# CHAPTER 2

# Endoscopic surveillance of the ileoanal pouch following restorative proctocolectomy for colitis-associated dysplasia

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## *Abstract*

### Introduction

Patients with ulcerative colitis (UC) who have undergone a restorative proctocolectomy (RPC) with an ileo pouch anal anastomosis (IPAA) may still be at risk of developing dysplasia in their IPAA. A recent systematic review suggested that dysplasia identified before or at operation is a significant predictor of the development of dysplasia in the IPAA. The aim of this prospective study was to assess the prevalence of dysplasia in the IPAA of patients with UC who have undergone RPC and demonstrated dysplasia in their resection specimen.

### Methods

Eligible patients were invited for surveillance endoscopy of their IPAA. The afferent and blind ileal loop, ileoanal pouch and rectal cuff were examined by standard endoscopy plus methylene blue dye-spraying. Mucosal abnormalities were sampled and random biopsies were taken from the afferent and blind ileal loop, pouch and rectal cuff each.

### Results

44 patients (25 male, mean 49 yrs) underwent pouch-endoscopy. The mean time between RPC and pouch surveillance was 8.6 years. Dysplasia was detected through standard endoscopy in two patients (4.5%). In one patient low-grade dysplasia was detected in the rectal cuff. In a second patient low-grade dysplasia was detected in random biopsies in the pouch and blind ileal loop.

### Conclusion

This prospective pouch-endoscopy study detected low-grade dysplasia in 2 out of 44 patients (4.5%). Chromo-endoscopy appeared to have no added value in pouch surveillance. Until the significance of low-grade dysplasia in the pouch is proven, the benefit of routine surveillance for dysplasia in the pouch is uncertain.

## *Introduction*

Long-standing ulcerative colitis (UC) increases the risk of developing colorectal dysplasia and cancer.[1] When multifocal dysplasia or cancer in the colitic colon is found, restorative proctocolectomy (RPC) with ileal pouch anal anastomosis (IPAA) is the preferred treatment. After surgery, patients may still be at risk of developing dysplasia. Although several cases of dysplasia and adenocarcinoma arising in the pouch and rectal cuff have been reported, it remains unclear to what extent patients are at risk of developing dysplasia in their pouch or rectal cuff.[2-7] Incidence rates in studies vary from 0.6% in a diverse group of patients with an IPAA to 71% in a small group of selected patients.[4;8] This discrepancy in prevalence may reflect differences in sample size or clinical diagnostic criteria. As a result, there is no pouch surveillance guideline and suggested initiation of surveillance differs greatly in time.[9-12]

In order to allow identification of a subgroup of patients with an IPAA who might require surveillance, risk factors need to be identified that account for the development of dysplasia in the pouch. Several risk factors are thought to increase the risk of developing dysplasia in the pouch or rectal cuff: long-standing pouchitis, dysplasia or carcinoma in the resection specimen and primary sclerosing cholangitis.[5-7;12;13] A recent systematic review demonstrated that dysplasia or carcinoma in the resection specimen was the only significant predictor for the development of dysplasia in the pouch and advocated a surveillance programme that takes this risk factor into account.[14]

Most studies examining patients with an IPAA use standard white light endoscopy. To our knowledge, there have only been two studies using chromoendoscopy in pouch surveillance, both in patients with familial adenomatous polyposis.[15;16] In the study by Friederich et al. the combined use of conventional and chromoendoscopy led to a higher detection of adenomas compared to using conventional endoscopy alone.[15] Chromoendoscopy has also shown to increase the detection of dysplasia in patients with inflammatory bowel disease (IBD) in several studies, but has never been subjected to research in pouch surveillance of patients with IBD.[17-20]

The aim of the current study was to assess the prevalence of dysplasia in the IPAA of

patients with UC who demonstrated dysplasia or carcinoma in their resection specimen as shown to be the only significant predictor for dysplasia in the pouch in a recent systematic review.[14] Furthermore, we evaluated the added value of chromoendoscopy in the detection of dysplasia in the pouch.

## *Methods*

All patients with UC who underwent RPC at the Academic Medical Centre at the University of Amsterdam between 1988 and 2008 were invited to participate when histopathology of their resection specimen displayed indefinite for dysplasia, dysplasia or carcinoma. Exclusion criteria were: non-correctable coagulopathy that precludes taking biopsies (international normalized ratio >2, or platelet count <90*109), age ≤ 18 years or an inability to obtain informed consent.

Data concerning age, sex, concurrent primary sclerosing cholangitis, previous episodes of pouchitis, indication of proctocolectomy, type of anastomosis, the type of dysplasia in the resection specimen, age at onset and duration of UC before proctocolectomy were recorded. Pouchitis was defined as an episode of symptoms (e.g. increased bowel movements) with endoscopic and histopathological evidence, for which antibiotics were prescribed.

All patients were prepared by 1L macrogol solution (Moviprep) on the morning of surveillance endoscopy of the IPAA. Just before the procedure, patients received an additional enema.With a standard video endoscope (GIF-Q160 or CF-Q160, Olympus Medical Systems Europe, Hamburg, Germany) all segments (the afferent ileal loop, the blind loop, the pouch and rectal cuff) were investigated with white light endoscopy. Hereafter, the mucosa of all segments was sprayed with methylene blue (0.1%) using a spray catheter and the mucosa was inspected for a second time. After targeted biopsies of every mucosal abnormality, 4 additional random biopsies were taken from each segment.

Histopathology was assessed by an expert gastrointestinal pathologist (SvE) according to the revised Vienna criteria, ranging from no intraepithelial neoplasia to invasive neoplasia.[21] In case of (indefinite) dysplasia a second expert gastrointestinal pathologist assessed histopathology to confirm the diagnosis. The histological diagnosis of all biopsies was used as the reference standard diagnosis in each patient.

*Statistical analysis*

Descriptive statistics were used to characterize the study population. SPSS for Windows software (Chicago, IL, USA) version 15.0.1 was used for analysis.

## *Results*

*Patient charateristics*

Between 1988 and 2008, 290 patients with IBD underwent RPC in the Academic Medical Centre in Amsterdam. Sixty-four of these patients had (indefinite for) dysplasia or carcinoma in their resection specimen and were eligible for inclusion. These patients were invited for

pouch surveillance endoscopy. Fourty-four patients participated. Of the 20 non-participants, 6 patients had deceased, 4 patients had undergone pouch excision, 5 patients were lost to follow-up, 3 patients had emigrated and 2 patients refused participation. Characteristics of non-participants are described in Table 1.

**Table 1** Characteristics non-participants (n=20)

| | |
|---|---|
| Irretrievable, n=5 | |
| Deceased, n=6 | Irradically resected rectumcarcinoma |
| | Cholangiocarcinoma |
| | Kahler's disease |
| | Pancreas carcinoma |
| | Pulmonary carcinoma |
| | Peritoneal carcinomatosis secondary to coloncancer |
| Pouch excision, n=4 | Irradically resected rectumcarcinoma |
| | Recurrent abcess |
| | Recurrent pouchitis |
| | Recurrent ileus secondary to adhesions after conversion to Crohn's disease |
| Refusal, n=2 | |
| Emigration, n=3 | |

Between January 2008 and July 2009 all 44 included patients underwent pouchoscopy. The mean age (25 male, 57%) was 49.3 years (SD 11.1). Characteristics of all included patients are described in Table 2.

**Table 2** Characteristics included patients (n=44)

| | | |
|---|---|---|
| Age (yr) | | 49.3 (range 17.1 - 67.8) |
| Gender (male) | | 25 (56.8%) |
| Primary Sclerosing Cholangitis | | 3 (6.8%) |
| ≥ 1 episode(s) of pouchitis | | 17 (39%) |
| Anastomosis | - Handsewn | 3 (6.8) |
| | - Stapled | 41 (93.2%) |
| Indication of IPAA | - Inflammation | 27 (61.4%) |
| | - Dysplasia | 7 (15.9%) |
| | - Carcinoma | 10 (22.7%) |
| Histopathology resection specimen | - IFD | 13 (29.5%) |
| | - LGD | 12 (27.3%) |
| | - HGD | 8 (18.2%) |
| | - Carcinoma | 11 (25.0%) |
| Disease duration* (yr) | | 12.8 (range 0.1 - 45.3) |
| Pouch duration (yr) | | 8.6 (range 0.9 – 19.1) |

IPAA = proctocolectomy and ileal pouch anal anastomosis / IFD = indefinite for dysplasia / LGD = low-grade dysplasia / HGD = high-grade dysplasia / *From time of diagnosis until pouch surgery

Two experienced colonoscopists performed 32 procedures. The remaining 12 procedures were performed by 8 other experienced colonoscopists. A dedicated research-fellow was present during all procedures during which no adverse events occurred.

*Endoscopic findings*

During standard endoscopy 25 lesions were detected in 12 patients; 12 in the afferent loop, 8 in the blind loop and 5 in the rectal cuff. One of the 25 biopsies showed low-grade dysplasia and was taken from an adenoma-like lesion in the rectal cuff.

During chromoendoscopy, 14 additional lesions were detected in 9 patients; 8 in the afferent loop, 2 in the blind loop, 3 in the pouch and 1 in the rectal cuff. None of the biopsies showed dysplasia.

In all patients 4 random biopsies were taken from each segment (the afferent loop, the blind ileal loop, the pouch and rectal cuff). In total, 672 random biopsies were taken. Due to

severe inflammation, no random biopsies were taken in 8 segments of 6 patients. Three out of 672 random biopsies demonstrated low-grade dysplasia (0.45%). Two biopsies (1 in the blind loop and 1 in the pouch) were from the same patient, the third random biopsy (rectal cuff) was from the patient who also demonstrated low-grade dysplasia in an adenoma-like lesion in his rectal cuff.

Thus, in 2 out of 44 patients (4.5%) biopsies revealed low-grade dysplasia. The characteristics of these two patients are shown in Table 3.

**Table 3** Characteristics of patients demonstrating dysplasia in their IPAA

| | **Patient 1** | **Patient 2** |
|---|---|---|
| Histopathology resection specimen | IFD | Diffuse LGD and focal HGD |
| Disease duration* (yr) | 18.2 | 15.7 |
| Primary Sclerosing Cholangitis | No | No |
| ≥ 1 episode(s) of pouchitis | Yes | Yes |
| Pouch duration (yr) | 4.7 | 17.3 |
| Stapled vs. handsewn | Stapled | Stapled |
| Histopathology pouch | LGD | LGD |
| Location | Rectal cuff | Blind loop and pouch |
| Random vs. targeted | Targeted and random | Random |

*From time of diagnosis until pouch surgery / IPAA = proctocolectomy and ileal pouch anal anastomosis / IFD = indefinite for dysplasia / LGD = low-grade dysplasia / HGD = high-grade dysplasia

## *Discussion*

Patients with UC who have undergone RPC with an IPAA could be at risk of developing dysplasia in their IPAA. The exact risk of developing dysplasia remains unknown despite several studies.[3-5;12;14;22-24]

In the current study we evaluated patients with UC who underwent RPC with an IPAA and who demonstrated dysplasia or carcinoma in their resection specimen. Dysplasia was detected in both the pouch and rectal cuff, through 1 targeted and 3 random biopsies in 2 patients. The yield of endoscopic surveillance for the detection of low-grade dysplasia in the IPAA was 4.5%. Chromoendoscopy did not increase the yield of detection of dysplasia.

In the first patient demonstrating low-grade dysplasia several lesions were detected in the rectal cuff which were biopsied, one biopsy demonstrating low-grade dysplasia. One random biopsy in the rectal cuff also demonstrated low-grade dysplasia. He was planned for follow-up 3 months later for resection of 3 lesions in the rectal cuff that initially remained in situ. All three lesions were adenomas with low-grade dysplasia. Follow-up 3 months after therapy did not show dysplasia. The second patient demonstrated low-grade dysplasia in random biopsies of the mucosa of the blind loop and in the pouch which was detected again upon follow-up at 6 months. Biopsies taken at follow-up at 12 months showed indefinite for dysplasia in the pouch and afferent loop. This patient is kept under close surveillance and pouch resection will be considered in the event of detecting high-grade dysplasia.

The study by Thompson-Fawcett et al., in which the percentage of included patients with dysplasia in the resection specimen was only 10%, demonstrated a low dysplasia prevalence in the pouch of 1%, which seems in concordance with the concept that dysplasia in the resection specimen is a risk factor for developing dysplasia in the pouch.[25] However, in a population of patients with an IPAA that underwent proctocolectomy for chronic relapsing or long-standing colitis the prevalence of dysplasia was similar to our study (4.4%).[26]

When dysplasia in the pouch is found, its predictive value remains unknown and recommended surveillance intervals differ greatly between centres. A recent study conducted amongst 931 UC patients with an IPAA concluded the risk for dysplasia and carcinoma is small but real and recommended intensified surveillance in a subgroup of patients.[13] In contrast, Thompson-Fawcett et al. concluded that surveillance of pouches for dysplasia is not indicated because the risk of dysplasia progressing to cancer is thought to be extremely small.[25] Some authors have also concluded that the risk of malignant transformation of dysplastic mucosa seems to be small and that even high-grade dysplasia can revert to normality with time.[23] Similar conversions have been described in the cervix with some cases reverting to normal histology.[27] This conversion might be a result of the poor agreement shown in inter-observer studies of pathologists regarding dysplasia in IBD.[28;29]

Other authors argue initial diagnosis of dysplasia is occasionally an overdiagnosis, which could also explain why cases with dysplasia occasionally revert to normal histology.[27] Therefore, the natural history of dysplasia in patients with IBD, particularly low-grade, remains uncertain and there is little agreement on the optimal strategy.[30;31] For patients who demonstrate low-grade dysplasia in the pouch, the optimal treatment also remains unknown. Mucosectomy with pouch advancement seems to be the recommended treatment upon consecutive findings of low-grade dysplasia or progression to high-grade dysplasia.[5;6]

In the current study, one of the two patients demonstrating low-grade dysplasia reverted to normal histology after 6 months while the other reverted to indefinite for dysplasia after one year. Although both gastrointestinal histopathologists agreed on the biopsies showing dysplasia, this reversion could be explained by the fact that both patients had a concurrent pouchitis at initial diagnosis of their dysplasia, complicating histopathological assessment.

The majority of patients in the current study (93%) underwent a stapled procedure, in-

cluding both patients who demonstrated low-grade dysplasia. A possible disadvantage of the double-stapled anastomosis is the remaining rectal cuff where dysplasia can arise, which was the case in 1 of the 2 patients. However, even with a handsewn ileoanal anastomosis, complete eradication of mucosa cannot reliably be achieved and remnants of residual mucosa can occur in up to 20 percent of cases after mucosectomy.[32] Furthermore, the systematic review by Scarpa et al. showed no difference in the prevalence of dysplasia in the ileal pouch and the rectal cuff, suggesting that both handsewn and double-stapled anastomosis carry a similar risk.[14]

Both patients in our study demonstrating low-grade dysplasia had one or more episodes of pouchitis. Previous studies have shown that long-standing pouchitis is a potential risk for neoplastic transformation in the pouch, although this was not confirmed in the systematic review by Scarpa et al.[4;12;14] In order to establish the diagnosis of long-standing pouchitis, regular biopsies are needed during the first three years of the pouch.[12] However, episodes of pouchitis in our patient population were defined as episodes of symptoms (e.g. increased bowel movements) with endoscopic and histopathological evidence, for which antibiotics were prescribed. Therefore, the contribution of long-standing pouchitis to the development of dysplasia in the current study is unknown, as it was not well recorded.

To evaluate a possible added value of chromoendoscopy to standard white light endoscopy, we performed a second inspection of the pouch with chromoendoscopy, resulting in 14 additional detected lesions. Although this was a considerable number of additional lesions, none of these showed dysplasia. Contrary to dysplasia surveillance in the colon of patients with UC, the added value of chromoendoscopy in the pouch of patients with UC appears limited.

In conclusion, there is a risk of developing dysplasia in the pouch and rectal cuff in patients with IBD and dysplasia in their resection specimen. Our study suggests this risk is limited. In this study, chromoendoscopy appeared not to have an added value in pouch surveillance. Until the significance of low-grade dysplasia in the pouch is clear, the benefit of routine surveillance is unproven. More data from larger cohorts are needed for risk assessment based on several risk factors which could more precisely predict the chance of developing dysplasia in the pouch.

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