

Clinical characteristics and imaging features of small bowel adenocarcinomas in Crohn's disease

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Abstract

Purpose: Small bowel adenocarcinoma is uncommon in patients with Crohn's disease but has an extremely poor prognosis. There is a paucity of data on the clinical characteristics and radiologic features of this entity. We sought to update our institutional experience with small bowel adenocarcinoma occurring in the setting of Crohn's disease and to systematically re-examine pre-operative imaging findings.

Methods: Medical records were abstracted to identify all patients with Crohn's disease and small bowel adenocarcinoma who were evaluated at Mayo Clinic, Rochester, Minnesota and Mayo Clinic, Scottsdale, Arizona between 1976 and 2012. Clinical, demographic, and outcomes data were obtained for each patient. Pre-diagnosis radiologic imaging was re-evaluated by two gastrointestinal radiologists.

Results: Thirty-four patients (21 males) were identified. Median ages at Crohn's disease and cancer diagnoses were 22.4 and 52.9 years, respectively. Median follow-up after cancer diagnosis was 272.0 days; 22 patients (64.7%) had persistent or recurrent adenocarcinoma at last follow-up. 1- and 2-year mortality rates were 29.6% and 48.0%. Pre-operative imaging studies were available for re-review in 14 cases. Features concerning for malignancy included annular mass, nodularity at the extraluminal margins of the mass, and perforation. Nearly all tumors arose in regions of chronic inflammation and caused luminal narrowing with pre-stenotic dilatation.

Conclusions: Small bowel adenocarcinoma is rare in patients with Crohn's disease but results in significant mortality. CT or MR imaging findings can be suggestive of the pre-operative diagnosis, but it is usually diagnosed at an advanced stage with laparotomy.

Key words: Adenocarcinoma—Crohn's disease—CT enterography (CTE)—MR enterography (MRE)

Abbreviations

CT	Computed tomography
CTE	CT enterography
IBD	Inflammatory bowel disease
MRE	Magnetic resonance enterography

Purpose

Small bowel adenocarcinoma is an uncommon development in patients with inflammatory bowel disease (IBD). It is typically reported as a complication in small bowel Crohn's disease, with chronic inflammation as a risk factor [1–9]. The prevalence is estimated at 2.2% after 25 years of small bowel inflammation [10, 11]. There are only a few tertiary care centers that have reported more than isolated case reports. Limited data have suggested a male predominance, a predilection for distal small bowel involvement (75% ileum), and a high 2-year mortality [1, 10–15].

Adenocarcinoma of the small intestine in the setting of Crohn's disease is exceedingly difficult to diagnose at

an early stage. This is likely related to its presentation, which is often similar to active or fibrostenotic Crohn's disease. Frequently reported symptoms include abdominal pain, nausea, vomiting, and weight loss [9–11]. Widmar et al. [10] reported that worsening obstructive symptoms (85%) were the most common presentation and indication for abdominal surgery. Only 4 patients (14%) were diagnosed prior to operative resection in that cohort of 29 patients. These features may explain why as many as 35% of small bowel adenocarcinomas are stage IV tumors at the time of diagnosis [1, 2, 10–16]. 2-year mortality rates in the Widmar cohort were 51% in patients with node-positive disease and 67% in patients with distant metastases [10].

Recent advances in computed tomography (CT) and magnetic resonance (MR) imaging may assist with the detection of small bowel malignancies. CT enterography (CTE) and MR enterography (MRE) are techniques that use large volumes of neutral oral contrast to enhance small bowel assessments. Soyer et al. published a series of 7 patients with Crohn's disease and small bowel adenocarcinoma. After a retrospective radiologic review, five tumors were identified on CTE. Radiographic patterns included strictures associated with a small bowel mass ($n = 2$), heterogeneous strictures ($n = 2$), strictures with pre-stenotic dilatation ($n = 2$), and irregular circumferential bowel wall thickening ($n = 1$) [3].

Due to the paucity of information on this rare but lethal complication of Crohn's disease, we sought to retrospectively update our institutional experience with Crohn's disease and small bowel adenocarcinoma [9].

Methods

Patient identification

Medical records were reviewed to identify patients with Crohn's disease who were diagnosed with small bowel adenocarcinoma and were evaluated at Mayo Clinic, Rochester, Minnesota or Mayo Clinic, Scottsdale, Arizona between 1976 and 2012. The diagnosis of Crohn's disease was established after an assessment by a gastroenterologist or colorectal surgeon. The diagnosis of small bowel adenocarcinoma was determined by a gastrointestinal (GI) pathologist. Patients with malignancy at an ileocolonic anastomosis which could not be clearly identified as a small bowel neoplasm were excluded.

Clinical characteristics

In addition to demographic data, clinical features were documented for each patient. This included symptoms at the time of cancer diagnosis, age at Crohn's disease diagnosis, history of small bowel stricture(s), history of internal penetrating disease, and previous abdominal surgery. IBD-related medical therapy was recorded before diagnosis, at the time of diagnosis, and at follow-up

after cancer resection. Tumor characteristics including location, stage, and the presence of active IBD at the site of resection were identified.

Patient outcomes

Outcomes for each patient were evaluated including the need for adjuvant chemotherapy, persistent or recurrent cancer at last follow-up, and mortality rates. Mortality rates were calculated with the denominator being those patients with follow-up information.

Radiology assessments

Pre-operative reports from abdominopelvic CT and MR exams were reviewed to determine indications for imaging and any suggestion of small bowel neoplasm. Cross-sectional imaging was evaluated by a GI radiologist unblinded to operative reports, who listed all imaging characteristics associated with the tumor in free text. From this exploratory evaluation, a list of 17 imaging features was created. This list included mass, obstruction (luminal narrowing or stricture with proximal bowel dilation) (Fig. 1), annular mass morphology, active inflammation, associated abscess cavity (with air-fluid level), perforation (free or loculated air), abrupt luminal margins (shouldering), nodularity at the extraluminal margins (mesenteric border) of the mass, homogenous enhancement pattern (absence of mural stratification) (Fig. 2), bowel wall thickening, presence of penetrating

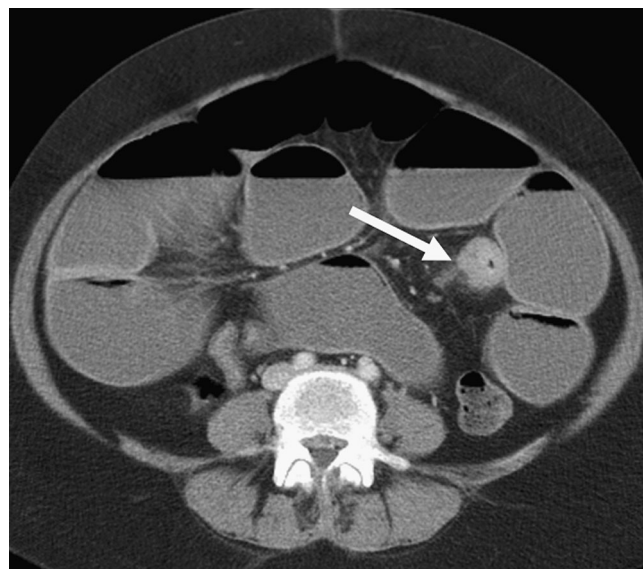


Fig. 1. A 40-year-old female with established Crohn's disease presents with a high-grade small bowel obstruction. CT shows marked small bowel dilatation with an annular, slightly asymmetric stricture (arrow) in the proximal ileum. The wall thickening is relatively homogeneous and there are small adjacent mesenteric nodes.



Fig. 2. A 56-year-old male with known Crohn's disease presents with a homogeneous soft tissue-density stricture with a nodular external contour and shouldering (arrow) in the ileum with proximal dilatation.

disease (fistula or sinus tract) near mass lesion, presence of penetrating disease elsewhere in the patient, aneurysmal bowel dilation, localized lymphadenopathy, mesenteric stranding in the peri-tumoral fat, liver metastases, and other evidence of distant disease (e.g., serosal metastases). Active inflammation was defined as wall thickening with segmental hyperenhancement or mural stratification.

Two GI radiologists (JGF and JLF), of which one formulated the list of 17 imaging features, systematically re-reviewed in an unblinded fashion the pre-operative imaging in each patient. Both radiologists had greater than 10 years' experience evaluating CT and MRE. Each malignancy was evaluated for the presence or absence of the 17 imaging features previously identified. If obstruction was present secondary to the cancer, the maximum diameter of the proximally dilated small bowel loop was measured. Bowel wall thickness at the site of the mass was recorded.

Statistical analysis

Descriptive statistics were utilized for clinical characteristics and patient outcomes. Data were reported as number of events, percentages, median values, and ranges when appropriate.

Results

Thirty-four patients (21 males) were identified (Mayo Clinic, Scottsdale, Arizona, $n = 1$) with Crohn's disease and small bowel adenocarcinoma. Nine patients were diagnosed with small bowel adenocarcinoma prior to referral to Mayo Clinic. All but 3 patients were diag-

nosed with Crohn's disease by tissue specimens obtained at our institution or from outside pathology reviewed at our institution. Two patients did not have biopsies available, and the diagnosis of IBD was based on chart review and clinical history. One patient had an outside pathology report confirming the diagnosis, but this had not been reviewed at our institution. Of the 34 patients, disease extent was known for 30 patients; 17 (56.7%) had isolated small bowel disease and 13 (43.3%) had small bowel and colonic involvement. For the 4 patients with uncertain disease extent, endoscopic reports were unavailable in the medical record. Biopsies around the tumor were consistent with Crohn's disease for 2 of these patients, and the other 2 patients carried the diagnosis from previous providers for 28 and 50 years, respectively. Median ages at Crohn's disease and cancer diagnoses were 22.4 years (range 13.0–69.3) and 52.9 years (range 31.6–74.2), respectively. Median interval between Crohn's disease diagnosis and cancer detection was 22.3 years (range 0.0–50.6). Of the 34 patients in our cohort, 20 patients (58.8%) had a history of small bowel stricture prior to cancer diagnosis. In addition, 11 patients (32.4%) had a history of fistulizing disease including enteroenteric fistulas ($n = 5$), perianal fistulas ($n = 3$), and fistulas at an unspecified location ($n = 3$). A prior IBD-related surgical procedure had been performed in 14 patients (41.2%) (Table 1). Previous Crohn's disease therapy included corticosteroids (79.4%), aminosalicylates (58.8%), immunomodulators (41.2%), and anti-tumor necrosis factor (anti-TNF) agents (29.4%) (Table 1). At the time of adenocarcinoma diagnosis, 16 patients (47.1%) were receiving corticosteroids, 6 patients (17.6%) an immunomodulator, 8 patients (23.5%) an anti-TNF agent, and 2 patients (5.9%) combination therapy (Table 1).

Symptoms at presentation included abdominal pain (85.3%), weight loss (55.9%), and nausea/vomiting (35.3%) (Table 1). In addition, 17 individuals (50.0%) were anemic at presentation, 7 (20.6%) reported diarrhea, and 2 patients (5.9%) presented with overt GI bleeding.

Malignancies were most commonly identified in the ileum (67.6%) and jejunum (14.7%), with one lesion located in the duodenum (2.9%) (Table 2). The exact location in the small bowel was uncertain based on pathology review for 14.7% of patients. All were felt to be primary lesions, and the median size was 4.3 cm (range 0.6–24.0). Cancers were typically histologic grade 3 or 4 (85.3%). Lymph node involvement or distant metastases were present at diagnosis in 64.7% of cases. Five patients (14.7%) had signet ring histology. Histology demonstrated active Crohn's disease at the tumor location in 19 patients (55.9%).

Of the 34 patients, 14 had pre-operative cross-sectional images available for review, and 13 of these 14 patients had preoperative reports available for review.

Table 1. Demographic and clinical characteristics in 34 patients with Crohn's disease-associated small bowel adenocarcinoma

Number of patients (<i>n</i>)	34
Gender (M/F)	21/13
Median age at Crohn's disease diagnosis (year)	22.4 (range 13.0–69.3)
Median duration of Crohn's disease (year)	22.3 (range 0.0–50.6)
Median age at cancer diagnosis (year)	52.9 (range 31.6–74.2)
Prior Crohn's disease therapy ^a (%)	
Corticosteroids	27 (79.4)
Aminosalicylate	20 (58.8)
Immunomodulator	14 (41.2)
Anti-TNF	10 (29.4)
History of small bowel stricture (%)	20 (58.8)
History of fistulizing disease (%)	11 (32.4)
History of prior IBD-related surgery ^a (%)	14 (41.2)
Strictureplasty	2 (5.9)
Partial small bowel	10 (29.4)
Ileocecal	3 (8.8)
Right hemicolectomy	2 (5.9)
Subtotal colectomy	1 (2.9)
IPAA	1 (2.9)
Symptoms at diagnosis ^a (%)	
Abdominal pain	29 (85.3)
Weight loss	19 (55.9)
N/V	12 (35.3)
Diarrhea	7 (20.6)
Hematochezia	2 (5.9)
Anemia (%)	17 (50.0)
IBD therapy at tumor diagnosis ^a (%)	
Corticosteroids	16 (47.1)
Aminosalicylate	7 (20.6)
Immunomodulator	6 (17.6)
Anti-TNF	8 (23.5)
Immunomodulator + anti-TNF	2 (5.9)
No therapy	8 (23.5)

^a Some patients had more than one prior abdominal surgery, more than one symptom at diagnosis, and/or more than one medication at diagnosis

Sixteen small bowel adenocarcinomas occurred in these 14 patients. Cross-sectional imaging included 6 abdominal CT scans, 8 CTE, and 1 MRE, performed a median of 6.5 days (range 0.0–24.0) prior to adenocarcinoma diagnosis. One patient had 2 different cross-sectional imaging modalities performed (CTE and MRE). In addition, 2 patients had a small bowel follow through in addition to their CT scan, and none of these 14 patients had capsule endoscopy performed pre-operatively. The most common single indication for imaging was for Crohn's disease activity assessments (50.0%) (Table 3). On the initial pre-operative imaging reports, a small bowel obstruction was noted in 84.6% ($n = 11/13$) of cases (Fig. 1), and 23.1% ($n = 3/13$) of patients presented with a bowel perforation. In addition, a small bowel malignancy was diagnosed or suggested in just 2 patients (15.4%, $n = 2/13$) in the initial radiologic report. One patient's CTE demonstrated four strictures; three were typical of Crohn's disease and one was concerning for a malignancy due to abrupt margins (shouldering) (Fig. 2). The other patient's CTE demonstrated aneurysmal jejunal dilatation with wall thickening (Fig. 3).

On consensus unblinded radiologic re-evaluation, GI radiologists (JGF and JLF) identified all 16 adenocarci-

Table 2. Characteristics and follow-up in 34 patients with Crohn's disease-associated small bowel adenocarcinoma

Median tumor size (cm)	4.3 (range 0.6–24)
Malignancy location (%)	
Ileum	23 (67.6)
Jejunum	5 (14.7)
Histologic tumor grade (%)	
III	20 (58.8)
IV	9 (26.5)
Signet ring histology (%)	5 (14.7)
Lymph node or distant metastases (%)	22 (64.7)
Location of distant metastases (%)	
Peritoneum ^a	6 (46.2)
Liver	2 (15.4)
Peritoneum/liver	2 (15.4)
Adipose	1 (7.7)
Umbilicus	1 (7.7)
Unknown	1 (7.7)
Adjuvant chemotherapy (%)	12 (35.3)
Median cancer follow-up (days)	272 (range 6.0–7151.0)
Recurrent cancer (%)	15 (44.1)
No recurrent cancer (%)	10 (29.4)
Recurrence unknown (%)	2 (5.9)
Persistent cancer (%)	7 (20.6)
Median time to recurrence (days)	421 (range 25.0–1473.0)
If recurrent cancer, post-resection IBD treatment ^b (%)	
Corticosteroids	5 (33.3)
Aminosalicylate,	4 (26.7)
Immunomodulator	1 (6.7)
Anti-TNF	1 (6.7)
No therapy	7 (46.7)
Deaths, <i>n</i> (crude %)	
1 year, $n = 27$	8 (29.6)
2 year, $n = 25$	12 (48.0)

^a Omental and/or mesenteric involvement was designated as peritoneal metastases

^b Some patients received more than one medication after adenocarcinoma treatment

Table 3. Indications for cross-sectional imaging in 14 patients with Crohn's disease-associated small bowel adenocarcinoma^a

Indication	<i>n</i> (%)
Crohn's disease	7 (50.0)
Unknown	5 (35.7)
SBO/perforation	3 (21.4)
Abdominal pain	2 (14.3)
Pneumatosis intestinalis	1 (7.1)
Abscess	1 (7.1)
GI bleeding	1 (7.1)
Weight loss	1 (7.1)

^aSome patients have more than one indication

SBO, small bowel obstruction

nomas and evaluated for the presence of imaging findings that may be suggestive of small bowel adenocarcinoma. Table 4 lists these exploratory imaging features and their frequency in these tumors. Fifteen (93.8%) adenocarcinomas were associated with an obstructive lesion with the median diameter of the proximal bowel measuring 4.7 ± 1.5 cm, and fourteen (87.5%) tumors developed in a region of chronic inflammation. Bowel wall thickness at the site of the small bowel adenocarcinomas was 12.0 ± 2.0 mm, and only 1 patient had a neoplasm with a bowel wall thickness under 10.0 mm. Half of the can-



Fig. 3. A 71-year-old male with Crohn's disease with CT demonstrating aneurysmal jejunal dilatation with irregular lobulated thickened small bowel wall (arrow).

Table 4. Consensus evaluation of small bowel adenocarcinoma imaging features in patients with Crohn's disease ($n = 16$ tumors)

Imaging feature	
Visible mass, n (%)	8 (50.0)
Obstruction, n (%)	15 (93.8)
Diameter of proximal loop (if stricture present) (mm \pm SD)	47.0 \pm 15.0
Annular morphology, n (%)	14 (87.5)
Active inflammation at lesion location, n (%)	14 (87.5)
Abscess (cavity with air-fluid level), n (%)	4 (25.0)
Perforation (free or loculated air), n (%)	2 (12.5)
Abrupt luminal margins, n (%)	8 (50.0)
Nodularity to extraluminal (mesenteric side) of lesion, n (%)	10 (62.5)
Homogenous enhancement, n (%)	9 (56.3)
Bowel wall thickening (mm \pm SD)	12.0 \pm 2.0
Penetrating disease near lesion, n (%)	4 (25.0)
Penetrating disease elsewhere in patient, n (%)	2 (12.5)
Localized lymphadenopathy, n (%)	5 (31.3)
Mesenteric stranding around tumor, n (%)	8 (50.0)
Liver metastases, n (%)	1 (6.3)
Other evidence of distant spread, n (%)	1 (6.3)

SD, standard deviation

cers were associated with a mass (8/16; 50.0%), and all of these masses had an annular morphology (Figs. 1, 4). In addition, 10/16 (62.5%) had nodularity at the extraluminal margin (mesenteric margin) of the lesion (Fig. 5). Four patients (4/16; 25.0%) had evidence of bowel perforation (Fig. 6A–C). If the criteria of mass, perforation, abscess (Fig. 7A, B), or distant disease are employed, 11/16 (68.8%) of patients would have been identified. The 5 remaining patients had bowel wall/mass thickness of 10 mm or more (Fig. 8).



Fig. 4. A 52-year-old male with Crohn's disease presented with an obstructing short annular constricting small bowel lesion (arrow) on CTE with abrupt shouldering and soft tissue density.



Fig. 5. A 32-year-old female with Crohn's disease presented with an irregular ileal stricture, nodularity, and adjacent adenopathy on CT worrisome for adenocarcinoma.

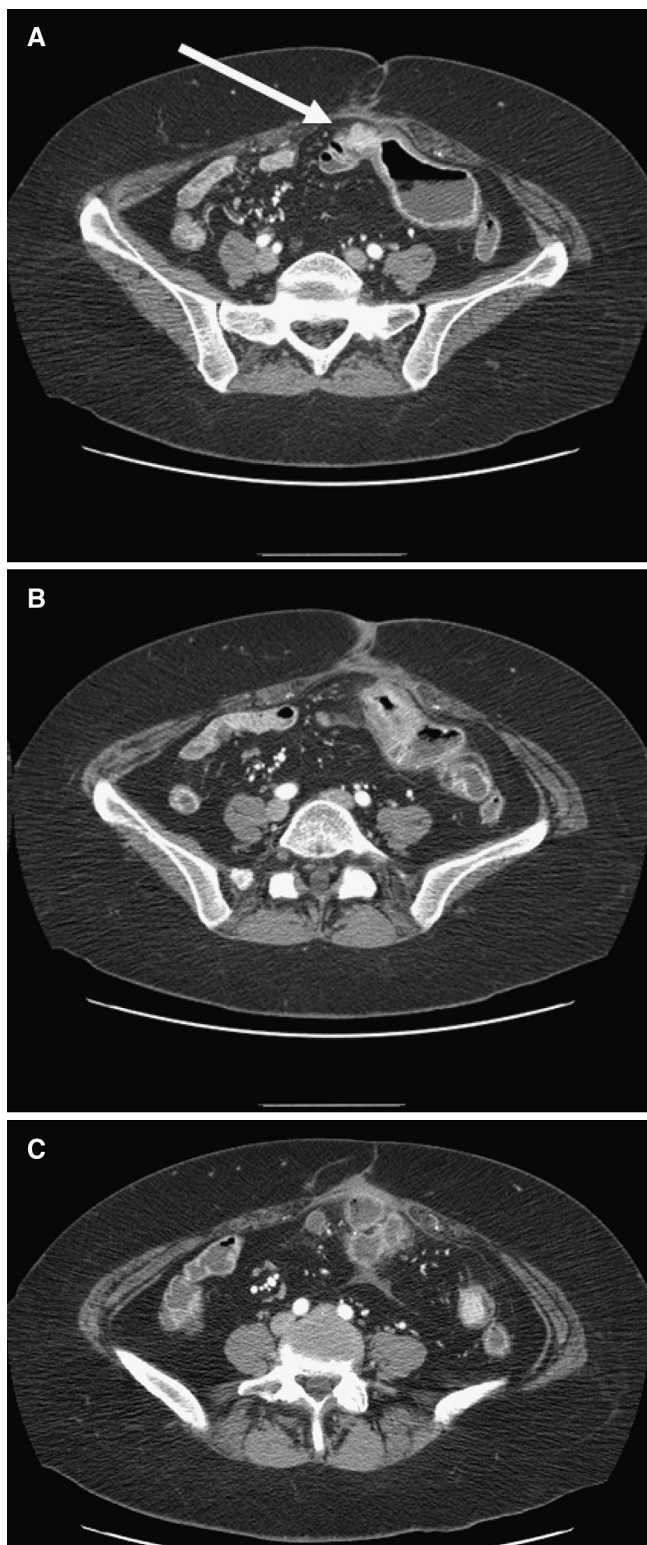


Fig. 6. A 54-year-old female patient with Crohn's disease presented with abdominal pain. CT images (**A–C**) through the abdomen and pelvis demonstrate multifocal small bowel strictures with proximal dilatation. One stricture (*arrow*) has a nodular configuration along the distal end worrisome for adenocarcinoma. This stricture also has a perforation with surrounding abscesses.



Fig. 7. A 45-year-old male with Crohn's disease presented with abdominal pain. CT (**A**) shows a stricture with irregular nodularity along the medial wall (*arrow*). There is localized perforation with inflammatory changes in the surrounding mesenteric fat. Image through the liver (**B**) shows multiple liver metastases.

12 of the 14 patients with imaging available had no evidence of metastases. For these patients, 7 had a worrisome mass noted on cross-sectional imaging. The remaining 5 patients had variable strictures present (i.e., homogenous, heterogenous, or stratified). Of the 2 patients with radiographic evidence of metastases, malignancy was not suspected on initial radiologic review for 1 patient. Repeat unblinded review for this patient demonstrated no worrisome primary mass, but a homogenous, annular stricture with abrupt luminal margins and nodularity of the extraluminal (mesenteric) margin was identified along with serosal metastases.

Of the 14 patients with imaging available, pre-stenotic bowel dilatation, obstruction, and/or perforation were identified in 13 patients on imaging and represented the primary indications for surgery. For these 13 patients,



Fig. 8. A 35-year-old male with Crohn's disease with CT obtained in the decubitus position demonstrates a focal area of wall thickening (*arrow*) with shouldering inferiorly.

there was no clinical or radiographic suspicion for small bowel adenocarcinoma in 10 patients. Two patients showed suspicion for malignancy on imaging, and there was clinical suspicion for 1 patient although the details are unknown. The 1 patient without bowel dilatation on imaging underwent surgery due to both clinical and radiographic suspicion of a bleeding mass and obstructive symptoms.

For the 20 patients without imaging available, there were no clear clinical findings that assisted in the diagnosis of malignancy. Sixteen patients presented with either bowel obstructive symptoms or perforation. The indication for surgery was not clear based on limited documentation for 3 patients. One patient underwent surgery for fistula closure, and a tumor was incidentally identified.

All patients underwent surgical resection, and 12 (35.3%) received adjuvant chemotherapy with fluorouracil (5-FU) and leucovorin, combination therapy with leucovorin, 5-FU, and oxaliplatin (FOLFOX), or leucovorin, 5-FU, and irinotecan (FOLFIRI). Median time from adenocarcinoma diagnosis to last follow-up visit was 272.0 days (range 6.0–7151.0) (Table 2). Fifteen individuals (44.1%) had recurrent adenocarcinoma and 7 individuals (20.6%) had persistent malignancy at last follow-up. The median number of days to first recurrence was 421.0 days (range 25.0–1473.0). Of the 15 patients with recurrent cancer, 5 (33.3%) had received steroids, 4 (26.7%) had received an aminosalicilate, 1 (6.7%) had received an immunomodulator, 1 (6.7%) had received

anti-TNF therapy, and 7 (46.7%) had received no Crohn's disease therapy after resection. 1- and 2-year mortality rates were 29.6% and 48.0%, respectively. The median time from adenocarcinoma diagnosis to death in this subgroup was 103.0 days, (range 37–650), (Table 2).

Discussion

Small bowel adenocarcinoma is an uncommon development in patients with Crohn's disease. Our series, the largest to date, supports several trends previously identified. Small bowel adenocarcinoma in patients with IBD occurs most often in those with small bowel Crohn's disease, has a male predominance, and it is typically located in the distal small intestine. It affects middle aged adults with a long-standing history of IBD [10–13, 16, 17]. Presenting signs and symptoms often overlap with active or fibrostenotic Crohn's disease, and include abdominal pain, weight loss, anemia, and obstructive symptoms [3, 9–11]. This overlap contributes to the likelihood of advanced disease at diagnosis with poor survival rates [1, 2, 10, 13–16].

Soyer et al. reported that five of seven small bowel adenocarcinomas arising in the setting of IBD were retrospectively identified on CTE images when reviewed by GI radiologists. Potential predictive features included a small bowel mass, heterogenous strictures, high-grade obstruction, or irregular and circumferential bowel wall thickening [3]. We also found that nearly all of our tumors were associated with obstruction (stricture with pre-stenotic dilatation), and half had an annular mass. Nodularity at the extraluminal (mesenteric) margin was present in the majority. We also found that many of the cancers were associated with a bowel thickness of over 10 mm. Teefey et al. [17] have previously suggested that abnormal bowel wall thickness of over 3 mm indicates inflammation or ischemia, and bowel wall thickness of over 10 mm suggests tumor. Approximately 25% of our patients had a perforation at the time of imaging. Combined, nearly 70% of individuals with a small bowel adenocarcinoma had a mass, perforation, abscess, or distant metastases on imaging. It should be noted, however, that in both our study and that by Soyer et al. [3], the radiologists were specialists in GI imaging.

As previous data have suggested, the majority of adenocarcinomas were identified in the ileum (67.6%) or jejunum (14.7%) and in regions of chronic inflammation [10–13, 16, 18]. Two tumors, although small bowel in origin on pathologic assessment, were located at an anastomotic site. On histologic review, 19 patients (55.9%) had active inflammation in the region of the malignancy.

Our study has limitations including its retrospective design and limited patient follow-up. We had 2-year follow-up data on only 73.5% of the patients. Referral bias may also be a concern, since as a tertiary care center,

many of our patients were referrals from other medical centers. Finally, the lack of a control group is a limitation. However, we believe that this would have been difficult as endoscopy with biopsies is not routinely attempted for benign appearing mid-small bowel strictures.

In conclusion, complications of Crohn's disease including the development of small bowel adenocarcinoma should be considered in patients with abdominal pain, weight loss, and a long history of Crohn's disease. Detailed evaluation of the imaging features in these patients should be performed to assess for findings suggestive of malignancy. CTE and MRE may assist with tumor identification. Findings which should raise concern for possible superimposed adenocarcinoma include a mass, obstructive stricture with abrupt margins/shouldering, and irregular nodularity along the serosal margin. Free perforation, which is uncommon in Crohn's disease, should also raise suspicion. Further progress needs to be made with early detection in order to reduce high mortality from this rare development.

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