



Retrospective Cohort Study

## Incidental adenocarcinoma in patients undergoing surgery for stricturing Crohn's disease

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### Abstract

#### AIM

To evaluate frequency and clinical course of incidental adenocarcinoma in patients with stricturing Crohn's disease (CD).

#### METHODS

In this study, consecutive patients, who were operated on for stricturing CD between 1997-2012, were included at an academic tertiary referral center. Demographic data and clinical course were obtained by an institutional database and individual chart review. Besides baseline characteristics, intraoperative findings and CD related history were also recorded. Colorectal cancer was classified and staged according to the Union for International Cancer Control (UICC).

#### RESULTS

During the study period 484 patients underwent resections due to stricturing CD. Incidental adenocarcinoma was histologically confirmed in 6 (1.2%) patients (4 males, 2 females). Patients diagnosed with colorectal cancer had a median age of 43 (27-66)

years and a median history of CD of 16 (7-36) years. Malignant lesions were found in the rectum ( $n = 4$ , 66.7%), descending colon ( $n = 1$ , 16.7%) and ileocolon ( $n = 1$ , 16.7%). According to the UICC classification two patients were stages as I (33.3%), whereas the other patients were classified as stage II A (16.7%), stage III B (16.7%), stage III C (16.7%) and stage IV (16.7%), respectively. After a median follow-up of 2 (0.03-8) years only 1 patient is still alive.

### CONCLUSION

The frequency of incidental colorectal cancer in patients, who undergo surgery for stenotic CD, is low but associated with poor prognosis. However, surgeons need to be aware about the possibility of malignancy in stricturing CD, especially if localized in the rectum.

**Key words:** Stenosis; Incidental; Colorectal; Crohn's disease; Cancer; Gastrointestinal

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**Core tip:** Incidental colorectal cancer can be expected in 1.2% of patients operated on for stricturing Crohn's disease. Predominantly, malignant lesions were localized in the rectum and are associated with poor prognosis.

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## INTRODUCTION

Patients affected by Crohn's disease (CD) face a 80% lifetime risk of undergoing a surgical resection<sup>[1,2]</sup>. Although novel medical strategies have been demonstrated to be effective, the stricturing phenotype still remains a common indication for surgical interventions<sup>[3]</sup>. Unfortunately, symptoms caused by malignant obstruction are similar to benign strictures in inflammatory bowel disease (IBD). Ruffolo *et al*<sup>[4]</sup> assessed the clinical presentation of intestinal adenocarcinoma in CD and concluded that rectal bleeding and weight loss were unrelated to cancer diagnosis. Therefore, personalized endoscopic surveillance plays a crucial role in cancer prevention<sup>[5]</sup>. Lutgens *et al*<sup>[6]</sup> analysed survival rates and tumor stages in IBD related colorectal cancer (CRC) and compared patients that underwent endoscopic screening to no surveillance. Interestingly, 5-year survival rates were significantly superior in the surveillance group, which was explained by cancer detection at an early stage. Nevertheless, a complete endoscopic passage may not be possible as a result of

stenotic lumina leading to an incomplete assessment. Importantly, Maykel *et al*<sup>[7]</sup> noted that the majority of adenocarcinoma in CD related surgery was not discovered preoperatively but incidentally following surgery.

Incidental postoperative diagnosis of adenocarcinoma after resections for stricturing CD confronts the colorectal surgeon with a fundamental issue. Primarily, strictures in CD are treated as benign and therefore the extent of resection differs from oncologic resections. Limited and inadequate lymph node surgery may be responsible for poor long-term outcomes compared to the general population<sup>[8]</sup>.

Unfortunately, to the authors knowledge, there are hardly any data focusing on incidental adenocarcinoma in stricturing CD<sup>[9,10]</sup>.

The aim of the current study was to evaluate frequency and clinical course of incidental CRC in patients undergoing surgery for stricturing CD.

## MATERIALS AND METHODS

### Study design

We enrolled consecutive patients, who underwent intestinal resections for symptomatic stricturing CD at a tertiary academic referral center between 1997 and 2012. Disease behaviour was confirmed by perioperative and histological examination.

All surgical procedures were performed or supervised by consultants, who were specialised in the treatment of CD.

Demographic data and information about the clinical course were obtained by an institutional database and by individual chart review, respectively. Besides baseline characteristics, intraoperative findings and CD related history was recorded. Exposure to steroids was defined as steroid intake until the day before surgery. Azathioprin/6-mercaptopurin (AZA/6MP) treatment was registered within 2 wk prior to surgery, whereas anti-tumor necrosis factor (anti-TNF) antibody therapy was documented within 1 wk preoperatively. Furthermore, resections were grouped into simple (1 intestinal resection) and complex (> 1 intestinal resection).

Colorectal cancer was classified and staged according to the Union for International Cancer Control (UICC).

The study was approved by the institutional ethics Committee.

### Statistical analysis

Continuous data are shown as mean with standard deviation if normally distributed, or with median and minimum-maximum otherwise. Categorical variables are described with absolute numbers and percentages. Comparison between groups were analysed by Wilcoxon and  $\chi^2$  test when appropriate. All calculations were performed using SPSS for Macintosh, Version 21.0 (IBM Corp., Armonk, NY).

**Table 1** Demographic and clinical characteristics of patients undergoing surgery for stricturing Crohn’s disease with and without incidental finding of colorectal cancer *n* (%)

	Stricturing CD	Stricturing CD and incidental cancer	P value
Patients	478	6	
Age (yr)	35.2 (11-82)	43 (27-66)	NS
Sex			NS
Female	214 (44.8)	2 (33.3)	
Male	264 (55.2)	4 (66.6)	
Body Mass Index (kg/m <sup>2</sup> )	21.4 ± 3.9	22.4 ± 4.4	NS
Age at CD diagnosis (yr)	26 (6-82)	26.5 (11-44)	NS
Smoking (yes)	227 (47.5)	1 (16.6)	NS
Medical therapy			NS
AZA/6-MP	105 (22)	1 (16.6)	
Corticosteroids	128 (26.8)	0	
Anti-TNF antibody	5 (1)	0	
CD related surgery	1 (1-25)	2 (1-3)	NS

CD: Crohn’s disease; AZA/6-MP: Azathioprin/6-mercaptopurin; TNF: Tumor necrosis factor.

**Table 2** Characteristics of patients with incidental adenocarcinoma after surgery for stricturing Crohn’s disease

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Age	66	27	48	36	38	60
Sex	Female	Female	Male	Male	Male	Male
BMI	17.6	19.5	20.0	21.7	28.0	27.7
Age at CD diagnosis	30	11	18	23	31	44
Smoking	Yes	No	No	No	No	No
Azathioprine/6-Mercaptopurine	No	Yes	No	No	No	No
Corticosteroids	No	No	No	No	No	No
Anti TNF-Antibodies	No	No	No	No	No	No
Previous CD Surgery	3	1	3	2	1	2
Indication	Elective	Acute	Elective	Elective	Acute	Elective
Resection typ	Simple	Simple	Complex	Simple	Complex	Complex
Operative Time (min)	130	100	90	199	70	135
Location of Stricture	Rectum	Descending Colon	Rectum	Rectum	Ileum	Rectum
UICC Staging	III C	III B	II A	I	IV	I

BMI: Body mass index; CD: Crohn’s disease; TNF: Tumor necrosis factor; UICC: Union for International Cancer Control.

## RESULTS

During the study period 484 patients were operated on for symptomatic stricturing CD. Further characteristics are listed in Table 1.

Patients underwent an ileocolic resection predominantly. This was performed in 346 (71.5%) patients, followed by 68 (14.0%) colonic resections, 53 (11.0%) small bowel resections and 9 (1.9%) rectal resections. In addition to stricturing disease behavior, 240 (49.6%) patients suffered from fistula, 195 (40.3%) patients from an inflammatory mass, with 104 (21.5%) patients having abscesses. Multiple stenoses were reported in 68 (14.0%) of patients.

Acute resections were performed in 53 (11.0%) patients and 431 (89.0%) of operations were conducted electively. Median operative time was 145 (30-495) min and 233 (48.1%) operations were performed minimal-invasively. Conversion to an open procedure was necessary in 32 (6.6%) patients.

### Incidental adenocarcinoma

Colorectal cancer was detected in structuring CD in seven (1.4%) patients. In six (85.7%) of these patients adenocarcinoma was an incidental finding, whereas 1 (14.3%) patient had a preoperative diagnosis of cancer and so was excluded from further analysis. Four males and 2 females were diagnosed with adenocarcinoma at a median age of 43 (27-66) years and a median history of CD of 16 (7-36) years.

Two (33.3%) operations had to be performed acutely due to bowel obstruction and 4 (66.7%) resections were electively because of symptomatic stenotic CD. All six patients had open surgery with a median operative time of 115 (70-199) min.

Four (66.7%) patients had rectal cancer, whereas descending colon (16.6%) and terminal ileum (16.6%) were origin of neoplasia in the other two patients (Table 2).

According to the UICC classification 2 (33.3%) patients had staged I disease, whereas the other four

**Table 3** Studies focusing on incidental finding of adenocarcinoma in patients undergoing surgery for Crohn's disease

	Patients (n) incidental adenocarcinoma (%)	Risk factors
Maykel <i>et al</i> <sup>[7]</sup> (2006)	222 (2.3)	Age, duration and extent of disease
Yamazaki <i>et al</i> <sup>[9]</sup> (1991)	132 (6.8)	Age, duration of disease
Fumery <i>et al</i> <sup>[10]</sup> (2015)	248 (0.8)	No active disease at surgery
Kristo <i>et al</i> (present study)	484 (1.2)	-

patients had stage II A (16.7%), stage III B (16.7%), stage III C (16.7%) and stage IV (16.7%), respectively.

After a median follow-up of 2 (0.03-8) years, 5 (83.3%) patients had died and 1 (16.7%) patient was still alive.

Concerning stage I, one patient died 12 d after surgery due to fulminant sepsis. The other patient experienced relapse of adenocarcinoma with palliative chemotherapy and died 8 years after cancer detection.

One patient staged as II A received postoperative chemotherapy but died 2 years after surgery due to cancer recurrence and progression of disease.

All patients with stage III received postoperative chemotherapy. Two years after surgery progression of disease led to early death in one patient, whereas the second patient experienced oxaliplatinium induced acute lung injury and underwent lung-transplantation. She is alive and cancer free 8 years after the incidental finding of cancer.

The patient classified as stage IV received postoperative chemotherapy and died one year after initial diagnosis of cancer due to progression of disease.

Interestingly, preoperative diagnosis of CRC in a chronic stenosis of the rectum with UICC stage II A led to neoadjuvant chemoradiation with subsequent resection in one patient. He is still alive and being treated with palliative chemotherapy for pulmonary metastases 9 years after surgery.

## DISCUSSION

This is the largest study to date addressing the incidental finding of cancer in patients undergoing surgery for stricturing CD. After final histological examination, 1.2% of patients were confronted with diagnosis of adenocarcinoma.

Importantly, these findings are of high clinical value since inflammatory bowel disease is linked to increased mortality due to colorectal cancer<sup>[11]</sup>. Although an elevated risk for CRC in ulcerative colitis was identified decades ago, data on CRC in CD patients are scarce<sup>[12]</sup>. A chronic pro-inflammatory environment and cellular damage have been associated with an increased risk of colonic cancer in patients with CD involving the colon<sup>[13]</sup>. In cases of paediatric onset, Peneau *et al*<sup>[14]</sup>

have found a higher risk of developing neoplasia. Furthermore, a changing paradigm in medical treatment and its impact on carcinogenesis are still under debate. Interestingly, monoclonal tumor necrosis factor alpha (TNF $\alpha$ ) antibodies have established anti-cancer effects while having considerable side effects when administered in therapeutically relevant doses<sup>[15]</sup>. In contrast, TNF $\alpha$  antibodies is also secreted by tumors to enhance neoplastic proliferation<sup>[16]</sup>. Additionally, immunosuppressive antimetabolites have also been shown to generate mutagenic oxidative DNA damage and may promote malignancy<sup>[17]</sup>. Recently, Axelrad *et al*<sup>[18]</sup> included 333 patients with IBD and history of cancer that subsequently were exposed to anti-TNF and/or antimetabolites in a retrospective study design. They concluded that anti-TNF $\alpha$  or antimetabolites were not associated with an increased risk of recurrent or new cancer in this cohort. These findings are comparable with our results, where patients with strictures and no cancer had even higher rates of medical therapy compared to patients with strictures and cancer. One could even speculate that novel potent therapeutic options may break the chain of chronic inflammation and even have beneficial results as far as incidental cancer is concerned. However, our number of cancers was so small that a very large multicenter trial would be needed to power such a hypothesis.

Interestingly, localized, diffuse or multifocal genomic changes precede cancer in IBD<sup>[19]</sup>. Point mutation and concomitant inactivation of p53 is associated with malignant transformation in ulcerative colitis<sup>[20]</sup>. Even in noncancerous tissue an increased frequency of p53 mutations was present as a consequence of chronic inflammation<sup>[21]</sup>.

Therefore, endoscopic surveillance is crucial to decrease risk of neoplasia by detecting pre-neoplastic lesions in patients at risk<sup>[22]</sup>. Unfortunately, stricturing CD may lead to incomplete surveillance, especially when multiple stenoses are present. Kamiya *et al*<sup>[23]</sup> followed 174 consecutive patients diagnosed with CD and revealed 2 cases of adenocarcinoma, which both of which were observed in patients with strictures. Intestinal obstruction was a sensitive symptom in 12 consecutive patients with intestinal adenocarcinoma in CD, as only the minority of patients was diagnosed preoperatively<sup>[4]</sup>. Moreover, overlapping clinical presentation may delay therapy and lead to poor prognosis<sup>[24]</sup>.

However, our results highlight that personalized endoscopic surveillance is not feasible in all patients with stricturing CD. We currently put further emphasis on the risk of incidental carcinoma especially in older patients with long disease duration that cannot be fully explored by endoscopic means. This strategy may lead to better long-term survival in patients with incidental carcinoma in future.

At present, there are only 2 studies that address the occurrence of CRC in stricturing CD (Table 3). Yamazaki *et al*<sup>[9]</sup> analyzed 132 patients between 1959

and 1985 that were admitted with colonic strictures in CD. Importantly, malignant strictures were present in 6.8% and did not show differences in clinical presentation compared to benign strictures. Nevertheless, these results represent a different therapeutic era and do not include incidental findings.

Recently, Fumery *et al.*<sup>[10]</sup> assessed frequency of dysplasia and cancer in patients undergoing resection for strictures in IBD. In this multi-center retrospective study 248 patients were included with stricturing disease behavior and screened for dysplasia and cancer. Interestingly, only 2 (0.8%) patients with CD were diagnosed to have cancer, whereas 4 (1.6%) were found to have dysplasia. This rate of intestinal adenocarcinoma is in accordance with our findings at a tertiary academic referral center.

Chronic inflammatory conditions can be misleading in preoperative imaging and result in inadequate surgical resections. As the majority of our incidental CRC findings were located in the rectum, the questions raises, whether patients, who require rectal resection for CD should be operated on oncologically routinely. Especially, patients with extensive disease, long disease duration or diagnosis at an older age, who are at increased risk to develop CRC might benefit from this approach<sup>[7]</sup>. Importantly, duration of disease is even more important when disease extends over 20 years<sup>[9]</sup>. These finding are consistent with our cohort, where cancer was diagnosed after a substantial history of CD. Therefore, caution has to be used in the interpretation of strictures of long-standing disease. However, if endoscopic screening fails, active surgical strategies should consider the possibility of incidental cancer.

Unfortunately, long-term survival of patients affected by incidental adenocarcinoma was poor in our analysis. Previously, unfavorable survival was also reported in CD even when the diagnosis of colorectal cancer was established preoperatively<sup>[25]</sup>. This hower could be due to their co-morbidities, such as the death from fulminant sepsis in a stage I patient or due to the advanced nature of cancer (3 patients stage III or IV) with a number of factors predisposing to this in CD patients.

Although stricturing phenotype is dominated by stenosis, penetrating behaviour may additionally occur. Long-standing anal fistula is an indicator for failed therapy or low medical response, which is an expression of aggressive disease behaviour and leads to prolonged inflammation. Therefore, these patients should be subject to periodic assessment and histological analyses<sup>[26]</sup>. Importantly, intestinal fistula should be discriminated from perianal fistulating disease, given that they differ in management and outcome<sup>[27]</sup>. There are hardly any data about cancer originating from extra-anal fistula formation in CD, but one has to be aware of the possibility of incidental cancer manifesting in penetrating CD<sup>[28]</sup>.

Few limitations of this study have to be addressed. Although the current analysis included a very large

consecutive cohort of patients, the study was designed retrospectively, thus selection bias cannot be ruled out. Additionally, tertiary referral centers may attract patients with complex clinical conditions, therefore incidental findings of adenocarcinoma may be overrepresented.

In conclusion, Patients, operated on for symptomatic stricturing CD have a low risk for incidental colorectal cancer. However, clinicians need to be aware that the most common location of cancer is in the rectum and that the long-term survival in these patients is low.

## COMMENTS

### Background

Most likely, patients that suffer from Crohn's disease (CD) undergo surgical resections during their course of disease. Stricturing phenotype, a common indication, limits preoperative endoscopic screening that may lead to postoperative diagnosis of incidental adenocarcinoma in resected specimen.

### Research frontiers

To date there is a lack of data focusing on incidental adenocarcinoma in patients undergoing surgery for stricturing CD. Furthermore, given that benign resections do not include lymph node surgery, a procedure that is considered inadequate in oncologic settings, surgery could be tailored for those areas more likely to have a cancer.

### Innovations and breakthroughs

The authors found that patients operated on for stricturing CD had a risk of 1.2% to be diagnosed with incidental cancer. Most lesions presented in the rectum and were associated with poor long-term survival.

### Applications

These findings will influence future clinical recommendations, especially in older patients with a long history of disease that cannot be fully assessed by endoscopic means. Nevertheless, prospective multicenter trials will be needed to raise evidence level and highlight risk factors for incidental cancer.

### Terminology

According to the Montreal and Vienna classifications, stricturing CD describes a distinct phenotype that is associated with stenosis and can be distinguished from penetrating and non-stricturing, non-penetrating behaviour. Endoscopic screening may be limited in these patients that clinically tend to present with symptoms from gastrointestinal obstruction.

### Peer-review

Patients with CD of the small and/or large intestine have an increased risk of developing cancer at these sites.

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