acute pouchitis	8 (38%)	16 (20%)	0.15
Immunomodulator/biologic for pouchitis	2 (9.5%)	4 (5.1)	0.6
Pelvic abscess	1 (4.8%)	9 (11%)	0.68
Fistulas	0	10 (13%)	0.11
Anastomotic strictures	3 (14%)	14 (18%)	1.0
Refashioning of temporary ileostomy post IPAA	1 (4.8%)	9 (11%)	0.68
Pouch excision	2 (9.5%)	5 (6.3%)	0.64
Second pouch formation	1 (4.8%)	3 (3.8%)	1.0
Pouch failure	1 (4.8%)	2 (2.5%)	0.51

Abbreviations: PSC-IPAA: patients with primary sclerosing cholangitis and ileal pouch anal anastomosis following colectomy for ulcerative colitis, UC-IPAA: patients with ileal pouch anal anastomosis following colectomy for ulcerative colitis, IPAA: ileal pouch anal anastomosis.

respectively for PSC-IPAA, UC-IPAA and UC-PSC. There were no significant differences between the median scores of the 3 groups in any of the other summary scores. However, PSC-IPAA had the lowest scores in all 10 summary categories when compared to UC-IPAA and in all bar one category (energy and vitality; VT) when compared to PSC-UC (Fig. 2).

3.7. Sexual function

The median scores for overall satisfaction in the IIEF were 8, 8 and 9 in PSC-IPAA (n = 9), UC-IPAA (n = 23) and PSC-UC (n = 12) respectively with no significant differences in any of the categories between the groups. The median FSFI for UC-IPAA (n = 19) was 26.1 but comparisons with the other groups were not possible as only two PSC-IPAA and three PSC-UC returned their FSFI questionnaires.

3.8. Sub-group analysis—*ld*PSC-IPAA vs UC-IPAA

In the group of PSC-IPAA (n = 21), 4 had small duct PSC and 17 had *ld*PSC. Out of the four patients who had small duct PSC, two had pouch dysfunction and acute pouchitis. In a post hoc analysis, we only included the data from the 17 *ld*PSC-IPAA and found that these patients were more likely to suffer pouch dysfunction than UC-IPAA (76% vs 47%; p = 0.03). Furthermore, *ld*PSC-IPAA had poorer pouch function with a higher mean Öresland score (7.7 vs 5.4 for UC-IPAA; p = 0.02), and a worse quality of life with a lower median SF-36 PCS (42 vs 50.5 for UC-IPAA; 47.7 in PSC-UC; p = 0.03; Fig. 2) and lower median SF-36 MCS (41.6 vs 51.2 for UC-IPAA; 42.3 in PSC-UC; p = 0.04; Fig. 2). There was no significant difference in episodes of acute pouchitis between the two groups (35% for *ld*PSC-IPAA vs 20% for UC-IPAA; p = 0.21) and there was no significant difference between the CGQOL scores (0.73) for both groups.

4. Discussion

Our results show that PSC-IPAA have more episodes of pouchitis, and worse quality of life, but no difference in surgical complications to those UC-IPAA. Patients with large duct PSC appear to be at particular risk of pouch dysfunction

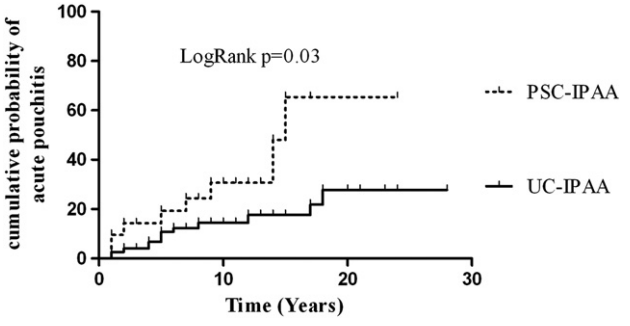

Fig. 1 Cumulative risk of acute pouchitis (Kaplan–Meier analysis). Patients with primary sclerosing cholangitis and ileal pouch anal anastomosis (PSC-IPAA) had a higher cumulative risk of acute pouchitis compared to patients with ulcerative colitis and ileal pouch anal anastomosis (UC-IPAA).

Table 4 Functional outcomes after ileal pouch anal anastomosis—Öresland score.

	Score	PSC-IPAA		UC-IPAA		p value*
		n	%	n	%	
Daytime bowel movements						
<5	0	2	7	8	17	0.76
5	1	4	29	16	34	
>5	2	9	64	23	49	
Nighttime bowel movements						
0	0	1	7	4	8	**0.0016**
>1/week	1	8	50	39	79	
>2/night	2	5	36	1	2	
Urgency[a]						
No	0	10	64	34	69	0.50
Yes	1	5	36	10	20	
Evacuation difficulties[b]						
No	0	11	79	33	67	1.0
Yes	1	3	21	12	24	
Daytime soiling or seepage						
No	0	11	71	38	78	0.67
>1/week	1	3	21	6	12	
Nighttime soiling or seepage						
No	0	6	36	30	61	0.21
>1/week	1	8	57	16	33	
Perianal soreness						
No	0	1	7	10	20	0.40
Occasional	1	13	86	33	67	
Permanent	2	1	7	4	8	
Daytime protective pad						
No	0	14	93	38	78	0.67
>1/week	1	1	7	7	14	
Nighttime protective pad						
No	0	13	86	35	71	0.49
>1/week	1	2	14	11	22	
Dietary restrictions						
No	0	5	29	26	53	0.23
Yes	1	9	64	20	41	
Medication (continuous or occasional)						
No	0	5	29	16	33	1.0
Yes	1	10	71	31	63	
Social handicap[c]						
No	0	13	86	40	82	1.0
Yes	1	2	14	7	14	

Abbreviations: PSC-IPAA: patients with primary sclerosing cholangitis and ileal pouch anal anastomosis following colectomy for ulcerative colitis, UC-IPAA: patients with ileal pouch anal anastomosis following colectomy for ulcerative colitis.

* statistically significant values in bold.

[a] Inability to defer evacuation for more than 30 min.

[b] >15 min spent on the toilet on any occasion for a week.

[c] Not able to resume full-time occupation or participate in social life.

and a poor quality of life. Our data should inform the pre-operative discussions with our patients with PSC and UC who need pouch surgery, but it appears that the main cause of poor quality of life is the underlying PSC, rather than pouch related complications.

There is currently no widely accepted standard definition of pouchitis. The Pouchitis Disease Activity Index (PDAI)[13] is most commonly used, and like other proposed scores[20,21] requires detailed clinical, endoscopic and histological information. In the context of a retrospective study like ours, and other studies looking at the impact of PSC on the incidence of pouchitis, these data cannot be obtained as they are not routinely reported. As a result, there is heterogeneity in the methods or criteria used in these studies to define episodes of pouchitis with some studies relying predominantly on the presence of clinical findings.[7,8] There is, however, evidence showing that clinical features alone do not correlate with endoscopic and histologic findings[22,23] suggesting that all 3 modalities (clinical, endoscopic and histological) are needed for a reliable diagnosis of pouchitis. In order to overcome this problem, in our study we used very stringent criteria for the diagnosis of acute pouchitis which included pre-defined clinical, endoscopic and histological characteristics. This is the likely reason that the overall rates of acute pouchitis reported here (24%) may seem lower than those in other studies (35.9%[24], 35.7%[7]).

Evidence that PSC-IPAA have worse pouch related complications comes from the Kaplan–Meier analysis we have performed here, showing higher rates of acute pouchitis at 1, 5, 10 and 20 years when compared to UC-IPAA. Furthermore, PSC-IPAA and in particular *ld*PSC-IPAA have worse functional outcomes (Öresland score).

Two previous studies have used a similar methodology to ours in order to compare outcomes in PSC-IPAA and UC-IPAA. Penna et al.[7] used primarily clinical criteria to define episodes of pouchitis and examined endoscopic and histologic findings only in a subset of patients. Similar to our findings, they report an increased cumulative risk of pouchitis in patients with PSC. Gorgun et al.[5] studied the incidence of chronic pouchitis and found no differences between PSC-IPAA and UC-IPAA. Even though endoscopic and histological features were incorporated into the diagnosis of pouchitis these had to be present only on a single occasion and not on every episode that was considered as pouchitis, raising the possibility that the incidence may have been over-estimated. Furthermore, in this study, it is not clear how the PSC diagnosis was established and what proportion of PSC patients had small duct disease. The distinction between small duct and large duct PSC seems to be an important one, as both in our study and in the study by Penna et al. [7] patients with large duct PSC seemed to have worse outcomes.

Two studies from Finland[2,6] examined the impact of PSC diagnosed on liver biopsy at the time of proctocolectomy. Both have shown that PSC patients are more likely to suffer pouchitis compared to UC-IPAA. In both these studies, a proportion of patients who were diagnosed with PSC on the peri-operative biopsy, were not known to have the disease previously and had normal liver function tests at the time of surgery. This raises the important question of whether such biopsies, which carry a negligible risk, should be undertaken routinely as the diagnosis of PSC can inform care in terms of the likelihood of pouchitis but also on the need for

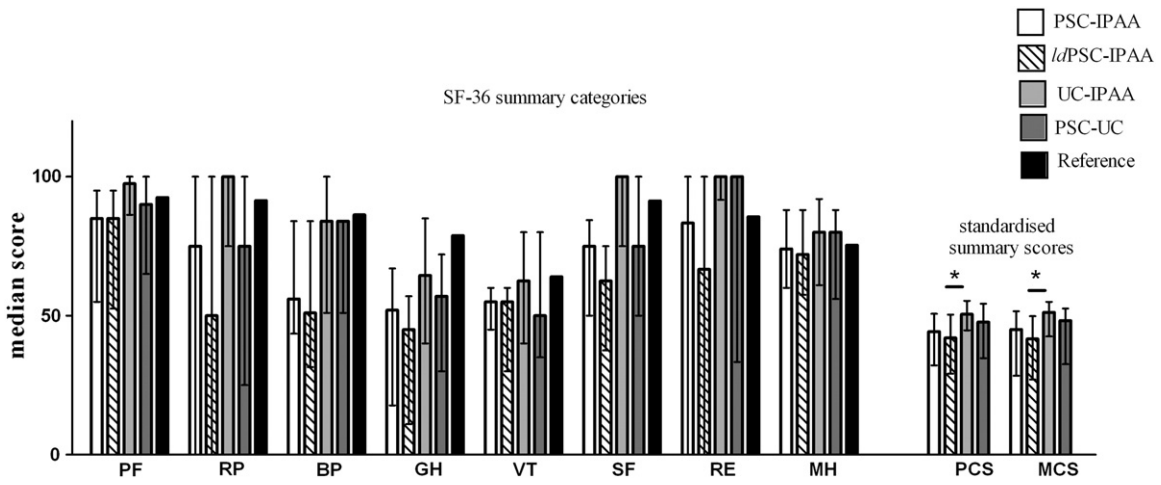

Fig. 2 SF-36 median scores for the 8 summary categories and 2 standardised summary scores. UC-IPAA had a tendency towards higher scores and PSC-IPAA had a tendency towards lower scores in all categories. *Ld*PSC-IPAA had worse PCS and MCS compared to UC-IPAA (*). Higher scores indicate better function. The mean scores for the 8 summary categories from a reference population of UK adults who reported no long-standing illness is also shown (black bars labelled "Reference").[36] Abbreviations: PSC-IPAA: patients with primary sclerosing cholangitis and ileal pouch anal anastomosis following colectomy for ulcerative colitis, *ld*PSC-IPAA: patients with large duct primary sclerosing cholangitis and ileal pouch anal anastomosis following colectomy for ulcerative colitis, UC-IPAA: patients with ileal pouch anal anastomosis following colectomy for ulcerative colitis, PSC-UC: patients with primary sclerosing cholangitis and ulcerative colitis who have not undergone colectomy and ileal pouch anal anastomosis. PF: physical functioning score, RP: role limitation due to physical problems score, BP: bodily pain score, GH: general health score, VT: energy and vitality score, SF: social functioning score, RE: role limitation due to emotional problems score, MH: mental health score, PCS: physical health summary score, MCS: mental health summary score).

endoscopic pouch surveillance for dysplasia and cancer. In our study, the majority of patients were diagnosed with PSC subsequent to UC (median delay of 4 years), and in some patients PSC was diagnosed after the formation of IPAA. This highlights the fact that subclinical PSC in UC-IPAA may be a confounder particularly in studies with short follow-up, as well as an important factor for the clinician to be aware of when considering IPAA.

The extent of UC is thought to be a risk factor for the development of pouchitis.[25,26] This may have confounded the results in our study as more PSC-IPAA had extensive disease (84%) compared to 43% (p = 0.01) in UC-IPAA. Previous studies have looked at groups matched with regard to the extent of disease and have found worse outcomes in PSC-IPAA,[7] suggesting that the increased rates of pouchitis are secondary to the PSC itself rather than the extent of colonic disease. Furthermore, patients with PSC, in addition to pouchitis, often have a long segment of inflammation in the pre-pouch ileum,[27] suggesting that the liver disease predisposes to a more extensive form of pouch and enteric inflammation.

Despite the varied methodology and definitions of pouchitis, the majority of the available evidence, as we have discussed here, suggests that patients with PSC are more likely to have troublesome pouch dysfunction from acute and chronic pouchitis. Despite this, we believe that IPAA should remain the operation of choice in these patients. The reason for this is that the alternative treatment for these patients would be a Brooke ileostomy, which is less favourable due to the development of peristomal varices and bleeding complications, which are not seen in patients with IPAA.[28,29]

As we are now gaining more experience of patients who have had their IPAA for more than 20 years, it is becoming evident that dysplasia and cancer can occur in the pouch mucosa, in the rectal cuff and in the anal transition zone, and PSC is a risk factor for this.[30] PSC-IPAA in our cohort were under a regular programme of endoscopic surveillance. In our study, there were no cases of dysplasia or cancer after the formation of IPAA. This is likely to reflect the fact that cancer developing in the pouch is still a rare occurrence.

Several studies have shown that quality of life and sexual function improve post operatively in patients who undergo IPAA for UC[31,32] but not many studies have examined the quality of life in PSC-IPAA. In our study, when the quality of life was measured using the CGQOL there were no differences between PSC-IPAA and UC-IPAA. As the CGQOL tool is designed to assess the impact of the pouch on the quality of life, this would suggest that despite the poorer pouch function and the greater number of complications seen in PSC-IPAA, the quality of life is not affected. This finding was also reproduced in another study.[5] However, the results were different when the SF-36 tool was used. SF-36 measures generic health related quality of life and PSC-IPAA had the worse scores in all bar one categories compared to UC-IPAA and PSC-UC. *Ld*PSC-IPAA seemed to be particularly at risk with significantly worse physical and mental health summary scores. The discrepancy between the results of the two scores (CGCOL and SF-36) would suggest that the quality of life of PSC-IPAA is worse, largely due to the presence of the liver disease and less due to pouch related factors.

For the first time, we were able to show that male PSC-IPAA had similar sexual function to UC-IPAA and PSC-UC with median IIEF scores of 8, 8 and 9, respectively. These scores are also similar to those observed in other studies of UC-IPAA (mean 7.94[33]). We were not able to assess female sexual

function in PSC-IPAA due to small numbers but the FSFI for UC-IPAA of 26.1 in our cohort is similar to that reported in other studies (median of 26.6[34] and mean of 27[35]).

In conclusion, our results would suggest that PSC-IPAA are more likely to suffer pouch dysfunction and acute pouchitis. Despite this, it appears that the presence of PSC, rather than the presence of the pouch is the factor that has the most significant adverse effect on the quality of life. This suggests that IPAA should remain as the operation of choice in patients with PSC who have to undergo colectomy, as the alternative options may have more complications. Our results should inform the discussions with our PSC-IPAA with regard to their post-operative expectations related to pouch function.

Conflict of interest

The authors have no conflict of interest to declare.

Statement of authorship

MP collected and analysed data and drafted the manuscript, JC collected data, and helped to draft the manuscript, MR designed the study, collected data, and helped to draft the manuscript, AC and JD collected data, RG analysed data and helped to draft the manuscript, ST drafted the manuscript and revised it critically for important intellectual content, NM participated in the design and co-ordination of the study and helped draft the manuscript, and RC conceived the study, participated in its design and co-ordination and helped to draft the manuscript. All authors read and approved the final manuscript.

Acknowledgements

This study was supported by a grant from PSC Support, a patient support group for patients with primary sclerosing cholangitis. The funders had no role in the study design, collection, analysis and interpretation of data, writing of the manuscript and decision to submit for publication.

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.crohns.2013.12.007.

References

1. MacFaul GR, Chapman RW. Sclerosing cholangitis. *Curr Opin Gastroenterol* 2004;**20**:275–80.
2. Lepisto A, Karkkainen P, Jarvinen HJ. Prevalence of primary sclerosing cholangitis in ulcerative colitis patients undergoing proctocolectomy and ileal pouch-anal anastomosis. *Inflamm Bowel Dis* 2008;**14**:775–9.
3. Soetikno RM, Lin OS, Heidenreich PA, Young HS, Blackstone MO. Increased risk of colorectal neoplasia in patients with primary sclerosing cholangitis and ulcerative colitis: a meta-analysis. *Gastrointest Endosc* 2002;**56**:48–54.
4. Richards DM, Hughes SA, Irving MH, Scott NA. Patient quality of life after successful restorative proctocolectomy is normal. *Colorectal Dis* 2001;**3**:223–6.
5. Gorgun E, Remzi FH, Manilich E, Preen M, Shen B, Fazio VW. Surgical outcome in patients with primary sclerosing cholangitis undergoing ileal pouch-anal anastomosis: a case–control study. *Surgery* 2005;**138**:631–7 [discussion 7–9].
6. Aitola P, Matikainen M, Mattila J, Tomminen T, Hiltunen KM. Chronic inflammatory changes in the pouch mucosa are associated with cholangitis found on peroperative liver biopsy specimens at restorative proctocolectomy for ulcerative colitis. *Scand J Gastroenterol* 1998;**33**:289–93.
7. Penna C, Dozois R, Tremain W, Sandorn W, LaRusso N, Schleck C, et al. Pouchitis after ileal pouch-anal anastomosis for ulcerative colitis occurs with increased frequency in patients with associated primary sclerosing cholangitis. *Gut* 1996;**38**:234–9.
8. Hoda KM, Collins JF, Knigge KL, Deveney KE. Predictors of pouchitis after ileal pouch-anal anastomosis: a retrospective review. *Dis Colon Rectum* 2008;**51**:554–60.
9. Dignass A, Eliakim R, Magro F, Maaser C, Chowers Y, Geboes K, et al. Second European evidence-based consensus on the diagnosis and management of ulcerative colitis part 1: definitions and diagnosis. *J Crohns Colitis* 2012:965–90.
10. Silverberg MS, Satsangi J, Ahmad T, Arnott ID, Bernsein CN, Brant SR, et al. Toward an integrated clinical, molecular and serological classification of inflammatory bowel disease: report of a Working Party of the 2005 Montreal World Congress of Gastroenterology. *Can J Gastroenterol* 2005;**19**(Suppl A):5A–36A.
11. Chapman R, Fevery J, Kalloo A, Nagorney DM, Boberg KM, Schneider B, et al. Diagnosis and management of primary sclerosing cholangitis. *Hepatology* 2010;**51**:660–78.
12. Shen B. Diagnosis and management of postoperative ileal pouch disorders. *Clin Colon Rectal Surg* 2010;**23**:259–68.
13. Sandborn WJ, Tremaine WJ, Batts KP, Pemberton JH, Phillips SF. Pouchitis after ileal pouch-anal anastomosis: a Pouchitis Disease Activity Index. *Mayo Clin Proc* 1994;**69**:409–15.
14. Shepherd NA, Jass JR, Duval I, Moskowitz RL, Nicholls RJ, Morson BC. Restorative proctocolectomy with ileal reservoir: pathological and histochemical study of mucosal biopsy specimens. *J Clin Pathol* 1987;**40**:601–7.
15. Oresland T, Fasth S, Nordgren S, Hulten L. The clinical and functional outcome after restorative proctocolectomy. A prospective study in 100 patients. *Int J Colorectal Dis* 1989;**4**:50–6.
16. Fazio VW, O'Riordain MG, Lavery IC, Church JM, Lau P, Strong SA, et al. Long-term functional outcome and quality of life after stapled restorative proctocolectomy. *Ann Surg* 1999;**230**:575–84 [discussion 84–6].
17. Ware Jr JE, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care* 1992;**30**:473–83.
18. Rosen R, Brown C, Heiman J, Leiblum S, Meston C, Shabsigh R, et al. The Female Sexual Function Index (FSFI): a multidimensional self-report instrument for the assessment of female sexual function. *J Sex Marital Ther* 2000;**26**:191–208.
19. Rosen RC, Riley A, Wagner G, Osterloh IH, Kirkpatrick J, Mishra A. The international index of erectile function (IIEF): a multidimensional scale for assessment of erectile dysfunction. *Urology* 1997;**49**:822–30.
20. Moskowitz RL, Shepherd NA, Nicholls RJ. An assessment of inflammation in the reservoir after restorative proctocolectomy with ileoanal ileal reservoir. *Int J Colorectal Dis* 1986;**1**:167–74.
21. Heuschen UA, Autschbach F, Allemeyer EH, Zöllinger AM, Heuschen G, Uehlein T, et al. Long-term follow-up after ileoanal pouch procedure: algorithm for diagnosis, classification, and management of pouchitis. *Dis Colon Rectum* 2001;**44**:487–99.

22. Shen B, Achkar JP, Lashner BA, Ormsby AH, Brzezinski A, Soffer EE, et al. Irritable pouch syndrome: a new category of diagnosis for symptomatic patients with ileal pouch-anal anastomosis. *Am J Gastroenterol* 2002;**97**:972–7.
23. Shen B, Achkar JP, Lashner BA, Ormsby AH, Remzi FH, Bevins CL, et al. Endoscopic and histologic evaluation together with symptom assessment are required to diagnose pouchitis. *Gastroenterology* 2001;**121**:261–7.
24. Fazio VW, Kiran RP, Remzi FH, Coffey JC, Heneghan HM, Kirat HT, et al. Ileal pouch anal anastomosis: analysis of outcome and quality of life in 3707 patients. *Ann Surg* 2013;**257**:679–85.
25. Schmidt CM, Lazenby AJ, Hendrickson RJ, Sitzmann JV. Preoperative terminal ileal and colonic resection histopathology predicts risk of pouchitis in patients after ileoanal pull-through procedure. *Ann Surg* 1998;**227**:654–62 [discussion 63–5].
26. Achkar JP, Al-Haddad M, Lashner B, Remzi FH, Brzezinski A, Shen B, et al. Differentiating risk factors for acute and chronic pouchitis. *Clin Gastroenterol Hepatol* 2005;**3**:60–6.
27. Shen B, Bennett AE, Navaneethan U, Lian L, Shao Z, Kiran RP, et al. Primary sclerosing cholangitis is associated with endoscopic and histologic inflammation of the distal afferent limb in patients with ileal pouch-anal anastomosis. *Inflamm Bowel Dis* 2011;**17**:1890–900.
28. Kartheuser AH, Dozois RR, LaRusso NF, Wiesner RH, Ilstrup DM, Schleck CD. Comparison of surgical treatment of ulcerative colitis associated with primary sclerosing cholangitis: ileal pouch-anal anastomosis versus Brooke ileostomy. *Mayo Clin Proc* 1996;**71**:748–56.
29. Kartheuser AH, Dozois RR, Wiesner RH, LaRusso NF, Ilstrup DM, Schleck CD. Complications and risk factors after ileal pouch-anal anastomosis for ulcerative colitis associated with primary sclerosing cholangitis. *Ann Surg* 1993;**217**:314–20.
30. Egan L, DInca R, Jess T, Pellino G, Carbonnel F, Bokomeyer B, et al. *Non-colorectal intestinal tract carcinomas in inflammatory bowel disease: results of the 3rd ECCO Pathogenesis Scientific Workshop (II), J Crohns Colitis* 2014;**8**:19–30.
31. Berndtsson I, Lindholm E, Oresland T, Borjesson L. Long-term outcome after ileal pouch-anal anastomosis: function and health-related quality of life. *Dis Colon Rectum* 2007;**50**:1545–52.
32. Delaney CP, Fazio VW, Remzi FH, Hammel J, Church JM, Hull TL, et al. Prospective, age-related analysis of surgical results, functional outcome, and quality of life after ileal pouch-anal anastomosis. *Ann Surg* 2003;**238**:221–8.
33. Gorgun E, Remzi FH, Montague DK, Connor JT, O'Brien K, Loparo B, et al. Male sexual function improves after ileal pouch anal anastomosis. *Colorectal Dis* 2005;**7**:545–50.
34. Ogilvie Jr JW, Goetz L, Baxter NN, Park J, Minami S, Madoff RD. Female sexual dysfunction after ileal pouch-anal anastomosis. *Br J Surg* 2008;**95**:887–92.
35. Davies RJ, O'Connor BI, Victor C, MacRae HM, Cohen Z, McLeod RS. A prospective evaluation of sexual function and quality of life after ileal pouch-anal anastomosis. *Dis Colon Rectum* 2008;**51**:1032–5.
36. Jenkinson C, Coulter A, Wright L. Short form 36 (SF36) health survey questionnaire: normative data for adults of working age. *BMJ* 1993;**306**:1437–40.