

Colorectal cancer in inflammatory bowel diseases: CT features with pathological correlation

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Abstract

Purpose: To describe CT features of inflammatory bowel disease (IBD)-related colorectal cancer and correlate the imaging findings with histopathological findings.

Materials and methods: CT imaging findings in 17 patients with IBD-related colorectal cancer were retrospectively evaluated. Imaging findings were correlated with surgical and histopathological findings. Univariate and multivariate analyses explored the relationships between CT and histopathological variables.

Results: Two different CT patterns were individualized including clearly visible soft tissue mass (8/17; 47%) (Type 1 tumor) or stenosis with marked circumferential thickening resembling inflammation (9/17; 53%) (Type 2 tumor). At univariate analysis, thickness of tumor-free colorectal wall at CT was greater in Crohn disease (median, 13 mm) than in ulcerative colitis (median, 7 mm) ($P = 0.011$). Significant association was found between presence of signet ring cells and Type 2 tumor at CT (6/9, 67% $P = 0.009$) and colonic dilatation proximal to tumor (5/6, 83%; $P = 0.035$). At multivariate

analysis, free-fluid effusion was the single independent CT variable predictive for the presence of signet ring cells (odds ratio = 50; 95% CI 2.56–977.02; $P = 0.01$).

Conclusion: Colorectal cancer in IBD displays two main features on CT. Type 2 tumors and free-fluid effusion correlate with presence of signet ring cells. Knowledge of these findings is critical to help suggest the diagnosis.

Key words: Inflammatory bowel disease—Imaging—Adenocarcinoma—Intestinal neoplasm—Crohn disease—Imaging—Computed tomography—Ulcerative colitis—Colorectal cancer—Signet ring cells

Patients with inflammatory bowel disease (IBD), especially those with extensive and long-standing colitis are at increased risk for developing colorectal cancer, which is the most frequent malignant complication of IBD [1–3]. The increased risk of IBD-related colorectal cancer results from chronic inflammation and depends on the duration and the extent of the colitis [2, 3]. Identification of increased colorectal cancer risks in individual patients with IBD has led to formal surveillance guidelines, which

are mainly based on surveillance colonoscopy [1, 4]. Several reasons may be advocated to explain failures in the prevention and early detection of colorectal cancers in IBD [5]. Of these, one reason is that patients or even physicians do not follow surveillance guidelines [6]. A second reason is that colorectal cancer may develop in strictured areas, which cannot be reached and properly evaluated by optical colonoscopy [7, 8]. A third reason is that IBD-related colorectal cancer may progress in the form of a flat lesion [9, 10]. As a result, colorectal cancer may be undetected in IBD patients using standard colonoscopy and it is now recommended to use chromoendoscopy and systematic biopsies to improve the diagnostic yield [7].

Cross-sectional imaging plays a valuable role in providing accurate information with respect to the severity of IBD and detecting the majority of potential complications [11–14]. In this regard, CT is often at the forefront of the evaluation of patients with colorectal involvement by IBD. It is well admitted that the major advantage of cross-sectional imaging in IBD is to provide information with respect to the status of the bowel wall itself but also of the adjacent structures [14–16]. Because of the difficulties in detecting IBD-related colorectal cancer with endoscopy, the role of the radiologist may be crucial to alerting the referring gastroenterologist when a patient with IBD presents with unusual CT findings.

To our knowledge, little attention has been given to the imaging appearance of IBD-related colorectal cancer. We are aware of only two papers that describe the radiologic appearance of IBD-related colorectal cancer [17, 18] and this condition has been described using a modern imaging technique such as helical CT in only one of these [18]. As a result, the CT presentation of IBD-related colorectal cancers is not well known. In addition, Crohn disease and ulcerative colitis have distinctive features at CT [14–16]. However, no study has compared the CT features of Crohn disease-related colorectal cancers to those of ulcerative colitis-related colorectal cancers. Moreover, IBD-related colorectal cancers have been found to contain signet ring cells with a frequency higher than that observed in sporadic colorectal cancers, resulting in a less favorable prognosis, so that one question would be to know whether or not the presence of signet ring cells within the tumor may correlate with a specific colorectal tumor presentation at CT [3].

Accordingly, this study was performed with two goals in mind. First, we wanted to illustrate the CT features of colorectal cancers that occur (either Crohn disease or ulcerative colitis) and to correlate the imaging findings with those observed at histopathological analysis. Second, we wished to more specifically determine if the CT presentation of IBD-related colorectal cancer correlates with the type of the underlying IBD and the presence of signet ring cells within the tumor.

Materials and methods

Patients

Our institutional review boards (IRB) granted approval for the study. The need for informed consent was waived. From January 2003 to August 2010, the archiving systems of three University Hospitals were retrospectively queried to identify IBD patients referred for suspected or confirmed colorectal tumor. The databases of the respective Imaging Departments were then used to retrieve the subgroup of patients who also had undergone helical CT imaging of the abdomen and pelvis. Only adult patients (age ≥ 16 years) with histopathological confirmation of IBD-related colorectal cancer were included. The study group comprised 17 patients (11 men, 6 women), with a median age of 43 years ($q1 = 39$; $q3 = 59$; range 25–78 years). All patients had IBD, the diagnosis of which was based on clinical, radiologic, and endoscopic findings and results of histopathological analysis: 12 patients (6 men, 6 women) with a median age of 45 years ($q1 = 38$; $q3 = 58$; range 25–71 years) had Crohn disease and five patients (5 men) with a median age of 43 years ($q1 = 39$; $q3 = 68$; range 38–78 years) had ulcerative colitis. All patients underwent surgical resection of their tumor. The results of the histopathological analysis of resected tumors as well as resected portions of colon or rectum were available for retrospective analysis in all patients.

For each patient, clinical data including clinical symptoms, type of IBD, duration of IBD until the diagnosis of colorectal cancer, median age at the onset of IBD, received treatment at the time of diagnosis of colorectal cancer, prior history of bowel resection, ileocolic involvement by IBD, and findings at optical colonoscopy were recorded. Similarly, histopathological data were reviewed with a special attention given to tumor location, tumor type and differentiation, local tumor staging (pT staging), lymph node involvement (pN staging), presence of signet ring cells, diffuse or localized colorectal involvement by tumor, peritoneal carcinomatosis, hepatic metastases, and activity of underlying IBD.

Imaging

CT studies were performed 1–42 days before surgery. Water enema was used as neutral intraluminal contrast agent to achieve colon distension in five patients, enema with a positive contrast agent was given in two patients and eight patients had no colonic distension. All CT examinations were performed using multidetector row systems (Somatom Plus 4 Volume Zoom, Sensation 16 or Somatom Sensation 64; Siemens Healthcare, Forchheim, Germany; Light Speed VCT 64, General Electric Healthcare, Milwaukee, WI, USA) with a number of rows varying from 4 to 64, an axial resolution of 0.625 to

2.5 mm, a beam collimation ranging from 10 to 40 mm, with 160–250 mAs and 120 kVp. All patients underwent unenhanced and contrast material-enhanced imaging through the abdomen and the pelvis. A mechanical power injector (Medrad, Pittsburgh, PA, USA) was used to administrate 100–120 mL of nonionic intravenous contrast material (300–350 mg of iodine/mL) at a rate of 2–3 mL/s. Helical scanning started 50–70 s after initiation of intravenous injection of contrast material. Helical CT was performed from the dome of the liver to the symphysis pubis, with a cephalocaudal direction during breath holding. After acquisition, CT data were reconstructed twice to obtain axial images, multiplanar reconstructions, and maximum intensity projection (MIP) views.

Image analysis

Images were retrospectively reviewed on a picture archiving and communication system (PACS) workstation (Directview, 11.3 sp1 version, Carestream Health Inc, Rochester, NY, USA) by two abdominal radiologists working in consensus. They had knowledge of the diagnosis of IBD and colorectal cancer but were blinded to all clinical information, the results of surgery and histopathological analysis and location of colorectal tumor.

During the review of CT examinations, the colon was divided into six segments as follows: cecum, ascending (or right) colon, transverse colon, descending (or left) colon, sigmoid colon, and rectum [19].

Unenhanced CT images were analyzed with respect to the presence of submucosal fat deposition and wall thickening (i.e., wall thickness more than 3 mm) [9, 20–22]. Wall thickness was defined as the maximum wall thickness of the colorectal wall. When a colorectal tissue mass was visible, thickness was measured in colorectal portions immediately adjacent to the mass. When present, wall thickening was further evaluated in terms of length, morphologic appearance (i.e., circumferential, irregular edges), and severity (<20 or >20 mm) [23]. Circumferential wall thickening was also classified as symmetric or asymmetric [9]. Finally, the presence of luminal narrowing and colonic dilatation proximal to luminal narrowing was noted [24–26]. Luminal narrowing was classified as severe ($>50\%$) or moderate ($<50\%$) by comparison with apparently normally distended colorectal segments.

CT images obtained after intravenous administration of iodinated contrast material were analyzed with respect to the presence of mural stratification, heterogeneous enhancement of the submucosal portion of the colorectal wall, adjacent mesocolic hypervascularity, colonic masses, and presence of pericolic lymph nodes [23, 24, 27]. Mural stratification was defined as a target or double halo appearance of the colorectal wall [9, 21]. Adjacent

mesocolic hypervascularity was defined as the presence of dilated, tortuous, and prominent vessels adjacent to the colorectal wall [9]. When a mass was visible, its location, size, and morphological presentation (i.e., intramural, intraluminal, or extraluminal) were noted. When present, adjacent lymph nodes were analyzed in terms of size (i.e., shortest axial diameter in millimeter) and further considered enlarged when the shortest axial diameter was >10 mm [9].

CT examinations were also reviewed for the presence of extracolonic abnormalities such as hepatic lesions, peritoneal nodules, free-fluid effusion, fistula, sinus tract and abscess, and other findings that are associated with IBD such as sclerosing cholangitis, cholelithiasis, sacroiliitis, and nephrolithiasis [9, 28]. Sclerosing cholangitis was considered in the presence of focal intrahepatic biliary duct dilatation or focal clustering of intrahepatic ducts [9].

Statistical analysis

Calculations were performed using SAS 9.2 software (SAS Institute, Cary, NC). Descriptive statistics were calculated for all the clinical variables and those evaluated at CT. For continuous data (age, duration of IBD, age at onset of IBD, tumor size, colorectal wall thickness, and length of stenosis), they included medians, first quartiles (q_1), third quartiles (q_3), and ranges. For the binary data, descriptive statistics included raw numbers, proportions, and 95% exact confidence intervals (CIs).

Continuous (quantitative) variables were compared using the Mann–Whitney U test. Categorical (binary) variables were compared using the Fisher's exact test. The relationships between each CT variable and the underlying IBD were tested at univariate analysis, as well as the relationships between each CT variable and the presence of signet ring cells within the tumor. Significant variables identified at univariate analysis were integrated into binary logistic regression model for multivariate analysis using a stepwise method. Results were showed as odds ratios with their 95% CIs.

CT variables exhibiting a significant association in the multivariate analysis were regarded as significant predictors for the presence of signet ring cells. All statistical tests were two tailed, and a P value of <0.05 was considered to indicate statistical significance.

Results

Clinical and histopathological findings

Clinical and histopathological findings in the 17 patients are summarized in Tables 1 and 2. The median duration of IBD until the diagnosis of colorectal cancer was 15 years ($q_1 = 14$; $q_3 = 21$; range 2–35 years). The median age at the onset of IBD was 26 years ($q_1 = 22$; $q_2 = 40$; range 7–69 years).

Table 1. Clinical and histopathological findings in 17 patients with IBD-related colorectal cancer

Quantitative variables	Median	q1–q3	Range
Age (years)	43	39–59	25–78
Duration of IBD (years)	15	14–21	2–35
Age at onset of IBD (years)	26	22–40	7–69
Categoric variables	Raw number	Proportion (%)	95% CI
Male gender	11	11/17 (65)	38–86
Crohn disease	12	12/17 (71)	44–90
Pancolitis	11	11/17 (65)	38–86
Associated ileal involvement	2	2/17 (12)	1–36
Active IBD	13	13/17 (76)	50–93
Visible tumor at colonoscopy	8	8/17 (47)	23–72
Tumor mass at gross examination	8	8/17 (47)	23–72
Presence of signet ring cells	6	6/17 (35)	14–62
Localized tumor involvement	8	8/17 (47)	23–72
Right-sided tumor	8	8/17 (47)	23–72
pT4 tumor	9	9/17 (53)	28–77
Peritoneal carcinomatosis	6	6/17 (35)	14–62
Lymph node metastases	12	12/17 (71)	44–90
Hepatic metastases	4	4/17 (24)	7–50

Note For quantitative data (continuous), data are medians; first quartiles (*q1*) and third quartiles (*q3*), and ranges. For categorical (binary) data, data are raw numbers; numbers in parenthesis are percentages; followed by 95% exact CIs. Right-sided tumor indicates cecum and right colon

All patients were under medical therapy at the time of diagnosis of colorectal cancer. The 12 patients with Crohn disease were receiving infliximab in combination with steroids ($n = 5$), adalimumab alone ($n = 3$), azathioprine alone ($n = 3$), or azathioprine in combination with infliximab ($n = 1$). The five patients with ulcerative colitis were receiving sulfasalazine ($n = 4$) or azathioprine ($n = 1$). Only three patients had prior history of bowel resection that consisted in ileocecal resection with ileocolic anastomosis ($n = 2$) or subtotal colectomy

($n = 1$). Two patients (2/17; 12%) both with Crohn disease had ileocolic involvement by IBD.

At the time colon cancer was diagnosed, all patients were clinically symptomatic and complained of abdominal pain. Five patients presented with colonic obstruction that did not respond favorably to medical treatment. Four patients presented with clinical symptoms suggesting worsening of IBD. Four patients presented with acute colonic obstruction with abdominal distension. Three patients complained of abdominal pain and had chronic iron deficiency anemia. Two patients complained of abdominal cramping, in association with weight loss and palpable abdominal mass.

The diagnosis of colorectal cancer was upheld during macroscopic endoscopic examination in eight patients (8/17; 47%); of these, endoscopy was part of a screening program in three patients. For seven other patients (7/17; 41%), endoscopy showed moderate to marked inflammation with ulcerations and/or inflammatory polyps without evidence for malignancy. For the remaining two patients (2/17; 12%), marked stenosis of the colon could not be passed by the endoscope. Histopathological analysis of biopsy specimens obtained during endoscopy showed tumor involvement in 13 patients (13/17; 76%). In the other four patients (4/17; 24%), histopathological confirmation of colorectal cancer was obtained only after surgery.

After surgical resection, examination of gross specimens showed that the tumor was located in one colorectal segment in 15 patients (15/17; 88%) (cecum, $n = 3$; right colon, $n = 5$; transverse colon, $n = 1$; left colon, $n = 1$; sigmoid, $n = 1$; rectum, $n = 4$) or in two or more colorectal segments in two patients (2/17; 12%). Histopathological analysis revealed that 16 patients (16/17; 94%) had adenocarcinoma, poorly ($n = 6$),

Table 2. Comparison of clinical and histopathological features between Crohn disease and ulcerative colitis group

	Crohn disease ($n = 12$)	Ulcerative colitis ($n = 5$)	<i>P</i> value
Age (years)	45 (38; 58)	43 (39; 68)	0.598*
Duration of IBD (years)	15 (13; 22)	17 (15; 20)	0.524*
Age at onset of IBD (years)	28 (20; 35)	26 (23; 52)	0.673*
Male gender	6 (50; 21–79)	5 (100; 48–100)	0.102†
Pancolitis	9 (75; 43–95)	2 (40; 5–85)	0.280†
Associated ileal involvement	2 (17; 2–48)	0 (0; 0–52)	>0.999†
Active IBD	11 (92; 62–100)	2 (40; 5–85)	0.053†
Visible tumor at colonoscopy	4 (33; 10–65)	4 (80; 28–99)	0.131†
Tumor mass at gross examination	5 (42; 15–72)	3 (60; 0–100)	0.620†
Presence of signet ring cells	5 (42; 15–72)	1 (20; 1–72)	0.600†
Localized tumor involvement	5 (42; 15–72)	3 (60; 15–95)	0.620†
Right-sided tumor	7 (58; 28–85)	1 (20; 1–72)	0.294†
pT4 tumor	7 (58; 28–85)	2 (40; 5–85)	0.620†
Peritoneal carcinomatosis	4 (33; 10–65)	2 (40; 5–85)	>0.999†
Lymph node metastases	8 (67; 35–90)	4 (80; 28–99)	>0.999†
Hepatic metastases	1 (8; 0–38)	3 (60; 15–95)	0.053†

Note For quantitative data (continuous), data are medians; numbers in parentheses are first quartiles (*q1*) and third quartiles (*q3*). For categorical data, data are raw numbers; numbers in parenthesis are percentages; followed by 95% exact CIs. Right-sided tumor indicates cecum and right colon. IBD indicates inflammatory bowel disease

* Calculated with the Mann–Whitney *U* test

† Calculated with the Fisher exact test

moderately ($n = 6$), or well differentiated ($n = 4$); of these, only one had mucinous adenocarcinoma. One patient (1/17; 6%) had a tumor located in the sigmoid colon that was a pT4N2M1 poorly differentiated neuroendocrine tumor. In all but one patient, the tumor invaded or went beyond the subserosa: nine tumors (9/17; 53%) were categorized as pT4, seven (7/17; 41%) as pT3, and one (1/17; 6%) as pT2. Signet ring cells were found in six patients (6/17; 35%); all with non-mucinous adenocarcinoma. A diffuse colorectal involvement by tumor was more frequently observed by tumors with signet ring cells (6/6; 100%) than by tumors that did not contain signet ring cells (3/11; 27%) ($P = 0.009$). Among the nine tumors not visible at endoscopy, six presented as diffuse tumor spreading and five contained signet ring cells.

The results of histopathological analysis for the whole study population are reported in Table 1. Twelve patients (12/17; 71%) had histopathologically confirmed lymph node involvement by tumor and five (5/17; 29%) were classified as pN0. Six patients (6/17; 35%) had histopathologically confirmed peritoneal carcinomatosis. Four patients (4/17; 24%) had hepatic metastases. All resected tumors were found in association with histological features consistent with underlying, long-standing IBD of the corresponding colorectal segments. IBD was considered active in 13 patients (13/17; 76%) and quiescent or inactive at histopathological analysis in four patients (4/17; 24%).

Imaging findings and pathological correlation

Colorectal tumors were visible on CT images in eight patients (8/17; 47%) and indiscernible from the underlying IBD in the other nine patients (9/17; 53%). Among the nine tumors not visible endoscopically, four were visible on CT. Among the four tumors that were not visible endoscopically and undetected at histopathological analysis of biopsy specimens, two with an extraluminal growth were detected at CT only.

On the basis of CT presentation, two distinct patterns were individualized. In eight (8/17; 47%) patients, the tumor presented as a colorectal tissue mass (Type 1 tumor) with a median axial diameter of 34 mm ($q1 = 30$; $q3 = 61$; range 20–95 mm). Among the eight tumors presenting as a tissue mass, four (4/17; 24%) had an intra- and extraluminal growth (Fig. 1), two (2/17; 12%) had an intraluminal growth only (Fig. 2) and two originating from the rectum had an extraluminal growth only, extending into the ischiorectal fossa (Fig. 3). In nine patients (9/17; 53%), CT showed a circumferential thickening of the colorectal wall (Type 2 tumor), with a median thickness of 11 mm ($q1 = 9$; $q3 = 21$; range 7–21 mm) and a median length of 60 mm ($q1 = 42$; $q3 = 85$; range 39–122 mm), in the absence of visible soft tissue mass (Figs. 4, 5). CT findings in the 17 patients are summarized in Tables 3 and 4.



Fig. 1. A 71-year-old woman with Crohn disease known for 2 years presenting with abdominal pain. Optical endoscopy (not shown) revealed incomplete stenosis of right colon due to tumor. Endoscopic biopsies confirmed active Crohn disease and colon cancer. **A** Helical CT image obtained in the axial plane after intravenous administration of iodinated contrast material shows a large, eccentric soft tissue mass of the right colon, with central necrosis (arrows) and mesenteric enlargement. **B** Photograph shows the gross appearance of colon tumor (arrows) after surgical resection of right colon. Histopathological analysis revealed a pT4N1 moderately differentiated adenocarcinoma of the right colon that did not contain signet ring cells (Courtesy of Marie-Danièle Diebold, MD).

None of the Type 1 tumors contained signet ring cells (0/8; 0%) whereas six of the Type 2 tumors contained signet ring cells (6/9; 67%) ($P = 0.009$) (Fig. 4). Table 5 reports the characteristics of colorectal tumors depending on whether or not the tumor contained signet ring cells.

The tumor developed in colorectal segments that displayed features consistent with active IBD at CT in

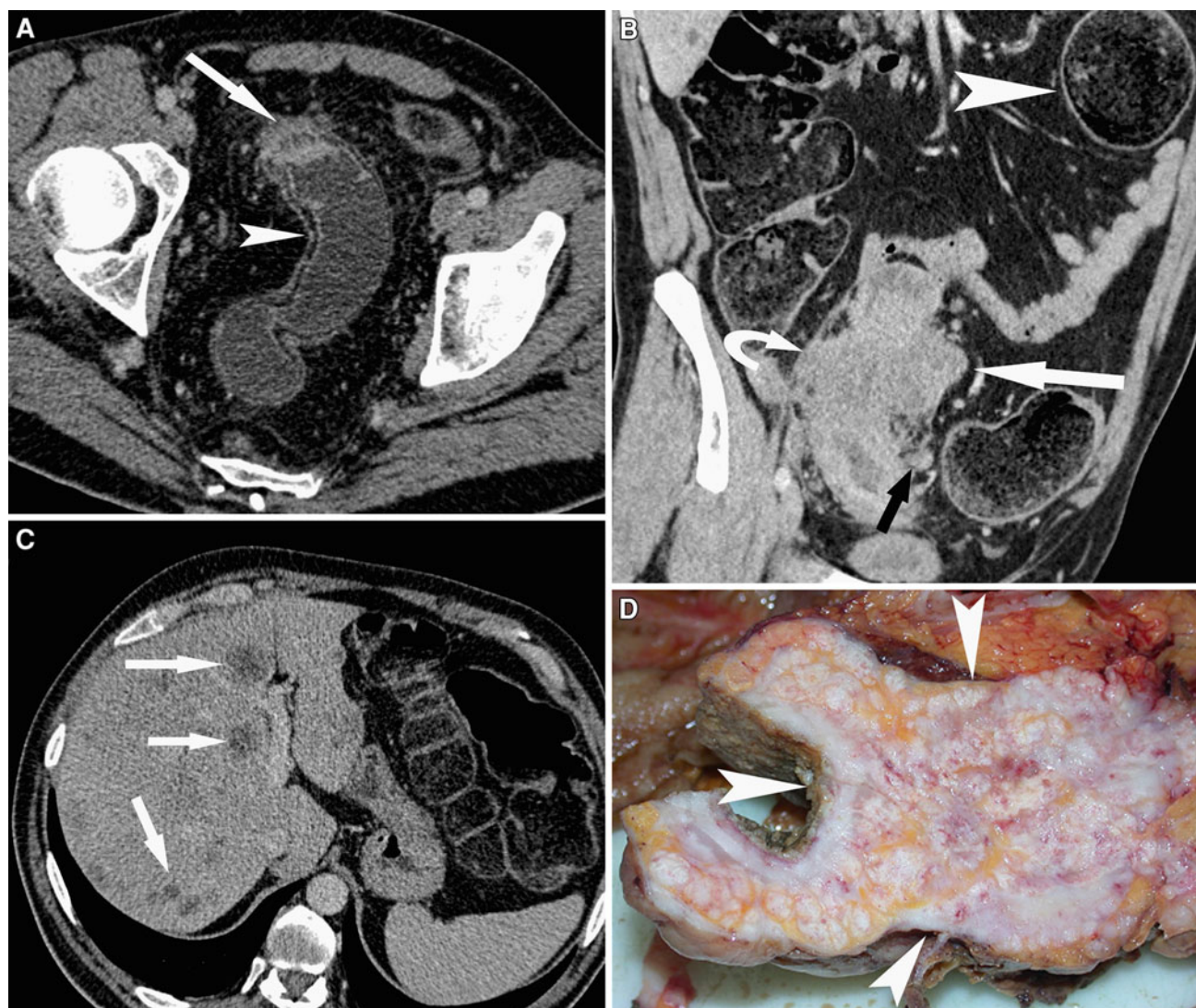
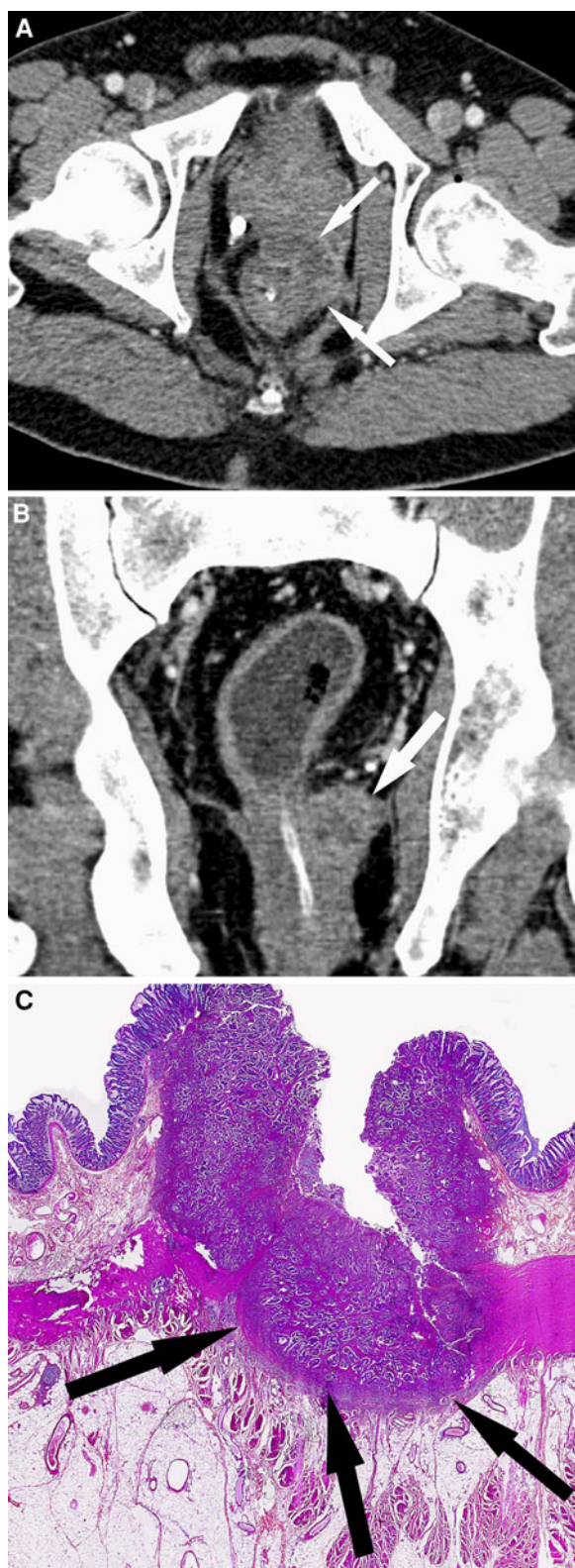


Fig. 2. A 43-year-old man with ulcerative colitis known for 17 years presenting with colonic obstruction. Optical endoscopy (not shown) revealed complete stenosis of sigmoid colon due to tumor and findings consistent with active ulcerative colitis. **A** Helical CT obtained in the axial plane after intravenous administration of iodinated contrast material shows moderately enhancing tissue mass (*arrow*) of the sigmoid colon. Submucosal fat accumulation is visible (*arrowhead*). **B** Helical CT obtained in the coronal plane shows large, intraluminal soft tissue mass of the sigmoid colon (*arrow*) involving

the mesosigmoid (*curved arrow*). Enlarged adjacent lymph node is visible (*black arrow*). Marked dilatation of the colon proximal to tumor is present (*arrowhead*). **C** At a different slice level, helical CT in the axial plane shows multiple hypoattenuating focal hepatic lesions (*arrows*) consistent with hepatic metastases. **D** Photograph shows the gross appearance of the resected specimen (*arrowheads*) after surgical resection of left and sigmoid colon. After histopathological analysis the tumor was categorized as a pT4N2 poorly differentiated neuroendocrine tumor.

eight patients (8/17; 47%), including stratification (8/17; 47%), adjacent fat infiltration (6/17; 35%), and prominent pericolic vascularity (4/17; 24%). Heterogeneous enhancement of the submucosal layers of the colorectal wall was present in six patients (6/17; 35%). Submucosal fat deposition was visible in two patients (2/17; 12%), one with Crohn disease and the other with ulcerative colitis, both in colonic segments free from tumor at CT and as further confirmed at histopathological analysis (Figs. 2, 5). The characteristics of CT presentation according to the underlying IBD are reported in Table 4.

Circumferential colorectal wall thickening (i.e., wall thickness >3 mm) was observed in all patients (17/17; 100%). The median wall thickness of the abnormal portion of the colon was 10 mm ($q1 = 8$; $q3 = 14$; range 4–21 mm). A severe thickening was present in two patients (2/17; 12%) with Crohn disease, with a colorectal wall thickness of 21 mm in both patients, which corresponded to diffuse involvement of the colon by tumor (Fig. 5). Colorectal wall thickness was greater in patients with Crohn disease (median 13 mm; $q1 = 10$ mm; $q3 = 15$ mm; range 5–21 mm) than in those with ulcerative



◀**Fig. 3.** A 47-year-old man with Crohn disease known for 22 years presenting with persisting healing of the rectal wall with intrarectal fistula. Optical endoscopy and endoscopic biopsies showed rectal fistula and findings consistent with inflammation and active Crohn disease, respectively, but failed to reveal the tumor. **A** Helical CT obtained in the axial plane after intravenous administration of iodinated contrast material shows rectal soft tissue mass (arrows) with an exophytic, extraluminal growth into the left ischiorectal fossa. **B** Helical CT obtained in the coronal plane confirms tumor (arrow) of the lower third of the rectum. **C** Microphotograph from histopathological analysis (HE stain, original magnification $\times 30$) reveals involvement of the subserosa (arrows). The tumor was categorized as a pT3N0 well-differentiated adenocarcinoma of the rectum that did not contain signet ring cells.

irregular edges with ulcerations in four patients (4/17; 24%) (Fig. 6) and was asymmetric in two of them (2/17; 12%). Luminal narrowing of colorectal lumen was observed in 12 patients (12/17; 71%) and was severe in all cases. An associated proximal colonic dilatation was present in seven patients (7/17; 41%) and correlated with the presence of signet ring cells within the tumor ($P = 0.035$) (Fig. 2).

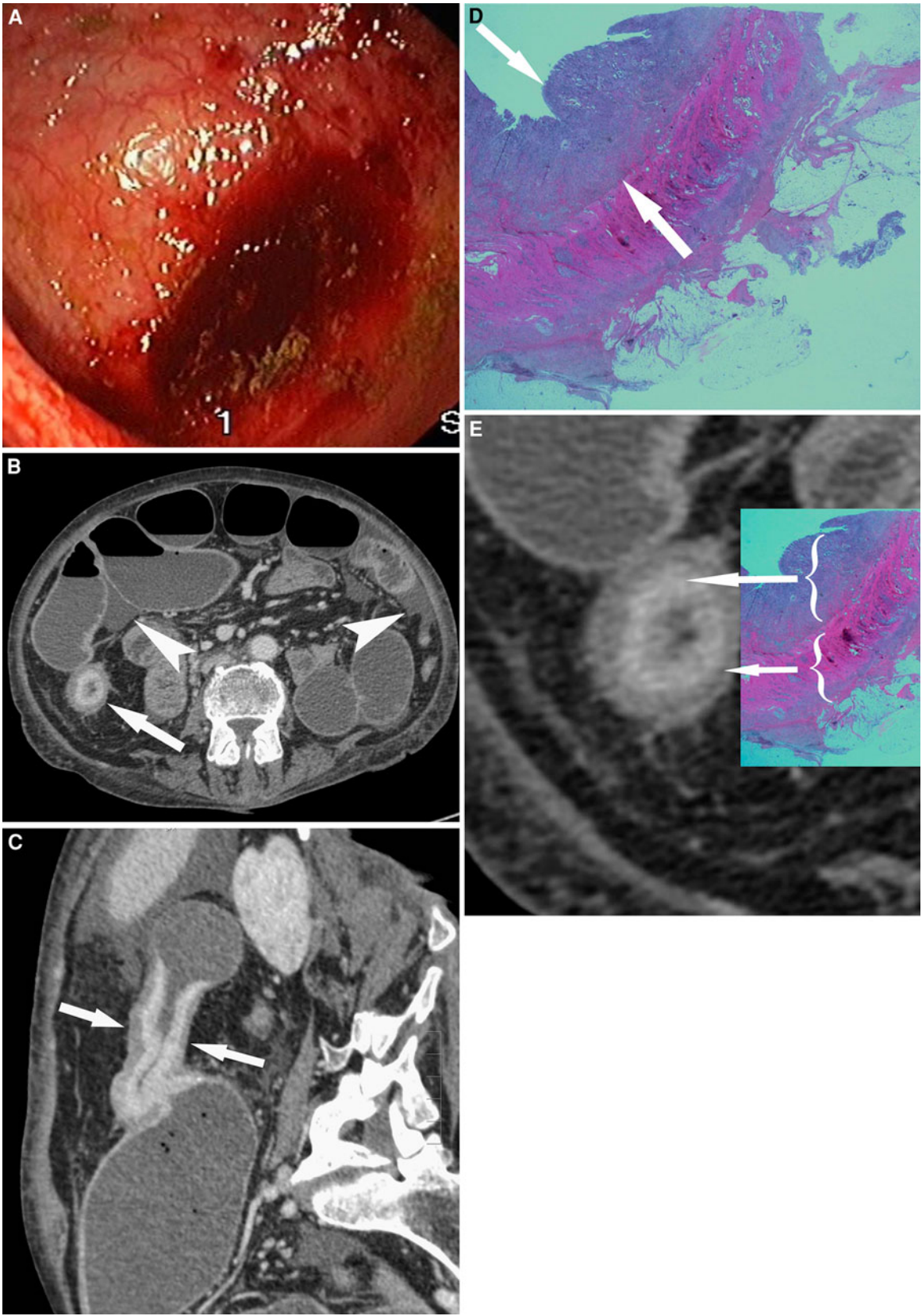
Enlarged lymph nodes were observed in 13 patients (13/17; 76%) on CT. Of these, four patients were found to have inflammatory lymph nodes at histopathological analysis and thus erroneously considered as having lymph node involvement by tumor at CT (four false-positives). Conversely, three patients without visible enlarged lymph nodes at CT were found to have lymph node metastases at histopathological analysis (three false-negatives) (Fig. 4).

Free-fluid effusion was present in six patients (6/17; 35%). Of these, five had tumors that contained signet ring cells (5/17; 29%) and one had tumor without signet ring cells (1/17; 6%) ($P = 0.005$). Free-fluid effusion was found in association with peritoneal nodules in two patients (2/17; 12%) and histopathologically confirmed peritoneal carcinomatosis. Conversely, free-fluid effusion was the single CT finding suggesting peritoneal carcinomatosis in another patient. In three patients (3/17; 18%) free-fluid effusion was present in the absence of peritoneal carcinomatosis.

Peritoneal nodules indicating peritoneal carcinomatosis were observed in five patients (5/17; 29%), three with Crohn disease and two with ulcerative colitis, and were further confirmed intraoperatively and pathologically. Conversely, peritoneal carcinomatosis was depicted intraoperatively in one patient (1/17; 6%) with Crohn disease and not seen preoperatively at CT (one-false-negative) (Fig. 4).

Four patients (4/17; 24%), three with ulcerative colitis and one with Crohn disease, had multiple focal liver lesions visible at CT, consistent with hepatic metastases from primary colorectal cancer that were histopathologically confirmed (Fig. 2). Fistula tracts originating

colitis (median = 7 mm; $q_1 = 4$ mm; $q_3 = 9$ mm; range 4–9 mm) ($P = 0.011$). At univariate analysis, this CT finding was the single one that was discriminating for differentiating Crohn disease-related tumors from ulcerative colitis-related ones (Table 4). Thickening had



◀ **Fig. 4.** A 60-year-old woman with Crohn disease known for 6 years presenting with abdominal pain. Optical endoscopy and endoscopic biopsies showed pancolitis due to active Crohn disease but failed to reveal the tumor. **A** Endoscopic view shows inflammation of the colon mucosa and no visible tumor. **B** Helical CT obtained in the axial plane after intravenous administration of iodinated contrast material shows circumferential and symmetric thickening of the right colon (*arrow*) with severe luminal narrowing and mural stratification. Neither enlarged lymph nodes nor peritoneal nodules are visible on CT. Conversely, free-fluid effusion (*arrowheads*) is seen at CT and was due to peritoneal carcinomatosis that was confirmed during surgery but undetected at CT. **C** Helical CT obtained in the oblique plane shows circumferential and symmetric thickening of the right colon (*arrows*) in association with a 45-mm long severe stenosis. Neither enlarged lymph nodes nor peritoneal nodules are visible. **D** Microphotograph from histopathological analysis (HE stain, original magnification $\times 20$) shows almost complete diffuse infiltration of the mucosa and submucosa (*arrows*) of the right colon by tumor cells, whereas the infiltration is less pronounced in the muscularis propria and serosa. **E** Photograph shows correlation between CT presentation and histopathological analysis. The mucosa and the submucosa are involved by marked tumor cell infiltration and show hyperenhancement at CT, whereas the involvement is less pronounced in the muscularis propria and serosa that are hypoattenuating at CT. **F** Microphotograph from histopathological analysis (HE stain, original magnification $\times 40$) reveals poorly differentiated adenocarcinoma. **G** Microphotograph from histopathological analysis (HE stain, original magnification $\times 50$) reveals presence of signet ring cells within the tumor. The tumor was categorized as a pT4N2 poorly differentiated adenocarcinoma containing 20% of signet ring cells.

from the rectum ($n = 2$), right colon ($n = 1$) (Fig. 6) or transverse colon ($n = 1$) were present in four patients (4/17; 24%). No cases of intrapelvic or intra-abdominal abscesses were found. Two patients, both with Crohn disease, had focal intrahepatic bile duct dilatation on CT images, consistent with primary sclerosing cholangitis.

No patients had CT findings suggestive for cholelithiasis, sacroiliitis, or nephrolithiasis.

Results of multivariate analysis showed that the presence of free-fluid effusion on CT was the single variable that was independently associated to the presence of signet ring cells within the colorectal tumor (Table 6).

Discussion

In this retrospective study, we analyzed the CT imaging features of 17 patients with IBD and histopathologically confirmed colorectal cancer. We found that this condition may display two markedly different presentations at CT. In 8/17 patients (47%), the tumor presented as a colorectal soft tissue mass (Type 1 tumor) that was visible at CT, whereas the tumor presented as a circumferential thickening of the colorectal wall (Type 2 tumor) in 9/17 patients (53%). One important result of our study, however, is that in a substantial number of cases, the tumor is indiscernible from the underlying IBD at CT, and the presentation mirrors that observed in acute inflammation [12, 24]. Another result is that the CT presentation significantly correlates with the presence or the absence of signet ring cells within the tumor and that some CT criteria such as free-fluid effusion are predictive for the presence of this histopathological variant. Conversely, except for the degree of wall thickening of tumor-free colonic portions that reflects the specific underlying IBD, no significant differences in CT presentation were found between Crohn disease-related colorectal and those that developed in patients with ulcerative colitis.

The imaging presentation of IBD-related colorectal cancer has rarely been reported and most cases were based on the findings at barium studies [17, 29]. Miller et al. [17] reported four cases of cancer in the right colon and one in the rectum with an appearance typical for malignancy at barium examination but the article did not

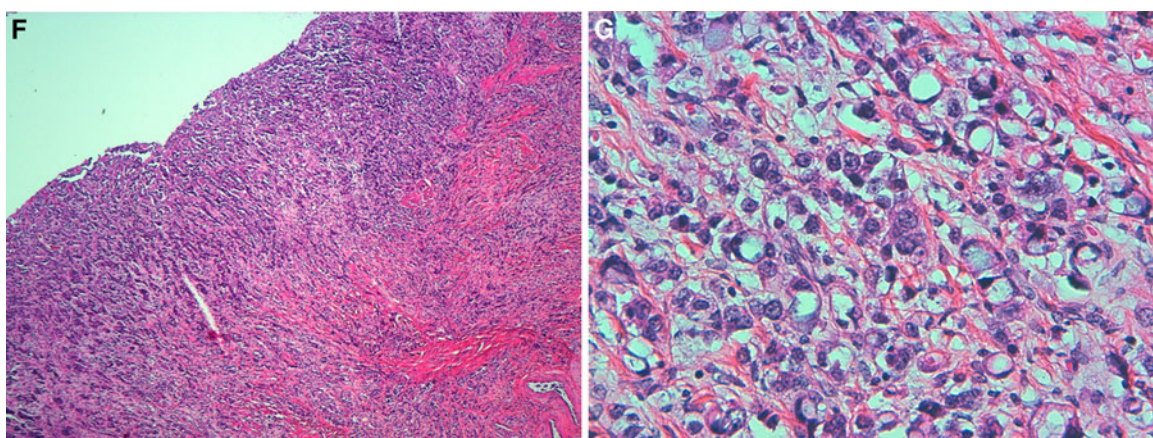
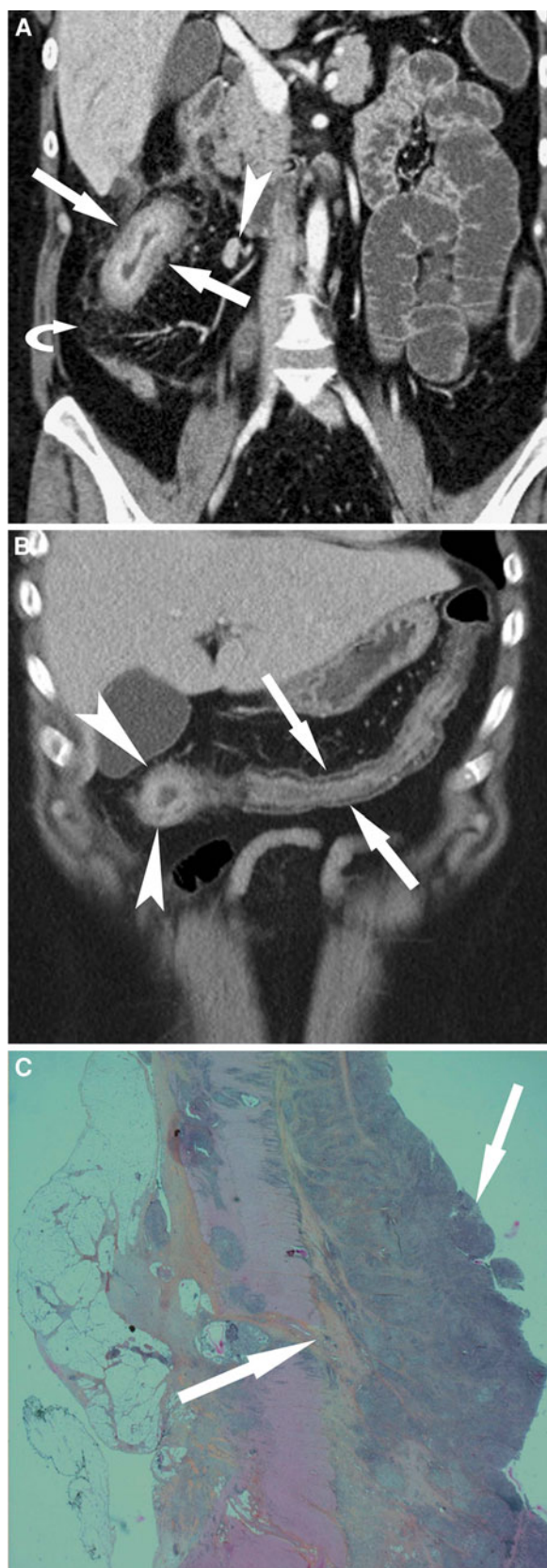


Fig. 4. continued



◀**Fig. 5.** A 37-year-old woman with Crohn disease known for 15 years presenting with abdominal pain. Optical endoscopy (not shown) revealed incomplete stenosis of transverse and right colon due to inflammation. Endoscopic biopsies confirmed active Crohn disease and colon cancer. **A** Helical CT obtained in the coronal plane after intravenous administration of iodinated contrast material shows marked thickening of the right colon, with stratification and heterogeneous enhancement of the submucosal layers of the colon (arrows). Infiltration of the adjacent fat is present in association with multiple tiny peritoneal nodules suggesting peritoneal carcinomatosis (curved arrow). Enlarged hyperattenuating lymph node is visible (arrowhead). **B** At a different slice level, helical CT in the coronal plane shows marked thickening of the right colon, with loss of stratification and heterogeneous enhancement of the submucosal layers (arrowheads). Submucosal fat accumulation is visible in portions of the transverse colon apparently free from tumor (arrows). **C** Microphotograph from histopathological analysis (HE stain, original magnification $\times 10$) shows diffuse infiltration of the mucosa and submucosa (arrows) of the right colon by tumor cells, whereas the infiltration is less pronounced in the muscularis propria and serosa. Signet ring cells stain blue and constitute the main part of the tumor. The tumor was categorized as a pT4N1 poorly differentiated adenocarcinoma containing 80% of signet ring cells.

carcinomas extending to the colon and not primary colon cancers. To our knowledge, Hayashi et al. [18] were the first to show the CT features of IBD-related colorectal cancer. In their paper, they described one case of rectal mucinous adenocarcinoma after subtotal colectomy in a patient with Crohn disease. In that case, the rectal tumor presented as a soft tissue mass, with an exophytic growth to the right ischiorectal fossa, similar to findings observed in two of our cases [18].

On CT imaging, the majority of sporadic colon cancers present as an annular lesion, a nodular mass or an ulcerated tumor and this is in contrast with the CT features of colon cancers in IBD patients as observed in our study [24]. In IBD patients, loss of mural stratification usually indicates chronic or fibrous disease, but may also be an alerting sign for malignancy when associated with marked thickening [9, 14]. Such loss of stratification in thickened colorectal wall was visible in 35% of the cases presented herein. We also found that heterogeneous enhancement of the submucosal layers of the colorectal wall was present in all patients with diffuse tumor involvement. However, further case-control studies are needed to determine the value of this sign for the diagnosis of colorectal cancer in IBD patients.

Several CT features have been shown to correlate with Crohn disease activity. Of these, stratification due to a combination of hyperemia and edema that results in a target appearance has been well described and correlates with active disease [13]. Occasionally, fat accumulation in the submucosal layer of the colon results in a different target appearance or produces the so-called fatty halo

show CT images. Kerber and Frank [29] have reported the imaging presentation of bowel carcinomas in patients with Crohn disease that were actually small bowel

Table 3. CT features in 17 patients with IBD-related colorectal cancer

	Raw numbers	Proportions (%)	95% CI
Visible tumor at CT	8	8/17 (47)	23–72
Soft tissue mass at CT	8	8/17 (47)	23–72
Wall thickening (>3 mm)	17	17/17 (100)	80–100
Severe wall thickening (>20 mm)	2	2/17 (12)	1–36
Submucosal fat deposition	2	2/17 (12)	1–36
Stratification	8	8/17 (47)	23–72
Prominent pericolic vascularity	4	4/17 (24)	7–50
Heterogeneous submucosal enhancement	5	5/17 (29)	10–56
Severe luminal narrowing (>50%)	12	12/17 (71)	44–90
Proximal colonic dilatation	7	7/17 (41)	18–67
Enlarged lymph nodes	13	13/17 (76)	50–93
Peritoneal nodules	5	5/17 (29)	10–56
Free-fluid effusion	6	6/17 (35)	14–62
Fistula tract	4	4/17 (24)	7–50
Hepatic metastases	4	4/17 (24)	7–50
Sclerosing cholangitis	2	2/17 (12)	1–36

Note Data are raw numbers; proportions, numbers in parenthesis are percentages; followed by 95% exact CIs

sign, which indicates chronic disease and is thought to be more frequent in ulcerative colitis than in Crohn disease [20]. In our series, we found this finding in only two patients, one with Crohn disease and the other with ulcerative colitis. Of interest, fat accumulation was present in the portion of the colon that was free from cancer and not in that involved by tumor in retrospect. Although we agree that it is not possible to draw definite conclusion with two observations because of the absence of statistical significance, we believe that these findings may warrant further study to determine to what extent disruption of the submucosal fatty layer, when present, should be an alerting feature.

Detection of colorectal cancer in IBD patients remains difficult. Colorectal obstruction in patients with

long-standing IBD is most likely to be due to a benign complication of the disease, but the diagnosis of cancer should be considered, especially in patients with a long period of quiescent activity presenting with symptoms of colonic obstruction [30]. Strictures are associated with a high frequency rate of colorectal cancer both in ulcerative colitis and in Crohn disease [1, 31]. A persisting fistula without evidence of healing despite apparently appropriate therapy should also raise the question of rectal cancer [32]. This occurrence was found in two of our patients in whom endoscopy failed to reveal the tumor that was ultimately detected owing to CT imaging. Similarly, CT should be considered when a colonic stricture cannot be adequately assessed by endoscopy as it was the case in other two patients of our series.

Table 4. CT features in 17 patients with IBD-related colorectal cancer according to the underlying IBD

	Crohn disease (<i>n</i> = 12)	Ulcerative colitis (<i>n</i> = 5)	<i>P</i> value
Tumor size at CT (mm) [‡]	33 (28; 45)	35 (31; 80)	0.549*
Maximal wall thickness (mm)	13 (10; 15)	7 (6; 8)	0.011*
Length of stenosis (mm)	60 (45; 79)	57 (42; 72)	0.770*
Visible tumor at CT	5 (42; 15–72)	3 (60; 15–95)	0.620 [†]
Soft tissue mass at CT	5 (42; 15–72)	3 (60; 15–95)	0.620 [†]
Wall thickening (>3 mm)	12 (100; 74–100)	5 (100; 48–100)	>0.999 [†]
Severe wall thickening (>20 mm)	2 (17; 2–48)	0 (0; 0–52)	>0.999 [†]
Submucosal fat deposition	1 (8; 0–38)	1 (20; 1–72)	>0.999 [†]
Stratification	7 (58; 28–85)	1 (20; 1–72)	0.294 [†]
Prominent pericolic vascularity	3 (25; 5–57)	1 (20; 1–72)	>0.999 [†]
Heterogeneous submucosal enhancement	5 (42; 15–72)	1 (20; 1–72)	0.600 [†]
Severe luminal narrowing (>50%)	10 (83; 52–98)	2 (40; 5–85)	0.116 [†]
Proximal colonic dilatation	5 (42; 15–72)	2 (40; 5–85)	>0.999 [†]
Enlarged lymph nodes	9 (75; 43–95)	4 (80; 28–99)	>0.999 [†]
Peritoneal nodules	3 (25; 5–57)	2 (40; 5–85)	0.600 [†]
Free-fluid effusion	5 (42; 15–72)	1 (20; 1–72)	0.600 [†]
Fistula tract	4 (33; 10–65)	0 (0; 0–52)	0.260 [†]
Hepatic metastases	1 (8; 0–38)	3 (60; 15–95)	0.053 [†]
Sclerosing cholangitis	2 (17; 2–48)	0 (0; 0–52)	>0.999 [†]

Note For quantitative data (continuous), data are medians; numbers in parentheses are first quartiles (*q*₁) and third quartiles (*q*₃). For categorical data, data are raw numbers; numbers in parenthesis are percentages; followed by 95% exact CIs

* Calculated with the Mann–Whitney *U* test

[†] Calculated with the Fisher's exact test

[‡] Tumor size was measured for tumors presenting as soft tissue mass only

Table 5. Clinical, histopathological, and CT features in 17 patients with IBD-related colorectal cancer according to the presence of signet ring cells

	Present (<i>n</i> = 6)	Absent (<i>n</i> = 11)	<i>P</i> value
Age (years)	38 (29; 42)	47 (43; 64)	0.021*
Duration of IBD (years)	14 (14; 15)	17 (14; 22)	0.362*
Age at onset of IBD (years)	20 (11; 24)	30 (25; 47)	0.035*
Tumor size at CT (mm) [‡]	34 (30; 61)	NA	NA
Maximal wall thickness (mm)	11 (9; 15)	9 (7; 14)	0.481*
Male gender	3 (50; 12–88)	8 (73; 39–94)	0.600 [†]
Crohn disease	5 (83; 36–100)	7 (64; 31–89)	0.600 [†]
Pancolitis	4 (67; 22–96)	7 (64; 31–89)	0.999 [†]
Visible tumor at endoscopy	1 (17; 0–64)	7 (64; 31–89)	0.131 [†]
Diffuse tumor involvement	6 (100; 54–100)	3 (27; 6–61)	0.009 [†]
Right-sided tumor	4 (67; 22–96)	4 (36; 11–69)	0.335 [†]
pT4 tumor	5 (83; 36–100)	4 (36; 11–69)	0.145 [†]
Soft tissue mass at CT	0 (0; 0–46)	8 (73; 39–94)	0.009 [†]
Visible tumor at CT	0 (0; 0–46)	8 (73; 39–94)	0.009 [†]
Wall thickening (>3 mm)	6 (100; 54–100)	11 (100; 72–100)	>0.999 [†]
Severe wall thickening (>20 mm)	1 (17; 0–64)	1 (9; 0–41)	>0.999 [†]
Submucosal fat deposition	1 (17; 0–64)	1 (9; 0–41)	>0.999 [†]
Stratification	4 (67; 22–96)	4 (36; 11–69)	0.335 [†]
Prominent pericolic vascularity	1 (17; 0–64)	3 (27; 6–61)	>0.999 [†]
Heterogeneous submucosal enhancement	3 (50; 12–88)	3 (27; 6–61)	0.600 [†]
Severe luminal narrowing (>50%)	6 (100; 54–100)	6 (55; 23–83)	0.102 [†]
Proximal colonic dilatation	5 (83; 36–100)	2 (18; 2–52)	0.035
Enlarged lymph nodes	5 (83; 36–100)	8 (73; 39–94)	>0.999 [†]
Peritoneal nodules	3 (50; 12–88)	2 (18; 2–52)	0.280 [†]
Free-fluid effusion	5 (83; 36–100)	1 (9; 0–41)	0.005
Fistula tract	1 (17; 0–64)	3 (27; 6–61)	>0.999 [†]
Hepatic metastases	1 (17; 0–64)	3 (27; 6–61)	>0.999 [†]
Sclerosing cholangitis	1 (17; 0–64)	1 (9; 0–41)	>0.999 [†]

Note For quantitative data (continuous), data are medians; numbers in parentheses are first quartiles (*q*₁) and third quartiles (*q*₃). For binary data, data are raw numbers; numbers in parenthesis are percentages; followed by 95% exact CIs

NA, not applicable because tumors containing signet ring cells were not measurable at CT

* Calculated with the Mann–Whitney *U* test

[†] Calculated with the Fisher's exact test

[‡] Tumor size was measured for tumors presenting as soft tissue mass only

Because of clinical similarities between colorectal cancer and inflammatory lesions, differentiation between the two entities may be difficult. One reason is that the most common clinical presentation of colorectal cancer is intestinal obstruction [24]. In addition, the other presenting symptoms include positive fecal blood test, chronic iron deficiency anemia, weight loss, diarrhea and fistulas, which all are also frequently observed in many patients with IBD. Consequently, the diagnosis of colorectal cancer is often difficult and delayed [33, 34]. Moreover, as shown in four patients of our present series, endoscopy and histopathological analysis of endoscopic biopsy specimens may result in false-negative findings for the presence of colorectal cancer so that the definite diagnosis is obtained only after surgery. Of interest in two of these four patients, CT demonstrated rectal tumor that had an exophytic development into the ischiorectal fossa. In the other two patients, CT showed intriguing, heterogeneous enhancement of the submucosal layers of the colon that was an alerting finding for considering surgery.

Several studies have showed an increased risk of colorectal cancer in patients with IBD [35, 36]. There is significant association between the segmental location of

the underlying IBD and the risk of cancer in that specific segment. Risk factors for the development of colorectal cancer in IBD patients include extended duration of the disease, young age at the time of diagnosis and coexisting primary sclerosing cholangitis [1, 2]. It is also well admitted that chronic inflammation plays an important role in the development of colorectal cancer as it was the case in our population [3, 37].

The majority of cancers in IBD patients are colorectal adenocarcinomas, which are more frequently located in the sigmoid colon and rectum [30]. Choi et al. found IBD-related colorectal cancers in the left portions of the colon (i.e., descending and sigmoid colon) in 52% of patients with Crohn disease and 64% of those with ulcerative colitis. By contrast, in our study, we found that the right colon and the cecum represented the most frequent location of the tumor.

Histologically, IBD-related colorectal cancers contain signet ring cells in a higher proportion of cases than that observed in sporadic colorectal cancers [38, 39]. It is well admitted that colorectal cancers with signet ring cells have a less favorable prognosis and are often discovered at an advanced stage with a high rate of peritoneal dissemination [40]. As a result, colorectal cancers with



Fig. 6. A 59-year-old woman with Crohn disease known for 29 years presenting with weight loss and abdominal pain. Optical endoscopy (not shown) revealed incomplete stenosis of the right colon due to tumor and findings consistent with active Crohn disease. Helical CT obtained in the axial plane after intravenous administration of iodinated contrast material shows marked stenosis due to segmental circumferential thickening of the right colon. No stratification is visible. Mucosal ulceration (*arrowhead*) and fistula tract (*arrow*) are visible. The tumor was categorized as a pT4N1, moderately differentiated adenocarcinoma that did not contain signet ring cells.

Table 6. Results of multivariate analysis for determining CT characteristics predictive for the presence of signet ring cells

Quantitative variables	<i>P</i> value*	Odds ratio	95% CI OR
Free-fluid effusion	0.01	50.00	2.56–977.02
Proximal colonic dilatation	Not retained		
Soft tissue mass at CT	Not retained		
Age at diagnosis of cancer	Not retained		

* Calculated with a logistic regression model for binary outcomes using stepwise method

Not retained in the logistic regression model

signet ring cells represent a distinctive condition by comparison with sporadic colorectal cancers [39]. In our study, we found that this subtype was more frequently undetectable at CT and often missed at endoscopy. It may be assumed that this difficulty in detection may account in part for a delayed diagnosis and a less favorable prognosis.

Signet ring cells are found in 7% of Crohn disease-related colorectal cancer and 6% of ulcerative colitis-related colon cancers, whereas they are found in only 0.6%

of all colorectal cancers [3]. This significant difference prompted us to analyze our results in terms of CT presentation, according to the presence or the absence of signet ring cells in the tumors at histopathological analysis. We found that signet ring cells were associated with a widespread disease at histopathological analysis, whereas all tumors that did not contain signet ring cells presented as a soft tissue mass, similar to sporadic colorectal cancer not related to IBD. This significant difference in terms of presentation has impact on tumor detection at CT because this specific tumor has often a presentation that is very similar to that of the underlying IBD.

In our series, the mean duration of Crohn disease until the discovery of colorectal cancer was 13 years, which is close to previously reported values [3]. In one patient of our series, adenocarcinoma was found 6 months only after the onset of symptoms of Crohn disease. As suggested by Choi and Zelig [3], it may be possible that this patient had, in fact, subclinical or indolent Crohn disease for a long period.

As reported by Larsen et al. [33], the higher mortality among patients with IBD-associated colorectal cancer is observed for tumors with regional spread. Consequently, surveillance programs have been developed because early detection is critical to help improve survival. However, because the tumor is usually initially flat or may have an extraluminal growth, endoscopy may miss an actual colorectal cancer. Similarly, because of sampling errors during endoscopic biopsies, the diagnosis can be overlooked in a substantial portion of patients. For these reasons, the radiologist should be aware of this rare but serious complication to alert the gastroenterologist. In our series, two patients with invisible tumors at endoscopy and undetected at histopathological analysis of biopsy specimens had their cancer detected at CT pre-operatively.

In our series, IBD was considered as active on histopathological examination in every patient, but a relative paucity of signs of activity was found on CT. In this regard, stratification and prominent vascularity were present in only eight and four patients, respectively. These results confirm that colorectal cancers in IBD patients can arise in areas of microscopic colitis [41], which generate mild abnormalities that are beyond the reach of the limited resolution of CT.

Our study shows that IBD-related colorectal cancers are often difficult to depict on CT. We found that colorectal cancers were invisible on CT imaging in the majority (53%) of patients. One reason is that colorectal cancers often develop in colorectal segments involved by IBD that show marked changes such as distortion, wall thickening, and luminal narrowing. In addition, invisible tumor is flat and diffuse as confirmed by histopathological analysis of resected specimens. As reported by Gore et al. [9], IBD-related colorectal cancers should be

searched for in patients with long-standing IBD and several features such as asymmetric mural thickening, focal loss of stratification, and mural thickening of >15 mm should raise suspicion for the presence of colorectal cancer. The results of our study may suggest that some CT findings such as the presence of free-fluid effusion and colonic dilation proximal to marked stenosis should be considered as alerting findings and rule out diffuse colorectal cancer containing signet ring cells. However, further case-control studies should be undertaken to determine the positive predictive values of these two CT signs.

In our series, one patient with long-standing ulcerative colitis had a high grade, poorly differentiated endocrine tumor that was discovered at an advanced stage. It has been suggested that neuroendocrine tumors might be more frequently found in patients with IBD, and more specifically in patients with Crohn disease [42]. However, this may apply for primary carcinoid tumor of the appendix only [39]. It may be possible that in our series, this association might be coincidental only.

Our study has several limitations. One relates to the number of patients so that comparison in CT presentation between the group of patients with Crohn disease and those with ulcerative colitis is limited to draw definite conclusions. A small number of patients had tumor with signet ring cells so that our results might be different in a larger population. The fact that we reviewed CT examinations for patients who had surgery and did not use a more general population of patients with IBD-related colorectal cancer might have introduced some degrees of selection bias.

Conclusion

Our study shows that colorectal cancer in IBD patients displays two main features on CT. Type 2 tumors and free-fluid effusion correlate with the presence of signet ring cells. Knowledge of these findings is critical to help suggest the diagnosis of this rare but severe complication of IBD. Our results show that the diagnosis can be suggested on CT when a soft tissue mass originating from the colon is present, which in our review was the least frequent scenario. Differentiation between the infiltrative form of colorectal cancer from inflammatory stenosis can be difficult, so that the diagnosis must be integrated into a comprehensive evaluation including clinical, biological, and endoscopic features. We do not advocate the use of CT as a screening method for the detection of colorectal cancers in patients with IBD. However, because of difficulties in cancer detection with surveillance colonoscopy, sampling errors during biopsy, the use of CT may be helpful in a number of cases. Further studies and more specifically case-control studies are still needed to better define the potential utility of CT for suggesting the diagnosis of IBD-related colorectal

cancer and its added value by comparison to endoscopy alone.

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