

# Three cases of adenocarcinoma following restorative proctocolectomy with hand-sewn anastomosis for ulcerative colitis: a review of reported cases in the literature

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## Abstract

Restorative proctocolectomy (RPC) has been accepted as optimal surgical therapy for most patients with ulcerative colitis. The occurrence of adenocarcinoma adjacent to the ileoanal anastomotic site for ulcerative colitis is a serious but rare outcome. There are 16 reported cases. We report three additional cases and review previous cases in the literature.

**Keywords** Adenocarcinoma, restorative proctocolectomy, hand-sewn anastomosis, ulcerative colitis, literature review

## Introduction

Restorative proctocolectomy (RPC) has been increasingly adapted as the optimal surgical treatment of ulcerative colitis. Since the time it was first described by Parks & Nicholls [1], the goal of RPC has been completely to remove the diseased colon and rectal mucosa while preserving the normal route of defaecation [2]. As patients age after surgery, there is naturally increasing concern that residual large bowel mucosa left behind might undergo malignant transformation. This has led to some concern about the double-stapled ileo-anal anastomosis (in which some columnar epithelium is left above the dentate line), vs the hand-sewn anastomotic technique where 'stripping' of all tissue cephalad to the dentate line is performed.

Despite the above concerns, the incidence of cancer following RPC is likely to be extremely low. There are 16 previously reported cases of cancer in the anal canal following this operation in the literature [3–18]. Of these, 10 underwent a mucosectomy followed by hand-sewn anastomosis and five a stapled anastomosis. In one case, there was no mention of the type of anastomosis performed. We report three further cases of adenocarcinoma at or around the anastomosis after RPC, all with

previous mucosectomy and hand-sewn anastomotic technique for ulcerative colitis.

## Case reports

### Case one

Case 1 is a 49-year-old male diagnosed with ulcerative colitis at the age of 19. For 27 years, the patient was in remission requiring occasional medical therapy for symptomatic relief. At the age of 47, the patient was found to have low-grade dysplasia in the distal rectum on routine surveillance. Colonoscopy was repeated several months later and low-grade dysplasia persisted in the rectum and high-grade dysplasia was also found in the sigmoid colon. At an outside institution, the patient underwent a RPC. The operation consisted of total proctocolectomy (TPC), complete rectal mucosectomy to the level of dentate line, formation of J-pouch, and hand-sewn anastomosis between the pouch and the anus at level of the dentate line. On surgical pathology, the patient was found to have polypoid high-grade dysplasia (DALM) and flat low-grade dysplasia in the anorectal mucosal stripping. The patient also had low-grade dysplasia distributed evenly throughout the distal descending, sigmoid, and rectal segments. The patient had an unremarkable postoperative course.

Six months following the surgery, the patient began having symptoms of constant anal pressure and pain when

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sitting. Patient's symptoms continued to worsen and the patient was evaluated by an orthopaedist. Work up at this time included plain films of the hips that was found to be normal. One month later, the patient presented with unremitting pelvic pain and underwent an examination under anaesthesia. The patient was found to have an anastomotic stricture and anal fistula, and underwent a fistulotomy. Despite this intervention, the patient's symptoms persisted.

The patient was seen in our department two years following RPC. On examination, a firm mass in the presacral area, posterior to the ileal pouch was noted. Endoscopic examination and biopsy of this area performed in our office were negative. The patient then underwent a CT scan of abdomen and pelvis that demonstrated a low-density mass in the presacral area measuring  $4 \times 2.7 \times 5$  cm. In light of these findings, the patient underwent a Trucut needle biopsy of the soft tissues adjacent to the anastomosis in the operating room which confirmed the diagnosis of adenocarcinoma. After a pre-operative radiation and chemotherapy (5-FU and leucovorin), the patient was taken to the operating room. At exploration, the cancer appeared to be originating from the lower portion of the pouch and was adherent to the sacrum and left seminal vesicle. The upper part of the pouch was found to be mobile and free of cancer. The patient underwent an excision of anal pouch with en bloc resection of the lower sacrum to the level of S3. The anal sphincters and left seminal vesicles were also excised. Histological study of the specimen showed moderately to poorly differentiated tumour arising from the ileal mucosa. There was no lymph node involvement. Post-operatively, patient underwent further chemotherapy. Patient is currently two years on from the surgery and has probable lung metastases.

#### Case two

Case 2 is a 44-year-old male who presented to our service in October 2002. The patient was diagnosed with ulcerative colitis when he was 29 years old. The patient had been treated with sulphasalazine for 12 years with good response. In 1995, during a routine surveillance, he was found to have high-grade dysplasia in the rectum. The patient underwent a RPC at an outside institution. The procedure consisted of total proctocolectomy, complete mucosectomy and hand-sewn ileo-anal anastomosis. The final surgical pathology revealed T3 N0 M0 rectal cancer. The distal margins were clear of dysplasia or cancer. The patient underwent a postoperative radiation and chemotherapy that consisted of 5-FU and leucovorin. The patient had an unremarkable course until four years after the surgery when he began complaining of vague

abdominal and pelvic pains. A lower endoscopy at that time was unrevealing. However, his symptoms continue to get worse. Five years after RPC, the patient underwent a CT scan which showed a nodularity in the presacral area which was interpreted as 'findings consistent with post-surgical changes but cannot rule out cancer'. A sigmoidoscopy demonstrated an anastomotic stricture that was subsequently dilated. Patient's symptoms initially improved following the dilatation, but returned several months later. Patient underwent two more CT scans of abdomen and pelvis that demonstrated similar finding in five and six months following the original scan.

Six and a half years post-RPC, the patient developed peri-anal abscess and fistula. A CT scan of the abdomen and the pelvis obtained soon after this procedure revealed multiple liver metastases and presacral soft tissue mass measuring at 3 cm. At this time, the patient referred himself to our institution. The patient was then taken to the operating room for an exam under anaesthesia. At surgery, patient had a firmly fixed mass adherent to the sacrum at the level of the anastomosis. Biopsy of the lesion confirmed the diagnosis of adenocarcinoma. Two weeks later, the patient underwent an exploratory laparoscopy and was found to have carcinomatosis. Because the patient presented with obstructive symptoms, a laparoscopic diverting loop ileostomy was performed. The patient subsequently underwent a placement of a morphine-infusion pump. The patient sought alternative medical options and is currently alive and undergoing holistic medical treatment.

#### Case three

Case 3 is a 37-year-old female who was diagnosed with ulcerative colitis at the age of 17. Since the diagnosis, the patient required progressively higher doses of corticosteroids becoming refractory to medical therapy after two years. In 1987, the patient underwent a RPC which consisted of total proctocolectomy, mucosectomy, and hand-sewn anastomosis at an outside institution for chronic refractory ulcerative colitis. The patient reportedly had an uncomplicated postoperative course. The patient did not have a regularly scheduled follow up after one year from the surgery. Fifteen years following RPC, the patient experienced an episode of rectal bleeding, which spontaneously resolved. Seven months later, she noted some perineal discomfort that she attributed to a vulvar lesion. She presented to a gynaecologist at an outside institution who recommended sitz baths. The pain continued to persist and she was referred to a gastroenterologist for further evaluation. A lower endoscopy showed a mass just proximal to anal verge measuring approximately 2 cm. The small bowel

proximal to the mass reportedly appeared normal. Biopsy showed moderately differentiated adenocarcinoma. Biopsy of the vulvar mass also showed a poorly differentiated adenocarcinoma present within the connective tissues of the vaginal wall and fragments of adenoma with focal high-grade dysplasia. A CT scan of the abdomen and pelvis showed a soft tissue thickening in the anus without any signs of distal metastasis.

Sixteen years after RPC, the patient underwent a pre-operative radiation and chemotherapy (5-FU and leucovorin). She presented to our institution in February 2002, one month after she finished her chemotherapy and radiation. On examination, anal cancer and vulvar mass were almost undetectable. The patient underwent an abdomino-perineal resection with partial resections of perineal body, posterior vaginal wall and the vulva. The tumour appeared to be arising from the anastomosis that was located approximately 6–7 cm from the dentate line. The final pathology (after neo-adjuvant therapy) showed no residual cancer (Tx N0 M0 G2) adenocarcinoma. The specimen showed histological features consistent with therapy effect (acellular mucin) and residual colonic-type mucosa with flat dysplasia. Based on clinical evidence, this case most likely represents cancer developing in residual rectal segment. The patient had an unremarkable recovery course and is currently free of disease one year postoperatively.

## Discussion

Although the risk of cancer following restorative proctocolectomy (RPC) is not known, the incidence judged by present data is extremely low. A recent review of over 1000 ulcerative colitis patients who underwent ileal pouch anal anastomosis did not reveal any incidence of cancer occurring at the ileoanal anastomotic site [19]. To date, there are now 19 cases of adenocarcinoma arising at the ileal–anal pouch anastomosis following RPC [3–18].

RPC is regarded as the gold standard in the surgical treatment of ulcerative colitis. Since the mid 1980s there has been a trend favouring a stapled anastomotic technique in which the ileal pouch is stapled to the anus while preserving the anal transitional zone. This has become popular because of the shorter operative time and better functional outcome [20]. A controversy still exists however, regarding the use of this technique due to the possibility of a higher risk of developing dysplasia or cancer in the retained anorectal mucosa. Despite this, the incidence of dysplasia in the anal transitional zone after stapled anastomosis appears to be very low [21,22]. Even after a macroscopically complete mucosectomy, islets of rectal mucosal cells probably remain in at least 20% percent of the patients [23,24]. Interestingly, the vast

majority of reported cases (13 (72%) of 18) of adenocarcinomas after RPC occurred in patients who underwent mucosectomy (Table 1). However, the higher incidence of adenocarcinoma in patients who had a mucosectomy reflects a longer follow up time given the higher number of patients who had this anastomotic technique carried out early in the development of RPC.

The incidence of colorectal cancer following subtotal colectomy with ileo-rectal anastomosis for patients with ulcerative colitis increases with the length of time elapsed from the surgery. This has reported to be 6% at 20 years and 15% at 30 years [25]. The risk of cancer in the ileal pouch after RPC is also expected to increase with the length of follow up after the surgery. The operation was not widely performed until the 1980s and 1990s. Sporadic reports of subsequent adenocarcinoma are expected to rise with the length of follow up. Since the first report in 1984, 18 additional cases have been reported (including the patients reported in this paper) and 13 (68%) have been reported in the last three years (Table 1).

The risk of developing dysplasia in the anal transitional zone is associated with the presence of cancer or dysplasia in the original proctocolectomy specimen [26]. Of the 17 reported cases, 15 had either dysplasia (8/17) or cancer (7/17) in the original specimen (Table 1). In two cases, the indication for surgery or the final pathology were not mentioned [3,5]. Of the above 15 patients, seven developed cancer in the ileo-anal pouch within three years from the time of the surgery. This short interval raises the possibility of either overlooked malignancy in dysplasia patients or tumour recurrence. In the present study, we report the second case of a patient who developed adenocarcinoma without a previous history of dysplasia or cancer in the colon or the rectum. Thus the risk of developing cancer in the ileal pouch anal anastomosis seems to be strongly associated with the presence of dysplasia or cancer at the time of RPC. When dysplasia or malignancy is identified pre-operatively, total mesorectal excision should probably be performed and consideration given for wider resection with possible end-ileostomy.

In the five cases of adenocarcinoma following stapled anastomosis (Table 1), two had a pre-operative diagnosis of either DALM or cancer in the rectum. Most supporters of stapled anastomosis would advocate a mucosectomy in this setting [22]. In the two other reported cases high-grade dysplasia was found at the distal resection margin of the rectum. In the same two patients an unusually long rectal cuff was left behind (4 cm and 10 cm). Ideally, a minimal length (2 cm or less) of the rectal mucosa should be left.

There is some controversy about the need for routine surveillance and biopsy in patients who have undergone

**Table 1** Details of previous cases reported in the literature.

First author	Year	Restorative proctocolectomy			Presentation with carcinoma				
		Age/ sex	Indication	Anastomosis	Pathology (original specimen)	t (years) s/p IPAA‡	F/U	Location	Stage
Ravitch	1984	?	?	M + HS*	?	?	?	?	?
Stern	1990	56/M	Dysplasia	M + HS	High grade dysplasia in the rectum	3	?	Pouch	T4NxMxGx
Puthu	1992	45/M	?	?	?	6	?	?	T4N2MxGx
Rodriguez-Sanjuan	1995	52/F	Dysplasia	M + HS	High grade dysplasia in the rectum	3.5	?	Pouch	T4NxM1G3
Sequens	1997	54/F	Cancer	Stapled†	Cancer in the rectum T2N0M0G2	1	Adequate	ATZ	T1N0M0G1
Veith	1998	35/F	Cancer	M + H	Multifocal dysplasia cancer in the transv. colon, T3N0M0G2	2	Adequate	Pouch	T3NxM1G2
Iwama	2000	32/M	CUC	M + HS	Low grade dysplasia	18	Inadequate – anal stenosis	Anastom	T2NxMxG1
Rotholtz	2001	65/M	CUC	Stapled	High grade dysplasia at distal resection margin	7	Adequate	ATZ	T4N2M1G3 10 cm rectal cuff
Heuschen	2001	45/M	Dysplasia	M + HS	Cancer in the descending colon T3N0M0G1	3	None for 28 months	Pouch	T3N1M0G3
Laureti	2002	46/M	Cancer	M + HS	Cancer in the ileo-rectal anastom. T2N0MxG2, PSC	2	Adequate	Anastom	T2N2MxG3
Hyman	2002	36/M	DALM	Stapled	High grade dysplasia in the transv., sigmoid colon and distal donut	5	None	Rectal stump	T3N0M0G? 4 cm rectal cuff
Baratsis	2002	47/M	CUC	Stapled	Multifocal dysplasia, caecal cancer, T3N0M0G1	2	None	ATZ	T3N1MxG3
Bentrem	2003	49/M	CUC	M + HS	Focal dysplasia, cancer in the ascending colon T1N0M0Gx	14	None after 2 year	Pouch	T4N0MxG2
Hassan	2003	38/M	CUC	M + HS	Chronic ulcerative colitis	2	Adequate	Pouch	T4N0M0G2 pouchitis
Negi	2003	23/M	Dysplasia	M + HS	High grade dysplasia	5	Adequate	Rectal stump	T3N1M0G3 pouchitis
Bell	2003	39/M	Dysplasia	Stapled	High grade dysplasia in the left colon	12	None after 6 year	Anastom	T4NxM1G3
Current series	2003	47/M	Dysplasia	M + HS	Polypoid high grade dysplasia (DALM) in the rectum	2	Adequate	Anastom	T4N0M0G3
Current series	2003	37/M	Dysplasia	M + HS	Cancer in the rectum T3N0M0G2	6.5	Adequate	Anastom	T4N2M1G2
Current series	2003	22/F	CUC	M + HS	Chronic ulcerative colitis, no dysplasia	16	None after 6 month	Rectal stump	T4NxM0G2 4 cm rectal cuff

\*M + HS: mucosectomy and hand-sewn anastomosis; †Stapled: Stapled anastomosis; ?: Not adequately described in the report; ‡: Time to presentation of adenocarcinoma from the IPAA surgery in years.

RPC for ulcerative colitis. In several studies, surveillance and biopsy did not find any incidence of dysplasia or cancer [21,22,27]. Herline *et al.* [27] performed biopsies of ileoanal pouch mucosa in 160 patients who underwent the procedure for ulcerative colitis. They found only one case of transient low grade dysplasia in the anal transitional zone. Coull *et al.* [21] followed 135 patients who underwent RPC for ulcerative colitis by taking biopsies from the 'cuff' of columnar epithelium retained between the pouch and ATZ. They did not find any case of dysplasia. Remzi *et al.* [22] recently published a prospective evaluation for dysplasia of the ATZ after ileal pouch anal anastomosis with a minimum follow up of 10 years. They found an incidence of 2.8% of dysplasia in the ATZ.

Another question is whether the development of cancer follows a progression from inflammation, to dysplasia, to cancer. There are many reports of patients with chronic ulcerative colitis who have developed cancer without prior evidence of dysplasia on surveillance [28]. Although it is possible that cancer may arise *de novo*, reports of cancer without a prior history of dysplasia are most likely to be due to the fact that no sufficient biopsy samples have been taken during colonoscopy to detect dysplasia with a reasonable degree of confidence. Published data suggest that to detect dysplasia with 90% confidence, 33 biopsies of the colon are needed, while 56 biopsies are required for 95% confidence [29].

In a recent survey of 298 British gastroenterologists, only 2% said they took 20 or more biopsies [30]. Regardless of this issue, the need for a close follow up in all patients after ileal anal pouch surgery should be emphasized, particularly if dysplasia or cancer were present at the time of RPC. Several of the reported patients with cancer after pouch surgery were lost to follow up. Although some experts do not feel the need for a routine surveillance 5 years after a mucosectomy, five of 13 patients who underwent mucosectomy presented later than 5 years after the surgery (median 10 years, range 5–16 years) (Table 1). As discussed previously, a complete mucosectomy may not be achieved in 20% of patients who later undergo pouch excision [23]. Thus, mucosectomy could result in a false sense of security with

a disastrous outcome. From this review of all reported patients who developed carcinoma after RPC, we feel most patients might have had a better outcome with at least yearly follow up.

Aside from the debate about differences in functional outcome and cancer risk between mucosectomy and hand-sewn *vs* stapled anastomosis, the ability to detect dysplasia or early cancer after mucosectomy needs to be studied more carefully. Mucosectomy is usually performed from the dentate line to the level of the transected rectum and the pouch is hand-sewn to the level of the dentate line. If islets of cells are left between the serosa of the pouch and the epithelial layer of the anal transitional zone, the residual rectal tissue may not be visualized nor easily accessed for biopsy on routine surveillance [23]. Therefore dysplasia or early cancer that arises from the residual rectal tissue after mucosectomy may not be easily detectable. Reviewing the reported cases, all of the patients who presented with cancer at the ileal pouch after mucosectomy presented with at least a locally advanced cancer (stage II or higher) including: three patients (stage II), five (stage III) and three (stage IV) disease. On the other hand, patients who underwent stapled anastomosis seemed to present with relatively earlier stage disease including: one patient with stage I, one with stage II, one with stage III and two with stage IV disease (Table 2). It is interesting to note that the only patient who presented with stage I cancer underwent stapled anastomosis and had an adequate follow up. It should also be emphasized that any ileal pouch patient who presents with nonspecific symptoms of abdominal discomfort or sacral pain should be closely investigated.

In reviewing the patients, we also noted that a significant number (6/12) of patients who developed cancer after mucosectomy and hand-sewn anastomosis developed cancer in the pouch, above the ileoanal anastomosis, while all patients from the stapled anastomosis group developed cancer in the anal transitional zone (Table 1). This may have different implications in terms of surveillance strategies for the two groups. For example, surveillance biopsy for the stapled anastomosis group may need to be concentrated in the ATZ whereas surveillance and random biopsy of the pouch

**Table 2** Distribution of patients who presented with cancer at the ileal pouch anastomotic site by cancer stage.

Type of anastomosis	No. of patients	Stage I	Stage II	Stage III	Stage IV
Mucosectomy and hand-sewn	11 patients*	0 (0%)	3 (27%)	5 (45%)	3 (27%)
Stapled	5 patients	1 (20%)	1 (20%)	1 (20%)	2 (40%)

\*There were total of 13 patients who developed cancer at the ileal pouch anastomotic site after mucosectomy and hand-sewn anastomosis. In two cases, the cancer stage at presentation was not reported.

mucosa may be more important for the mucosectomy group.

Another possible mechanism for the development of cancer in the anal pouch may be related to metaplasia of the ileal pouch mucosa. There are reports of primary stomal adenocarcinoma after total proctocolectomy for ulcerative colitis [31]. Histological studies of mucosa in the ileal pouch have found colonic metaplasia characterized by goblet cell multiplication, persistent severe villous atrophy, and formation of crypts [32–34]. In patients with chronic pouchitis, dysplasia has been found in up to 71% [34]. Five patients who developed recurrent cancer at the ileal pouch-anal anastomosis also had severe pouchitis (Table 1).

## Summary

The risk of developing adenocarcinoma in the anal canal following RPC for ulcerative colitis appears to be extremely low. Factors common to patients who have developed pouch related cancer include a long (>10–15 years) history of antecedent ulcerative colitis, dysplasia or cancer in the original specimen especially in the rectum, poor postoperative surveillance, or severe or delayed presentation of pouchitis. It should also be emphasized that any patient who presents with nonspecific symptoms of abdominal discomfort, anal or sacral pain should be closely investigated.

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