

Risk of dysplasia and adenocarcinoma following restorative proctocolectomy for ulcerative colitis

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Received 31 October 2005; accepted 3 March 2006

Abstract

Objective Restorative proctocolectomy (RPC) with or without mucosectomy is the treatment of choice for most patients with ulcerative colitis (UC) requiring surgery. The ileal mucosa in the reservoir and the anorectal columnar epithelium below the ileo-anal anastomosis are at risk of neoplastic transformation.

Method The literature has been reviewed to identify patients developing this complication and an attempt has been made to develop a rational follow-up policy based on the data available.

Results Dysplasia in the ileal reservoir is rare. It is associated with histological type C changes, sclerosing cholangitis and unremitting pouchitis in the ileal mucosa and to the presence of sclerosing cholangitis. Nine patients who have developed adenocarcinoma in the residual anorectal mucosa and seven in the reservoir have been reported in the literature. A further hitherto unreported patient treated by the authors brings the total to 17 patients. Twelve of these had histopatho-

logical data on either dysplasia or carcinoma in the original operative specimen. The time intervals from the onset of UC and from the RPC to the development of cancer were 120–528 (median 246) and 16–216 (median 60) months respectively. Cancer appeared to be related to the duration of disease rather than to the interval from RPC. In all the reported patients the interval from the onset of UC was 10 years.

Conclusion Based on these data a surveillance programme should begin at 10 years from the onset of disease. Patients with dysplasia or carcinoma in the original specimen, those with type C ileal mucosal changes and patients with sclerosing cholangitis should be selected for surveillance. This will involve multiple biopsies of the ileal reservoir and the anorectal mucosa below the ileo-anal anastomosis.

Keywords Restorative proctocolectomy, ulcerative colitis, dysplasia, cancer, pouchitis, surveillance

Introduction

One of the original principles of restorative proctocolectomy (RPC) was 'complete' removal of all disease-prone mucosa. Excision of the colon and rectum with mucosectomy of the residual ano-rectal stump was intended to achieve this. In practice, a few patients have subsequently developed carcinoma in the mucosa below the ileo-anal anastomosis demonstrating that this approach cannot entirely abolish the risk of malignant transformation in the anal canal. The use of stapling inevitably leaves a

segment of mucosa potentially at risk and the incidence of carcinoma might be expected to rise as more such patients are followed over time.

The ileal reservoir is also at risk of neoplastic transformation. Dysplasia has been reported in some series [1,2] although not in others [3]. There are several reports of adenocarcinoma occurring in the ileal pouch.

An extensive review of the literature has been carried out to identify studies and case reports dealing with the development of dysplasia and adenocarcinoma in patients who have undergone RPC for ulcerative colitis (UC). A patient treated by the authors has been added. Furthermore, an attempt has been made to define a follow-up system based on the information obtained.

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Method

An Ovid MEDLINE search for all articles published in all languages between the years 1966 and July 2005 was performed using keywords 'restorative proctocolectomy, ulcerative colitis, ileal pouch-anal anastomosis, ileal reservoir, dysplasia, precancerous conditions, tumour, cancer, adenocarcinoma, pouchitis, investigation, treatment and surveillance'. All articles were manually cross-checked for relevance for this review.

Morphological changes in the pouch

During the first 6 months following RPC, infiltration of inflammatory cells in the mucosa occurs and there is a degree of villous atrophy. Features of colonic metaplasia may occur with the sialomucin staining characteristics of colonocytes. Disaccharidase activity may be lost. This process is patchy in nature [4]. Morphological changes begin within the first days to weeks after closure of the defunctioning ileostomy [5–10] and by 6 months most patients who are likely to develop chronic unremitting pouchitis manifest the acute and chronic inflammation of the so-called type C changes [1,7] which are associated with this condition (see below).

Inflammation of the ileal pouch mucosa

Although complete colonic metaplasia does not occur [8,11], it is possible that the 'colonic adaptation' seen within the pouch may act as an immunological target especially in patients with UC who already have a heightened immunogenicity and genetic susceptibility to inflammatory bowel disease. This leaves UC patients liable to developing inflammation of the pouch, a condition only rarely seen in familial adenomatous polyposis (FAP) patients after RPC. There are those who believe pouchitis itself may reflect the pathogenesis of inflammatory bowel disease.

It has been suggested that dysbiosis (alteration in the balance of bacterial flora) may play a major role in the aetiology of pouch inflammation. A recent study [12] suggested that a higher total load of faecal anaerobic bacterial flora was strongly associated with a degree of colonic metaplasia, villous atrophy and inflammatory activity after surgery for UC.

On the background of these adaptive pouch mucosal and flora changes, there are luminal environmental alterations. These include an increase in the bile acid and short-chain fatty acid (SCFA) concentrations. SCFAs are typically produced in the colon by anaerobic fermentation of carbohydrate and endogenous mucus. Butyric acid is metabolized by colonocytes in preference to glucose. This

has been shown to be beneficial in stimulating colonic mucosal cell metabolism, proliferation and healing in rats [13–16]. The whole process of butyrate oxidation has been shown to be impaired in UC where there is an increase in the oxidation of glucose and glutamine instead [17]. A protective effect from SCFA is suggested by work revealing a correlation between high faecal concentrations of SCFA and a lower degree of villous atrophy [18].

Pouchitis

Inflammation of the pouch mucosa histologically similar to UC was first described in the continent ileostomy described by Kock *et al.* in 1977 and given the term pouchitis when histological and endoscopic evidence of inflammation was associated with symptoms of frequency, urgency and fluid stool consistency [19]. The same term found its way in the medical literature to describe similar changes in the ileo-anal pouch. Endoscopically the pouch appeared oedematous, with granularity, friability, erythema, flattening of mucosal surface and erosions or frank ulceration. The acute histological changes included superficial ulceration with polymorphonuclear cell infiltration and crypt abscess formation. Moskowitz *et al.* [20] devised a histopathological scoring system based on the severity of acute and chronic changes whereby a score of ≥ 4 out of 12 was suggestive of pouchitis. Some degree of chronic inflammatory change was found in 87% of all pouches [20], and may merely have been a secondary consequence of small bowel mucosal adaptation to faecal stasis and to the huge (million fold) increase in bacterial concentration which results in the reservoir after RPC.

Mucosal type changes

Veress *et al.* [1,21] and Setti Carraro *et al.* [7] independently studied the pattern of pouch mucosal inflammation through serial biopsies taken over time. Veress *et al.* [21] performed a histomorphological study of the ileal pouch mucosa in 11 consecutive patients having RPC for UC over a follow-up period of 2 years. Two types of mucosal adaptation were noted. Type A response (five patients) showed stable slight atrophy, normal numbers of goblet cells and numerous sulphated mucin positive cells. The frequency of mitoses was higher than in the normal ileum. The degree of acute and chronic inflammation was low. Dysplasia was never seen. Type B response (five patients) comprised progressive, finally severe atrophy accompanied by an increasing degree of acute inflammation. The number of mitoses was higher than in the type A response. In two patients, the number of goblet cells was moderately or severely decreased and epithelial atypia or low-grade dysplasia

occurred repeatedly. The response was regarded as indeterminate in one patient.

In a later study [1], they divided the patients into three clinicopathological subgroups; Type A, B and C. In type A patients, the pouch mucosal biopsies revealed little or no inflammation or villous atrophy. This accounted for 51% of the study population. Type B patients (40%) were those in whom transient moderate-to-severe villous atrophy followed by architectural normalization was seen. Type C patients (9%) developed severe pouchitis within months of surgery, with constant subtotal or total (moderate-to-severe) villous atrophy noted over the course of the follow-up period.

In a follow-up study, over a median period of 97 months of 60 patients who had had RPC for UC between the years 1978 and 1985, Setti Carraro *et al.* [7] studied the histological appearance of the pouch mucosa. Similarly, the patients were divided into three groups. In group A (45%), chronic changes were minor and acute changes were not seen. In group B (42%), chronic changes were more severe with transient episodes of acute inflammation. In group C (13%), severe chronic and acute inflammation was constantly present. Such differentiation of the three groups could be made as early as 6 months after ileostomy closure. Only patients with type C mucosa appeared to develop chronic pouchitis and this group could be identified histologically within weeks after ileostomy closure.

Factors related to chronic pouchitis and dysplasia

Gullberg *et al.* [22] studied six patients with long-standing severe pouchitis and a type C mucosal pattern following RPC for UC. DNA aneuploidy, loss of heterozygosity (LOH) at chromosome 5q14-22, 17p12-13 and 18q12-22 and point mutations of the *K-ras* and adenomatous polyposis coli (APC) genes were looked for. The patients had varying degrees of dysplasia and one displayed DNA aneuploidy. Loss of heterozygosity at 5q was detected in three of five biopsies in one patient. No alterations of either the *K-ras* or the APC genes or LOH of 5q, 17p or 18q were seen in any of the other patients. They concluded that dysplasia, aneuploidy and LOH in 5q may all reflect different parts of an atrophic mucosa-dysplasia-carcinoma sequence, in line with current concepts of carcinogenesis for colorectal carcinoma in long-standing pouchitis.

Extra intestinal manifestations

Preoperative extra-intestinal manifestations (EIM) of inflammatory bowel disease appear to be associated with

chronic pouchitis [23,24]. One study [25] reviewing the outcome of RPC for UC patients found pouchitis in 39% of those with preoperative extra-gastrointestinal manifestations of inflammatory bowel disease when compared with 26% without. The same study reported that patients who developed EIM postoperatively had an incidence of pouchitis of 53% compared with 25% in patients without EIM.

Sclerosing cholangitis

The most striking association of EIM with chronic pouchitis is primary sclerosing cholangitis (PSC), which significantly increases the cumulative risk of developing pouchitis, but this does not appear to be related to the severity of the liver disease [23,26]. Aitola *et al.* [27] carried out a liver biopsy during RPC on 73 patients and found histological evidence of PSC in 10 (14%). Of these, nine suffered acute pouchitis and seven subsequently developed chronic pouchitis, whilst of the 63 without PSC only 20 and seven developed acute and chronic pouchitis respectively. More recently Ståhlberg *et al.* [28] published the results of a case-control study involving 16 RPC patients with UC and PSC and 16 matched RPC patients with UC but without PSC. The UC patients with PSC developed persistent moderate or severe atrophy in the pouch significantly more often and seemed to have a higher risk of neoplastic transformation in the pouch mucosa than patients with UC without sclerosing cholangitis. Flow cytometric analyses revealed DNA aneuploidy at multiple locations in three of the patients, all with dysplasia and PSC. All patients with dysplasia had had the RPC more than 8 years previously. PSC is also known to be associated with an increased incidence of other gastrointestinal and colorectal malignancies [29-33] with or without UC.

Inflammation of the anorectal mucosa

In UC, the disease process is present in the columnar epithelium in the lower rectum and anal canal. After RPC, some remnants of anorectal mucosa is therefore inevitably left behind. Thus, in a study of resected pouches, it was shown that 20% had persisting columnar epithelium in the anal canal even after mucosectomy [34]. When a stapling technique is used, anorectal mucosa will remain distal to the ileo-anal anastomosis. When this leads to symptoms because of inflammation, the term 'cuffitis' or 'strip proctitis' has been used [35,36]. Some degree of inflammation in the anorectal mucosa has been noted in up to 8.2% of all patients undergoing RPC [35].

Neoplastic transformation

The ileo-anal pouch mucosa and the anorectal mucosa below the ileo-anal anastomosis are at potential risk of developing dysplasia.

Dysplasia in the ileo-anal pouch mucosa

The first case of dysplasia in the ileo-anal pouch was reported in 1991 in a 36-year-old male patient with UC who had undergone a colectomy and mucosal proctectomy, and S-reservoir reconstruction [37]. No dysplasia was found in the histological review of the original proctocolectomy specimen. The patient suffered chronic pouchitis, and was diagnosed with low-grade dysplasia 4 years after the RPC. DNA aneuploidy was detected in a biopsy taken from the mid-pouch level.

The incidence of dysplasia in the pouch mucosa itself has been reported to be as high as 7.5% [2,38–41]. Veress *et al.* [1] followed 87 patients prospectively over a median period of 6.3 years (range 3–14 years). Three developed low-grade dysplasia. All three had a type C mucosal pattern with chronic pouchitis and all demonstrated DNA aneuploidy raising the possibility of future malignant change [37]. In total, 3.4% of the patients developed dysplasia, but this risk of dysplasia increased to 37% when analysing the type C patients independently. Another study from the same institution [42] noted the development of dysplasia in 71% (five out of seven patients) of the patients with type C mucosa.

Another prospective study of 30 patients after RPC was carried out with regular endoscopic review and multiple biopsies taken from the afferent limb, mid-pouch anteriorly, mid-pouch posteriorly and the anastomotic area. Four were found to demonstrate endoscopic evidence of inflammation, all had mild-to-moderate chronic inflammatory changes on histological examination of their biopsies and one had low-grade dysplasia with a background history of chronic pouchitis [43].

In a study of 55 patients who had had RPC at a median of 14 years (range 10.7–19.8 years), pouchoscopy was performed with four biopsies taken from the lower and four from the upper pouch. There was no patient of dysplasia in the 440 biopsy samples obtained and all were negative for p53 antigen [3].

Thompson-Fawcett *et al.* [2] followed 106 high-risk patients including 29 who had had a Kock ileostomy more than 14 years previously, 42 who had had RPC for more than 12 years and 34 patients with chronic pouchitis from a cohort of 1221 patients. Eleven had a history of dysplasia or cancer in the original proctocolectomy specimen. Thirty-three patients had severe villous atrophy but only one of the 106 patients had dysplasia. This was

multifocal and low grade. DNA analysis by flow cytometry showed aneuploidy in this patient and in two others.

Hulten *et al.* [38] reported long-term mucosal adaptation patterns and the incidence of dysplasia in 40 patients at a mean interval of 30 years following a Kock continent ileostomy for UC. Sequential small intestinal biopsy specimens were examined by two groups of pathologists. Type A and type B mucosal patterns, based on the criteria described by Veress *et al.* [1,37] and Setti Carraro *et al.* [7] were found in 29 patients and a type C pattern was observed in 11. There were only three cases of dysplasia which was low grade and found exclusively in the type C group. There was no patient of high-grade dysplasia or adenocarcinoma. There was, however, a significant disagreement between the pathologists in reporting low-grade and indefinite categories of dysplasia. Thus, the incidence of indefinite and low-grade dysplasia of 27.5% and 7.5% reported by one group of pathologists was reported by the second group to be 7.5% and 5% respectively.

Herline *et al.* [40] reviewed 222 biopsy specimens from ileo-anal pouches from 160 patients with UC followed for an average period of 8.4 years. With over 1800 pouch-years of surveillance only one patient had focal, low-grade dysplasia which resolved on further surveillance.

Börjesson *et al.* [41] reported that dysplastic transformation within the ileal pouch mucosa in patients operated for ulcerative proctocolitis was rare even after a long follow up regardless of the type of mucosal adaptation. Sequential mucosal biopsies of 45 patients taken at a median interval of 24.8 years from the onset of disease were reviewed by three independent pathologists in two different centres. Two pathologists considered two patients (4.4%) to have low-grade dysplasia while the third pathologist felt that one of these was indefinite for dysplasia and one showed reactive changes only. No patient of high-grade dysplasia or invasive carcinoma was found.

It is clear that dysplasia within the ileal reservoir is rare. It is important, however, to note that dysplasia is strictly a histological diagnosis and it suffers from an extreme degree of subjectivity. Differentiating reactive adaptive and hyperplastic changes from low-grade dysplasia can be a challenge for many histopathologists. It is therefore recommended that such cases are reported by two gastrointestinal histopathologists; at least, one of them should have a special interest in dysplasia.

Dysplasia in the anorectal mucosa

The ileo-anal anastomosis is made between the ileal pouch and either the anal canal or the lower rectum. The

level will depend on whether a manual anastomosis with mucosectomy or a stapled anastomosis without mucosectomy has been performed. In the former case, the level can be controlled directly by the level at which the mucosectomy is made while this is more difficult when carrying out a stapled anastomosis [44]. In some patients, there may therefore be a considerable length of anorectal mucosa below the anastomosis which will be theoretically at risk of developing neoplastic transformation.

Inflamed anorectal mucosa following a stapled anastomosis may be symptomatic in up to 25% of patients [35] indicating that residual mucosa, the so-called 'strip proctitis' or 'cuffitis' may be clinically important. The longitudinal length of this segment will vary according to the level of the ileo-anal anastomosis. In some publications, it may be referred to as the anal transitional zone (ATZ). Thompson Fawcett *et al.* [45] showed considerable variation in the position and extent of the ATZ both from individual to individual and to some extent within the same individual. The median longitudinal length of the ATZ was 4.5 mm (range 0.4–10 mm). The position of the most distal point was at a median of 7 mm (range 0.9–12.9 mm) and the most proximal at a median of 23 mm (range 8.9–29.3 mm) from the lower border of the internal anal sphincter.

In almost all patients, the ileo-anal anastomosis will be more proximal leaving a varying length of columnar epithelium. When referring to the epithelium below the ileo-anal anastomosis, the term ATZ is therefore not accurate and should be replaced by the phrase 'residual anorectal mucosa'. Thus, there is a risk of dysplasia or cancer occurring below the ileo-anal anastomosis after both a stapled and manual anastomosis. This has been observed in practice with a reported incidence of focal dysplasia within the preserved anorectal mucosa of up to 16% [46–54].

Incidence of dysplasia in the residual anorectal mucosa

Tsunoda *et al.* [46] studied the incidence of dysplasia in the mucosectomy specimen taken from the anorectal stump during RPC of 118 patients with UC, 12 (10%) of whom had dysplasia at other sites in the large bowel resection specimen. Dysplasia in the anorectal mucosa was found in three patients. There was a positive correlation between this and the presence of carcinoma in the operative specimen and the duration of disease.

Ziv *et al.* [47] reported a significant incidence of dysplasia in the ATZ of UC patients after RPC. Low-grade dysplasia was found in 3.1% of patients and had developed at a median period of 16 months after surgery. No association was found between dysplasia and the duration of disease, the use of a double-stapled *vs* single-stapled

technique or the distance of the anastomosis from the dentate line. O'Riordain *et al.* [48], from the same institution, later reported the incidence and natural history of dysplasia of the ATZ in patients undergoing RPC for UC after a median follow up of 77 months. Dysplasia developed in seven (3%) of 210 patients. High-grade dysplasia was seen in one patient and the risk of dysplasia was significantly increased in patients with prior cancer or dysplasia in the large bowel. In a larger series [49], 289 patients again from the same institution were followed by regular examinations and biopsies of the ATZ. Patients with rectal carcinoma within 8 cm of the anal verge were treated by mucosectomy with manual anastomosis and were therefore excluded from the surveillance programme which included 178 patients with a minimum follow up of 120 months (median 130 months). Dysplasia was found in eight (4.5%) patients at a median period of 9 months after RPC. High-grade dysplasia was seen in two patients, one with a history of chronic pouchitis and the other with preoperative dysplasia in the colon. All eight of the patients with dysplasia were either followed closely or underwent mucosectomy with pouch advancement and re-anastomosis via an endo-anal approach. No patient developed carcinoma. There was no association between the occurrence of dysplasia and gender, age, preoperative disease duration or extent of colitis; however, dysplasia was significantly associated with cancer or dysplasia in the colon or rectum in the proctocolectomy specimen. The authors concluded that dysplasia in the ATZ was rare but that long-term surveillance was warranted in these patients.

Thompson-Fawcett *et al.* [50] assessed the risk of dysplasia and the presence of aneuploidy in the columnar cuff epithelium after stapled ileo-anal anastomosis in 113 patients with UC. The mean follow up after pouch formation was 2.5 years. Successful columnar cuff biopsies were performed in 93% of patients and no patient of dysplasia was found. Two biopsy specimens from one patient showed aneuploidy.

Coull *et al.* [51] reviewed 135 patients who underwent stapled RPC for UC. The median postoperative follow up was 56 months and the median interval from the diagnosis of UC was 8.8 years. There was no evidence of either dysplasia or carcinoma in the anorectal mucosa up to 12 years after RPC and they suggested that cuff surveillance in the first decade after stapled RPC, in the absence of dysplasia or carcinoma in the original colectomy specimen, may be unnecessary.

Case reports of adenocarcinoma

The first description of a 'cancer in an ileal pouch' was published by Stern *et al.* [55] in 1990. Careful reading of

the report, however, shows that the carcinoma almost certainly was derived from dysplasia which was already present in the rectum preoperatively given the short interval (4 years) from operation to clinical presentation and to the finding of 'severe dysplasia' in the rectum of the original specimen. For this reason this patient has not been included in the analysis. Lee *et al.* [56] reported three patients who had developed carcinoma after RPC. In patient 1, it is almost certain that it was already present in the rectum as severe dysplasia in the rectum was reported preoperatively and the interval to the clinical presentation of the carcinoma from the RPC was only 2 years. In patient 2, a rectal carcinoma was already present at the time of the RPC and the subsequent presentation of the tumour at 6 years is very likely to have been a recurrence. patient 3 appears to be a carcinoma in the anorectal mucosa presenting at 15 years from the RPC. There was no information on the histopathology of the original specimen. This case nevertheless would appear to be one of malignancy occurring as a result of neoplastic transformation in the anorectal mucosa. The first two of the patients of Lee *et al.* [56] have been excluded while the third has been included in the analysis.

Authentic adenocarcinoma in the pouch or anorectal mucosa

There are 16 unequivocal reported examples in the literature of cancer including seven patients occurring in the pouch mucosa and nine in the anorectal mucosa [56–63,64–71]. In three [56,67,71] of the nine anorectal patients, cancer developed following mucosectomy and handsewn anastomosis and in five after stapled ileo-pouch anal anastomosis without mucosectomy [65,66,68–70]. Operative details were not mentioned in one report [64].

We have recently encountered a further patient who developed a carcinoma in the anorectal mucosa 25 years after the RPC and 27 years after the onset of UC which was confirmed on review of the original histological slides. The total number of patients to date with cancer in the pouch or the anorectal mucosa is therefore 17 (Table 1).

Of these 17 patients, 12 had either dysplasia or carcinoma or both in the original specimen, two did not and in two patients no information on the original histopathology of the operative specimen was available. Other associated features included: backwash ileitis in the original colonic specimen [60,71], dysplasia of the rectal mucosal remnant, PSC [67] and chronic atrophic pouchitis [63]. The median interval from the onset of UC to the presentation of carcinoma was 24 (range 120–528) months. The median interval from RPC to presentation was 60 (range 16–216) months (Fig. 1). The minimum

interval from the onset of UC to the development of carcinoma was 10 years.

Ten reports of adenocarcinoma either in the anorectal mucosa or ileo-anal pouch in patients with FAP have been published in the literature [72–80] and two patients of adenocarcinoma in the ileo-anal anastomotic region have been reported following RPC in patients with Crohn's disease [81,82]. Two patients of lymphoma [83,84] in the ileo-anal pouch and one patient of adenocarcinoma in a Kock pouch [85], all following the diagnosis of UC have also been reported. Ravitch [86], in his presidential address to the American College of Surgeons, had mentioned a patient of squamous cell carcinoma of the anal mucosa following RPC and this year there has been another report [87] of a squamous cell carcinoma at the anorectal ring.

Risk factors for neoplastic transformation

1 Cancer or dysplasia in the operative specimen. Most studies have shown that the incidence of dysplasia following RPC is increased with a preoperative history of dysplasia or carcinoma or finding of the same in the original operative specimen. Indeed many of the patients (12/17) (Table 1) developing cancer in the anorectal mucosa or in the ileo-anal pouch had dysplasia or cancer identified before RPC or found subsequently in the operative specimen. This appears to be the most important predisposing risk factor for the development of neoplasia following RPC.

2 Interval from the diagnosis of UC. The risk of colorectal cancer in patients with long-standing UC increases with time [88–90] and is related to the anatomical extent of the disease in the operative specimen [28,46]. Pouch-related cancer did not occur in any of the patients shown in Table 1 before 10 years from the onset of UC and the median interval was 20 years. The interval from RPC (median 5 years; range 16 months to 18 years) has a greater variance (Fig. 1) and it seems likely that the time of onset of the disease is the important interval when considering surveillance.

3 Type C mucosal changes. A type C mucosal pattern of the pouch mucosa is associated with chronic pouchitis and also with dysplasia and aneuploidy. There is evidence [7] that these patients can be identified within months of RPC by histopathological examination of the biopsy material. Other studies, however, have not demonstrated an association between chronic pouchitis and dysplasia [2], and furthermore some have not found dysplasia at all in patients undergoing pouch surveillance [91–94].

4 Extra intestinal manifestations. The relationship between type C changes and EIM including sclerosing cholangitis and their apparent association with dysplasia

Table 1 Reported patients of carcinoma involving the ileo-anal pouch in patients with ulcerative proctocolitis.

Reference	Year	Site	Mucosectomy	Risk factors	Interval from diagnosis of ulcerative colitis in months	Interval from pouch surgery in months	Follow-up protocol	Histology
Puthu <i>et al.</i> [64]	1992	Starting at 1.5 cm proximal to anal region	Not stated	Not stated	204	72	Not stated	Adenocarcinoma
Rodriguez-Sanjuan <i>et al.</i> [57]	1995	Ileal pouch (exact site not stated)	Yes, 5-cm rectal cuff	Dysplasia of remnant rectal mucosa	264	43	Not stated	Adenocarcinoma
Sequens [65]	1997	Anal canal mucosa (transition zone)	No, double-stapled anastomosis	Upper rectal cancer	120	16	Routine	Adenocarcinoma
Vieth <i>et al.</i> [58]	1998	Pouch mucosa near side to side pouch anastomosis	Not stated	pT3 transverse colon cancer and other three pT1 lesion	216	24	Routine	Adenocarcinoma
Iwama <i>et al.</i> [59]	2000	Ileal pouch reservoir	Yes	Dysplasia of the colonic mucosa	252	216	Routine	Adenocarcinoma
Heuschen <i>et al.</i> [60]	2001	Proximal part of ileo-anal pouch	Yes, handsewn anastomosis	Focal dysplasia and pT3 adenocarcinoma of descending colon, backwash ileitis, dysplasia of pouch mucosa, severe pouchitis	312	38	Routine	Poorly differentiated adenocarcinoma
Rotholtz <i>et al.</i> [66]	2001	Residual rectal mucosa	No, stapled anastomosis, 10-cm rectal cuff	High-grade dysplasia at distal resection margin, severe pouchitis, high-grade dysplasia of pouch mucosa	156	84	Routine	Poorly differentiated adenocarcinoma
Lauret <i>et al.</i> [67]	2002	Anal canal, below anastomosis, malignant change in villous adenoma	Yes, handsewn anastomosis	Malignant polyp, transverse colon (precolectomy), malignant ulcer at ileo rectal anastomosis region, primary sclerosing cholangitis	336	24	Routine	Adenocarcinoma

Table 1 (Continued).

Reference	Year	Site	Mucosectomy	Risk factors	Interval from diagnosis of ulcerative colitis in months	Interval from pouch surgery in months	Follow-up protocol	Histology
Baratsis <i>et al.</i> [68]	2002	Anal canal (transition zone)	No, double-stapled anastomosis	Focal grade I dysplasia of colon, T3, N0 caecal carcinoma (on colectomy)	312	216	Not stated	Adenocarcinoma
Hyman [69]	2002	Residual rectal mucosa	No, double-stapled anastomosis	High-grade dysplasia transverse and sigmoid colon, distal donut	216	60	Routine	Mucinous adenocarcinoma
Bentrem <i>et al.</i> [61]	2003	Arising from ileal mucosa, well proximal to anastomosis	Yes, handsewn anastomosis	Focal dysplasia and pT1 adenocarcinoma in the ascending colon	528	168	None between 2 and 13 years	Grade 2 adenocarcinoma
Hassan <i>et al.</i> [62]	2003	?Pouch mucosa spreading towards the IPAA	Yes, handsewn anastomosis	Chronic pouchitis, dysplasia in the ileal mucosa	144	24	Routine	Moderately differentiated (intestinal type) adenocarcinoma
Bell <i>et al.</i> [70]	2003	Anal canal (transition zone)	No, double-stapled anastomosis	Severe high-grade dysplasia in the left colon	324	144	Regular up to 7 years, no biopsy	Adenocarcinoma
Negi <i>et al.</i> [71]	2003	Residual rectal mucosa	Yes, handsewn anastomosis, 4-cm rectal muscular cuff	Backwash ileitis, high-grade dysplasia in transverse colon	Not stated	60	Routine	Poorly differentiated adenocarcinoma
Lee <i>et al.</i> [56] (patient 3)	2005	Residual rectal mucosa	Yes, handsewn	No information on original specimen	216	180	Poor	Adenocarcinoma
Knupper <i>et al.</i> [63]	2005	Pouch reservoir mucosa	No, double-stapled anastomosis	Chronic atrophic pouchitis, nil else	240	Not stated	Not stated	Adenocarcinoma
This study	2006	Residual anal mucosa	Yes, handsewn	No previous dysplasia or cancer in original operative specimen	324	312	Routine, not regular	Moderately differentiated adenocarcinoma

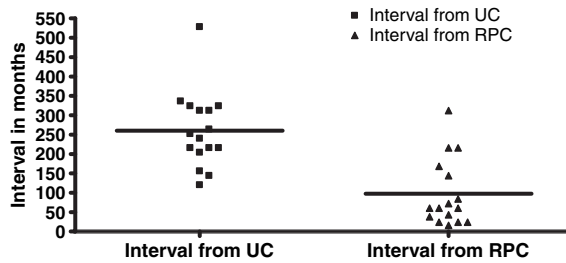


Figure 1 Vertical scatter plot showing intervals of onsets of reported pouch cancers from onset of ulcerative colitis and restorative proctocolectomy.

suggests that these patients are at increased risk of developing neoplastic transformation in the pouch.

5 Manual vs stapled anastomotic technique. Ten patients [56,64–71] of carcinoma in the ano-rectal mucosa have been reported including the patient reported here. Of these, five [65,66,68–70] occurred after stapled anastomosis without mucosectomy and three [67,71] after mucosectomy and manual anastomosis (in two, the method of anastomosis was not stated) indicating that carcinoma can occur after either form of anastomosis. While there is no information to date of the cumulative risk of carcinoma in the anorectal mucosa from prospective life table analysis, it is possible that patients having a stapled anastomosis may be at significant risk with the passage of time where there is residual rectal mucosa particularly if dysplasia was present preoperatively.

Surveillance for neoplastic transformation

The risk surveillance is costly

The incidence of carcinoma in the ileal reservoir or anorectal mucosa appears to be low, certainly up to 10–20 years following RPC. Thus, it is essential to minimize this potential burden by identifying patients at risk. The literature suggests that patients with preoperative neoplastic transformation, type C pouch mucosal changes and PSC are at higher risk of developing dysplasia or invasive adenocarcinoma than the normal population of patients who have undergone RPC and should be included in a surveillance programme. Both the ano-rectal and the pouch mucosa should be monitored by biopsy. Biopsies from the pouch are easily obtained at endoscopy. It is more difficult, however, to take biopsies from the anorectal mucosa. This area is sensitive and it may be impossible in some patients to pass a proctoscope owing to narrowing of the ileo-anal anastomosis. Such patients may require an examination under anaesthetic. This has practical implications for medical resources. Patients diagnosed as having dysplasia should be confirmed after

a second opinion from another gastrointestinal histopathologist.

Suggested plan of surveillance

It is recognized that patients having RPC will be followed for various reasons including the need to maintain contact with the patient to assess late complications, well-being and function. The proposed scheme below deals with the risk of neoplastic transformation only and should be added to the general follow-up system.

Inclusion. Patients with the following features should be included:

- dysplasia or adenocarcinoma in the original operative specimen;
- interval From onset of UC of greater than 10 years;
- type C mucosa;
- primary sclerosing cholangitis;
- ileal pouch-rectal anastomosis.

Method

Initial biopsies from the pouch should be taken at 6–12 months to identify the appearance of type C changes. From 10 years onward from the onset of disease the following should be carried out:

- 1 pouchoscopy with multiple biopsies (four quadrant, in the upper and lower pouch);
- 2 anorectal mucosal biopsies, taken under anaesthesia if necessary.

This should be repeated annually from 10 years from the onset of UC in this small high-risk group.

Other possible methods of surveillance

There have been conflicting reports of the validity of the mucosal dysplasia–carcinoma sequence [22,41]. Alternative forms of surveillance have been proposed including examination for p53 overexpression and aneuploidy of biopsies in addition to histopathological assessment for dysplasia [95]. A method of surveillance of the anorectal mucosa using high-magnification chromatoscopic pouchoscopy has recently been described [96]. The method gives an accurate assessment of anorectal surface microanatomy, permitting accurate biopsy targeting. It is possible that these approaches may become part of future surveillance.

References

- 1 Veress B, Reinholt FP, Lindquist K, Lofberg R, Liljeqvist L. Long-term histomorphological surveillance of the pelvic ileal pouch: dysplasia develops in a subgroup of patients. *Gastroenterology* 1995; **109**: 1090–7.
- 2 Thompson-Fawcett MW, Marcus V, Redston M, Cohen Z, McLeod RS. Risk of dysplasia in long-term ileal pouches and

- pouches with chronic pouchitis. *Gastroenterology* 2001; **12**: 275–81.
- 3 Tarroni D, Wilkinson KH, Saunders B, Talbot I, Nicholls RJ. Long-term histological assessment of the ileal reservoir following restorative proctocolectomy for ulcerative colitis for inflammation and dysplasia. *Dis Colon Rectum* 2002; **45**: A7.
 - 4 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.
 - 5 Herbst F, Ciclitira PJ, Talbot IC, Nicholls RJ. Early changes of ileoanal pouch mucosa in patients with ulcerative colitis. *Eur J Gastroenterol Hepatol* 2000; **12**: 899–905.
 - 6 Goldberg PA, Talbot IC, Nicholls RJ. Ileo-anal pouch histology. *Int J Colorectal Dis* 1993; **8**: 226.
 - 7 Setti Carraro P, Talbot IC, Nicholls RJ. Longterm appraisal of the histological appearances of the ileal reservoir mucosa after restorative proctocolectomy for ulcerative colitis. *Gut* 1994; **35**: 1721–7.
 - 8 Apel R, Cohen Z, Andrews CW Jr, McLeod R, Steinhart H, Odze RD. Prospective evaluation of early morphological changes in pelvic ileal pouches [see comment]. *Gastroenterology* 1994; **107**: 435–43.
 - 9 Arai K, Fukushima T, Sugita A, Shimada H. Urinary changes in patients following restorative proctocolectomy. *Surgery* 1997; **27**: 801–5.
 - 10 Arai K, Koganei K, Kimura H, Akatani M, Kitoh F, Sugita A, Fukushima T. Incidence and outcome of complications following restorative proctocolectomy. *Am J Surg* 2005; **190**: 39–42.
 - 11 de Silva HJ, Millard PR, Kettlewell M, Mortensen NJ, Prince C, Jewell DP. Mucosal characteristics of pelvic ileal pouches. *Gut* 1991; **32**: 61–5.
 - 12 Kuisma J, Mentula S, Luukkonen P, Jarvinen H, Kahri A, Farkkila M. Factors associated with ileal mucosal morphology and inflammation in patients with ileal pouch-anal anastomosis for ulcerative colitis. *Dis Colon Rectum* 2003; **46**: 1476–83.
 - 13 Roediger WE. Utilization of nutrients by isolated epithelial cells of the rat colon. *Gastroenterology* 1982; **83**: 424–9.
 - 14 Roediger WE, Heyworth M, Willoughby P, Piris J, Moore A, Truelove SC. Luminal ions and short chain fatty acids as markers of functional activity of the mucosa in ulcerative colitis. *J Clin Pathol* 1982; **35**: 323–6.
 - 15 Roediger WE, Rae DA. Trophic effect of short chain fatty acids on mucosal handling of ions by the defunctioned colon. *Br J Surg* 1982; **69**: 23–5.
 - 16 Rolandelli RH, Koruda MJ, Settle RG, Rombeau JL. Effects of intraluminal infusion of short-chain fatty acids on the healing of colonic anastomosis in the rat. *Surgery* 1986; **100**: 198–204.
 - 17 Roediger WE. Anaerobic bacteria, the colon and colitis. *Aust N Z J Surg* 1980; **50**: 73–5.
 - 18 Shepherd NA, Hulten L, Tytgat GN *et al.* Pouchitis. *Int J Colorectal Dis* 1989; **4**: 205–29.
 - 19 Nicholls RJ, Belliveau P, Neill M, Wilks M, Tabaqchali S. Restorative proctocolectomy with ileal reservoir: a pathophysiological assessment. *Gut* 1981; **22**: 462–8.
 - 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 Veress B, Reinholt FP, Lindquist K, Liljeqvist L. Different types of mucosal adaptation in the ileal reservoir after restorative proctocolectomy. A two-year follow-up study. *Apmis* 1990; **98**: 786–96.
 - 22 Gullberg K, Lindfors U, Zetterquist H, Stalberg D, Reinholt FP, Veress B, Tribukait B, Olivecrona H, Lofberg R. Cancer risk assessment in long-standing pouchitis. DNA aberrations are rare in transformed neoplastic pelvic pouch mucosa. *Int J Colorectal Dis* 2002; **17**: 92–7.
 - 23 Stahlberg D, Gullberg K, Liljeqvist L, Hellers G, Lofberg R. Pouchitis following pelvic pouch operation for ulcerative colitis. Incidence, cumulative risk, and risk factors. *Dis Colon Rectum* 1996; **39**: 1012–8.
 - 24 Achkar JP, Al-Haddad M, Lashner B, Remzi FH, Brzezinski A, Shen B, Khandwala F, Fazio V. Differentiating risk factors for acute and chronic pouchitis. *Clin Gastroenterol Hepatol* 2005; **3**: 60–6.
 - 25 Lohmuller JL, Pemberton JH, Dozois RR, Ilstrup D, van Heerden J. Pouchitis and extraintestinal manifestations of inflammatory bowel disease after ileal pouch-anal anastomosis [see comment]. *Ann Surg* 1990; **211**: 622–7; discussion: 627–9.
 - 26 Penna C, Dozois R, Tremaine W, Sandborn W, LaRusso N, Schleck C, Ilstrup D. 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.
 - 27 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.
 - 28 Stahlberg D, Veress B, Tribukait B, Broome U. Atrophy and neoplastic transformation of the ileal pouch mucosa in patients with ulcerative colitis and primary sclerosing cholangitis: a case control study. *Dis Colon Rectum* 2003; **46**: 770–8.
 - 29 Nuako KW, Ahlquist DA, Sandborn WJ, Mahoney DW, Siems DM, Zinsmeister AR. Primary sclerosing cholangitis and colorectal carcinoma in patients with chronic ulcerative colitis: a case-control study. *Cancer* 1998; **82**: 822–6.
 - 30 Broome U, Lofberg R, Veress B, Eriksson LS. Primary sclerosing cholangitis and ulcerative colitis: evidence for increased neoplastic potential [see comment]. *Hepatology* 1995; **22**: 1404–8.
 - 31 Brentnall TA, Haggitt RC, Rabinovitch PS *et al.* Risk and natural history of colonic neoplasia in patients with primary sclerosing cholangitis and ulcerative colitis [see comment]. *Gastroenterology* 1996; **110**: 331–8.

- 32 Nagengast FM, Grubben MJ, van Munster IP. Role of bile acids in colorectal carcinogenesis. *Eur J Cancer* 1995; **31A**: 1067–70.
- 33 Marchesa P, Lashner BA, Lavery IC, Milsom J, Hull TL, Strong SA, Church JM, Navarro G, Fazio VW. The risk of cancer and dysplasia among ulcerative colitis patients with primary sclerosing cholangitis. *Am J Gastroenterol* 1997; **92**: 1285–8.
- 34 O’Connell PR, Pemberton JH, Weiland LH, Beart RW Jr, Dozois RR, Wolff BG, Telander RL. Does rectal mucosa regenerate after ileoanal anastomosis? *Dis Colon Rectum* 1987; **30**: 1–5.
- 35 Lavery IC, Sirimarco MT, Ziv Y, Fazio VW. Anal canal inflammation after ileal pouch-anal anastomosis. The need for treatment. *Dis Colon Rectum* 1995; **38**: 803–6.
- 36 Thompson-Fawcett MW, Mortensen NJ, Warren BF. “Cuffitis” and inflammatory changes in the columnar cuff, anal transitional zone, and ileal reservoir after stapled pouch-anal anastomosis. *Dis Colon Rectum* 1999; **42**: 348–55.
- 37 Lofberg R, Liljeqvist L, Lindquist K, Veress B, Reinholdt FP, Tribukait B. Dysplasia and DNA aneuploidy in a pelvic pouch. Report of a case. *Dis Colon Rectum* 1991; **34**: 280–3; discussion 283–4.
- 38 Hulten L, Willen R, Nilsson O, Safarani N, Haboubi N. Mucosal assessment for dysplasia and cancer in the ileal pouch mucosa in patients operated on for ulcerative colitis – a 30-year follow-up study. *Dis Colon Rectum* 2002; **45**: 448–52.
- 39 Duff SE, O’Dwyer ST, Hulten L, Willen R, Haboubi NY. Dysplasia in the ileoanal pouch. *Colorectal Dis* 2002; **4**: 420–9.
- 40 Herline AJ, Meisinger LL, Rusin LC, Roberts PL, Murray JJ, Coller JA, Marcello PW, Schoetz DJ. Is routine pouch surveillance for dysplasia indicated for ileoanal pouches? *Dis Colon Rectum* 2003; **46**: 156–9.
- 41 Borjesson L, Willen R, Haboubi N, Duff SE, Hulten L. The risk of dysplasia and cancer in the ileal pouch mucosa after restorative proctocolectomy for ulcerative proctocolitis is low: a long-term follow-up study. *Colorectal Dis* 2004; **6**: 494–8.
- 42 Gullberg K, Stahlberg D, Liljeqvist L, Tribukait B, Reinholdt FP, Veress B, Lofberg R. Neoplastic transformation of the pelvic pouch mucosa in patients with ulcerative colitis. *Gastroenterology* 1997; **112**: 1487–92.
- 43 Barrett M, Schoetz D, Semple J, Rusin L, Cohen J, Roberts P, Murray J, Coller J. Long-term risk of neoplastic changes in ileoanal pouches in patients with ulcerative colitis. *Dis Colon Rectum* 1998; **41**: A26.
- 44 Seow-Choen F, Ho YH, Goh HS. The ileo-anal reservoir: results from an evolving use of stapling devices. *JR Coll Surg Edinb* 1994; **39**: 13–6.
- 45 Thompson-Fawcett MW, Warren BF, Mortensen NJ. A new look at the anal transitional zone with reference to restorative proctocolectomy and the columnar cuff. *Br J Surg* 1998; **85**: 1517–21.
- 46 Tsunoda A, Talbot IC, Nicholls RJ. Incidence of dysplasia in the anorectal mucosa in patients having restorative proctocolectomy. *Br J Surg* 1990; **77**: 506–8.
- 47 Ziv Y, Fazio VW, Sirimarco MT, Lavery IC, Goldblum JR, Petras RE. Incidence, risk factors, and treatment of dysplasia in the anal transitional zone after ileal pouch-anal anastomosis. *Dis Colon Rectum* 1994; **37**: 1281–5.
- 48 O’Riordain MG, Fazio VW, Lavery IC, Remzi F, Fabbri N, Meneu J, Goldblum J, Petras RE. Incidence and natural history of dysplasia of the anal transitional zone after ileal pouch-anal anastomosis: results of a five-year to ten-year follow-up. *Dis Colon Rectum* 2000; **43**: 1660–5.
- 49 Remzi FH, Fazio VW, Delaney CP *et al*. Dysplasia of the anal transitional zone after ileal pouch-anal anastomosis: results of prospective evaluation after a minimum of ten years. *Dis Colon Rectum* 2003; **46**: 6–13.
- 50 Thompson-Fawcett MW, Rust NA, Warren BF, Mortensen NJ. Aneuploidy and columnar cuff surveillance after stapled ileal pouch-anal anastomosis in ulcerative colitis. *Dis Colon Rectum* 2000; **43**: 408–13.
- 51 Coull DB, Lee FD, Henderson AP, Anderson JH, McKee RF, Finlay IG. Risk of dysplasia in the columnar cuff after stapled restorative proctocolectomy. *Br J Surg* 2003; **90**: 72–5.
- 52 Haray PN, Amarnath B, Weiss EG, Nogueras JJ, Wexner SD. Low malignant potential of the double-stapled ileal pouch-anal anastomosis. *Br J Surg* 1996; **83**: 1406.
- 53 Gilchrist KW, Harms BA, Starling JR. Abnormal rectal mucosa of the anal transitional zone in ulcerative colitis. *Arch Surg* 1995; **130**: 981–3.
- 54 Schmitt SL, Wexner SD, Lucas FV, James K, Nogueras JJ, Jagelman DG. Retained mucosa after double-stapled ileal reservoir and ileoanal anastomosis. *Dis Colon Rectum* 1992; **35**: 1051–6.
- 55 Stern H, Walfisch S, Mullen B, McLeod R, Cohen Z. Cancer in an ileoanal reservoir: a new late complication? [see comment]. *Gut* 1990; **31**: 473–5.
- 56 Lee SW, Sonoda T, Milsom JW. Three cases of adenocarcinoma following restorative proctocolectomy with hand-sewn anastomosis for ulcerative colitis: a review of reported cases in the literature. *Colorectal Dis* 2005; **7**: 591–7.
- 57 Rodriguez-Sanjuan JC, Polavieja MG, Naranjo A, Castillo J. Adenocarcinoma in an ileal pouch for ulcerative colitis. *Dis Colon Rectum* 1995; **38**: 779–80.
- 58 Vieth M, Grunewald M, Niemeyer C, Stolte M. Adenocarcinoma in an ileal pouch after prior proctocolectomy for carcinoma in a patient with ulcerative pancolitis. *Virchows Arch* 1998; **433**: 281–4.
- 59 Iwama T, Kamikawa J, Higuchi T, Yagi K, Matsuzaki T, Kanno J, Maekawa A. Development of invasive adenocarcinoma in a long-standing diverted ileal J-pouch for ulcerative colitis: report of a case. *Dis Colon Rectum* 2000; **43**: 101–4.
- 60 Heuschen UA, Heuschen G, Autschbach F, Allemeyer EH, Herfarth C. Adenocarcinoma in the ileal pouch: late risk of cancer after restorative proctocolectomy. *Int J Colorectal Dis* 2001; **16**: 126–30.
- 61 Bentrem DJ, Wang KL, Stryker SJ. Adenocarcinoma in an ileal pouch occurring 14 years after restorative proctocolectomy: report of a case [erratum appears in *Dis*

- Colon Rectum* 2003; **46**(5): 628]. *Dis Colon Rectum* 2003; **46**: 544–6.
- 62 Hassan C, Zullo A, Speziale G, Stella F, Lorenzetti R, Morini S. Adenocarcinoma of the ileoanal pouch anastomosis: an emerging complication? *Int J Colorectal Dis* 2003; **18**: 276–8.
- 63 Knupper N, Straub E, Terpe HJ, Vestweber KH. Adenocarcinoma of the ileoanal pouch for ulcerative colitis – a complication of severe chronic atrophic pouchitis? *Int J Colorectal Dis* 2006; **21**: 478–82.
- 64 Puthu D, Rajan N, Rao R, Rao L, Venugopal P. Carcinoma of the rectal pouch following restorative proctocolectomy. Report of a case. *Dis Colon Rectum* 1992; **35**: 257–60.
- 65 Sequens R. Cancer in the anal canal (transitional zone) after restorative proctocolectomy with stapled ileal pouch-anal anastomosis. *Int J Colorectal Dis* 1997; **12**: 254–5.
- 66 Rotholtz NA, Pikarsky AJ, Singh JJ, Wexner SD. Adenocarcinoma arising from along the rectal stump after double-stapled ileorectal J-pouch in a patient with ulcerative colitis: the need to perform a distal anastomosis. Report of a case. *Dis Colon Rectum* 2001; **44**: 1214–7.
- 67 Laureti S, Ugolini F, D'Errico A, Rago S, Poggioli G. Adenocarcinoma below ileoanal anastomosis for ulcerative colitis: report of a case and review of the literature. *Dis Colon Rectum* 2002; **45**: 418–21.
- 68 Baratsis S, Hadjidimitriou F, Christodoulou M, Lariou K. Adenocarcinoma in the anal canal after ileal pouch-anal anastomosis for ulcerative colitis using a double stapling technique: report of a case. *Dis Colon Rectum* 2002; **45**: 687–91; discussion 691–82.
- 69 Hyman N. Rectal cancer as a complication of stapled IPAA. *Inflamm Bowel Dis* 2002; **8**: 43–5.
- 70 Bell SW, Parry B, Neill M. Adenocarcinoma in the anal transitional zone after ileal pouch for ulcerative colitis: report of a case. *Dis Colon Rectum* 2003; **46**: 1134–7.
- 71 Negi SS, Chaudhary A, Gondal R. Carcinoma of pelvic pouch following restorative proctocolectomy: report of a case and review of the literature. *Dig Surg* 2003; **20**: 63–5.
- 72 Hoehner JC, Metcalf AM. Development of invasive adenocarcinoma following colectomy with ileoanal anastomosis for familial polyposis coli. Report of a case. *Dis Colon Rectum* 1994; **37**: 824–8.
- 73 von Herbay A, Stern J, Herfarth C. Pouch-anal cancer after restorative proctocolectomy for familial adenomatous polyposis. *Am J Surg Pathol* 1996; **20**: 995–9.
- 74 Vuilleumier H, Halkic N, Ksontini R, Gillet M. Columnar cuff cancer after restorative proctocolectomy for familial adenomatous polyposis. *Gut* 2000; **47**: 732–4.
- 75 Brown SR, Donati D, Seow-Choen F. Rectal cancer after mucosectomy for ileoanal pouch in familial adenomatous polyposis: report of a case. *Dis Colon Rectum* 2001; **44**: 1714–5.
- 76 Remzi FH, Church JM, Bast J et al. Mucosectomy vs. stapled ileal pouch-anal anastomosis in patients with familial adenomatous polyposis: functional outcome and neoplasia control. *Dis Colon Rectum* 2001; **44**: 1590–6.
- 77 Bassuini MM, Billings PJ. Carcinoma in an ileoanal pouch after restorative proctocolectomy for familial adenomatous polyposis. *Br J Surg* 1996; **83**: 506.
- 78 Palkar VM, deSouza LJ, Jagannath P, Naresh KN. Adenocarcinoma arising in “J” pouch after total proctocolectomy for familial polyposis coli. *Indian J Cancer* 1997; **34**: 16–9.
- 79 Ooi BS, Remzi FH, Gramlich T, Church JM, Preen M, Fazio VW. Anal transitional zone cancer after restorative proctocolectomy and ileoanal anastomosis in familial adenomatous polyposis: report of two cases. *Dis Colon Rectum* 2003; **46**: 1418–23; discussion 1422–3.
- 80 Campos FG, Habr-Gama A, Kiss DR, da Silva EV, Rawet V, Imperiale AR, Perez R, da Silva JH, Sousa AH Jr, Gama-Rodrigues J. Adenocarcinoma after ileoanal anastomosis for familial adenomatous polyposis: review of risk factors and current surveillance apropos of a case. *J Gastrointest Surg* 2005; **9**: 695–702.
- 81 Kotanagi H, Kon H, Iida M, Ito M, Koyama K. Adenocarcinoma at the site of ileoanal anastomosis in Crohn's disease: report of a case. *Dis Colon Rectum* 2001; **44**: 1210–3.
- 82 Ben Temime L, Gherib BS, Daldoul S, Bel Hadj Salah R, Abdesselem Mel M, Zaouche A. Adenocarcinoma at the site of ileo-anal anastomosis in Crohn's disease: report of a case. *Tunis Med* 2005; **83**: 55–8.
- 83 Nyam DC, Pemberton JH, Sandborn WJ, Savchenko M. Lymphoma of the pouch after ileal pouch-anal anastomosis: report of a case. *Dis Colon Rectum* 1997; **40**: 971–2.
- 84 Frizzi JD, Rivera DE, Harris JA, Hamill RL. Lymphoma arising in an S-pouch after total proctocolectomy for ulcerative colitis: report of a case. *Dis Colon Rectum* 2000; **43**: 540–3.
- 85 Cox CL, Butts DR, Roberts MP, Wessels RA, Bailey HR. Development of invasive adenocarcinoma in a long-standing Kock continent ileostomy: report of a case. *Dis Colon Rectum* 1997; **40**: 500–3.
- 86 Ravitch MM. The reception of new operations. *Ann Surg* 1984; **200**: 231–46.
- 87 Schaffzin DM, Smith LE. Squamous-cell carcinoma developing after an ileoanal pouch procedure: report of a case. *Dis Colon Rectum* 2005; **48**: 1086–9.
- 88 Gyde SN, Prior P, Allan RN, Stevens A, Jewell DP, Truelove SC, Lofberg R, Brostrom O, Hellers G. Colorectal cancer in ulcerative colitis: a cohort study of primary referrals from three centres. *Gut* 1988; **29**: 206–17.
- 89 Shelton AA, Lehman RE, Schrock TR, Welton ML. Retrospective review of colorectal cancer in ulcerative colitis at a tertiary center. *Arch Surg* 1996; **131**: 806–10; discussion 810–11.
- 90 von Herbay A, Herfarth C, Otto HF. Cancer and dysplasia in ulcerative colitis: a histologic study of 301 surgical specimen. *Z Gastroenterol* 1994; **32**: 382–8.
- 91 Giarnieri E, Giovagnoli MR, Montesani C, Nagar C, Pronio AM, Alderisio M, Ribotta G, Vecchione A. Image analysis in multisample biopsy after ileal pouch-anal anastomosis. *Anticancer Res* 1996; **16**: 3207–11.

- 92 Giebel GD, Sabiers H. Ileal pouch-anal anastomosis for ulcerative colitis and polyposis coli: is the risk of carcinoma formation conclusively averted? *Eur J Surg Oncol* 1996; **22**: 372–6.
- 93 Setti-Carraro P, Ritchie JK, Wilkinson KH, Nicholls RJ, Hawley PR. The first 10 years' experience of restorative proctocolectomy for ulcerative colitis. *Gut* 1994; **35**: 1070–5.
- 94 Sarigol S, Wyllie R, Gramlich T, Alexander F, Fazio V, Kay M, Mahajan L. Incidence of dysplasia in pelvic pouches in pediatric patients after ileal pouch-anal anastomosis for ulcerative colitis. *J Pediatr Gastroenterol Nutr* 1999; **28**: 429–34.
- 95 Elkowitz D, Daum F, Markowitz J, Proccaccino J, Boas E, Cuomo J, Kahn E. Risk factors for carcinoma of the pelvic ileal pouch/anal canal in ulcerative colitis. *Ann Clin Lab Sci* 2004; **34**: 143–9.
- 96 Hurlstone DP, Shorthouse AJ, Cross SS, Brown S, Sanders DS, Lobo AJ. High-magnification chromoscopic pouchoscopy: a novel in vivo technique for surveillance of the anal transition zone and columnar cuff following ileal pouch-anal anastomosis. *Tech Coloproctol* 2004; **8**: 173–8; discussion 178.