

Malignancies in IBD

Noam Harpaz

Mount Sinai School of Medicine, New York, NY

Bullet Points

- Extensive long-standing ulcerative colitis and colonic Crohn's disease both confer substantial risks for the development of colorectal adenocarcinoma.
- They also predispose to various other malignancies, both intestinal and extraintestinal, some of which are complications of standard therapeutic interventions and others possibly tied to underlying immunological defects.
- Specific examples are to be discussed in light of available information regarding their etiologies, established or suspected risk factors and clinical characteristics.

The threat of malignancies faced by patients with IBD, even long after their disease has been controlled medically, has been a subject of concern since the first published reports of colorectal cancer (CRC) in ulcerative colitis (UC) in 1925¹ and Crohn's disease (CD) in 1948.² Although most attention has focused on CRC and its prevention, IBD also predisposes to other intestinal and extraintestinal malignancies, some of which are complications of standard medical and surgical interventions and others possibly related to underlying immunological defects.

Colorectal cancer

Although the risks for development of CRC in the IBD population have been difficult to quantify, the literature is in near-unanimous agreement that they exceed those of the age-matched general population by a factor of 3-5 or more and that the two major risk factors are the duration of disease and its extent.³ A meta-analysis of papers published prior to 2001 estimated the cumulative incidence of CRC in patients with UC as 2% at 10y, 8% at 20y and 18% at 30y of disease.⁴ However, recent estimates have been lower,⁵ leading some authorities to propose that the risks may be declining, perhaps as a benefit of increased endoscopic surveillance, anti-inflammatory chemoprophylaxis or other factors. The association of CRC with CD was overlooked in early studies which failed to evaluate cases with colitis as a separate risk group, but there is now irrefutable evidence that CD poses similar risks to UC of equal duration and extent.⁶

Patients with left-sided UC, who collectively account for ~20% of cancer cases, face lower risks than those with pancolitis, and those with proctitis and proctosigmoiditis face little or none.^{7,8} The mean age at which CRC is diagnosed in IBD is in the 5th to early 6th decade, 10-20y earlier than in the general population, and corresponds to a colitis-cancer interval of ~20y.⁹ Patients who develop IBD at an early age face high risks of CRC (40% according to one study⁷) which most authorities attribute to prolonged risk exposure and a higher prevalence of pancolitis in younger patients.

The severity of microscopic inflammation in colonic biopsies has been implicated as an independent risk factor in a case-control study from St. Marks Hospital¹⁰ and a cohort study from The Mount Sinai Hospital.¹¹ Using comparable 4-tier scales to score inflammation, both studies concluded that the actuarial risk of developing CRC or dysplasia increases 3-5-fold per unit increase in the inflammation score. The seemingly contradictory fact that CRC is often

diagnosed in patients with clinically quiescent disease may be explained by (1) the greater likelihood that they will retain their colon indefinitely, (2) their lower likelihood of seeking regular medical care, and (3) poor correlation between microscopic and clinical indices of disease severity.¹²⁻¹⁵

Case-control and cohort studies have reported that the already high incidence of CRC in IBD patients is doubled if there is a first-degree relative with CRC and increased 9-fold if the relative developed CRC before age 50, implying that genetic susceptibility contributes to the overall cancer risk.^{16,17}

Most studies maintain that the incidence of CRC is increased substantially in UC patients with primary sclerosing cholangitis (PSC).¹⁸ Since PSC is a marker of extensive but mild or asymptomatic colitis, it may be serving merely as a surrogate marker for longstanding extensive UC rather than as an independent risk factor.¹⁹

Cancers in IBD arise almost exclusively in areas of chronic inflammation. Most series have described a preponderance of left-sided tumors both in UC and CD but others have described cancers evenly distributed on either side of the splenic flexure. Multiple synchronous cancers, including instances of 3 or more, account for 10-30% of cases and are most common in younger patients.²⁰

Macroscopically, cancers in IBD are heterogeneous and usually poorly delimited and asymmetrical compared with sporadic tumors. They are often deceptively flat and inconspicuous or mimic inflammatory strictures, ulcers and inflammatory polyps,^{20,21} challenging the skills of even the most experienced endoscopists.

Histologically, most cases are conventional adenocarcinomas. Fifteen to 30% are mucinous compared with 10-15% in the general population²² and up to 7% are signet ring cell adenocarcinomas compared with ~1% in the general population.²² Another 10% are remarkably well-differentiated tubuloglandular adenocarcinomas with distinctive properties including direct origin from low-grade surface dysplasia, coexpression of cytokeratins 7 and 20, frequent silencing of MLH1 and progression to high-grade cancers in over half.²³ Rarely, squamous cell carcinoma occurs in the distal colon or rectum, often in conjunction with islands of squamous metaplasia.^{24,25} Other uncommon variants of CRC have been described including neuroendocrine,²⁶ adenosquamous²⁷ and hepatoid carcinomas,²⁸ but their associations with IBD are probably fortuitous.

The TNM stage distributions reported in patients with IBD are similar to those for sporadic CRC and the reported 5-year survival rates are virtually identical.^{29,30}

In addition to its serious clinical implications, CRC in IBD is the prototype of the inflammation-dysplasia-cancer sequence in the lower GI tract. As such, it is the culmination of unique histogenetic and molecular pathways, the details of which cannot simply be extrapolated from the sporadic adenoma-cancer sequence.³¹ Dysplasia is the earliest recognizable precursor of CRC in IBD and the most reliable marker of imminent cancer risk. The main supporting evidence can be summarized as follows:³² (1) dysplasia occurs in proximity to CRC in approximately 90% of cancer-bearing resected colons, including nearly all cases with multiple cancers, and occurs remotely in approximately 75% of cases of UC and 27-100% of cases of CD; (2) patients with IBD who undergo colectomy with a prior biopsy diagnosis of dysplasia are diagnosed with CRC in 20-50% of cases; (3) nearly all published results of endoscopic surveillance programs have documented neoplastic progression to CRC or high-grade dysplasia by way of lower grades of dysplasia; (4) IBD-associated dysplasia and CRC share common gene mutations and altered gene expression profiles; (5) although ethical constraints preclude

randomized prospective studies to prove that endoscopic surveillance for dysplasia can reduce the incidence of CRC in the IBD population, there is direct evidence that it leads to the detection of cancers at relatively early stages and circumstantial evidence that it is an effective strategy to reduce cancer-related mortality.³³

Cancer complicating perianal CD

Chronic fistulizing perianal and rectovaginal CD predispose to squamous cell carcinoma and mucinous adenocarcinoma with an overall incidence of <0.7%.³⁴ The interval from the original diagnosis of CD is frequently >20y and rarely less than 10.^{34,35} The presence of malignancy is easily overlooked on routine examination, which may be limited by pain, stricture and other inflammatory manifestations of CD, but is suspected in patients who experience an abrupt clinical deterioration with new onset of pain, feculent discharge or bleeding. A definitive diagnosis may require multiple examinations under anesthesia, resulting in delayed diagnosis and advanced stage by the time treatment is initiated.³⁴⁻³⁶

The cancers usually originate in luminal mucosa at one end of a preexisting inflammatory fistula, squamous cell carcinoma from the anal mucosa and mucinous adenocarcinoma from the rectal mucosa. However, there have been reports of adenocarcinoma and dysplasia that were limited to a fistula tract, having apparently arisen de novo from anal duct epithelium.^{37,38}

Adenocarcinoma following ileal pouch-anal anastomosis (IPAA)

Since their introduction in 1978, IPAA procedures have replaced the permanent ileostomy as the standard for surgical management of patients with UC (and carefully selected cases of CD) who undergo proctocolectomy. In addition to its other benefits, the IPAA is credited with reducing mortality from CRC in UC by helping overcome patient resistance to surgery for dysplasia prior to an established diagnosis of CRC. However, as the number of patients undergoing IPAA has increased, so have reports of post-IPAA adenocarcinoma in the anastomotic region, currently numbering 29 (27 in UC^{39,40} 1 in CD⁴¹ and 1 in indeterminate colitis⁴²).

Established or suspected risk factors for post-IPAA cancer include CRC or dysplasia in the pre-pouch colectomy, duration of postoperative follow-up, type of anastomosis, the presence of chronic pouchitis and synchronous PSC.^{39,43} Of 26 published cases of post-IPAA carcinoma in UC with sufficient data, 20 were preceded by colorectal neoplasia (10 CRC, 10 dysplasia).³⁹ Assuming that most colectomies are performed for non-neoplastic indications, these data implicate pre-IPAA neoplasia as a risk factor for post-IPAA cancer. The median interval from IPAA to cancer for cases with prior CRC is shorter (<3y) than for those with dysplasia or non-neoplastic indications (both 6.5y), suggesting that some cases were recurrences of the original tumor.³⁹

Those who have advocated performing the IPAA by means of an anal canal mucosectomy and hand-sewn anastomosis rather than a low rectal stapled anastomosis have maintained that a complete mucosectomy should minimize the long-term risk of neoplasia. However, reported post-IPAA cancers following mucosectomy currently outnumber those following stapled anastomosis, 17 vs. 9, respectively, indicating that mucosectomy does not eliminate all sources of cancer. One likely source is residual rectal mucosa, remnants of which have been observed in 21% of excised post-mucosectomy pouches, some extending to the dentate line.⁴⁴ Another is the pouch itself. Long-term studies have described atrophy and colonic metaplasia in 9-10% of ileal pouches and associated dysplasia in 0-3%.⁴⁵⁻⁴⁷ These have been implicated as the source of

post-IPAA cancer in 9 of 26 published cases.^{39,48} Theoretically, a 3rd source is the perianal gland epithelium, which is not ablated by either surgical technique.

The pathologic features of post-IPAA adenocarcinomas have not yet been adequately described in the literature. A series from the Cleveland Clinic, recently reported in abstract form, described 4 of 9 cancers as having mucinous features; 6 cases had adjoining high-grade dysplasia, including 4 with hypermucinous features.⁴⁹

Small intestinal adenocarcinoma in CD

An association between CD and small intestinal cancer was first reported by Ginzburg in 1956.⁵⁰ A meta-analysis of 8 population and hospital-based studies reported a relative risk of 33.2 (95% CI, 15.9–60.9).⁵¹ Nearly all cases occur in patients with disease of >10y duration,^{52,53} and a case-control study estimated the mean cumulative incidence as 0.2% after 10y and 2.2% after 25y.⁵³ The mean age at diagnosis is approximately 45, with males predominating (M:F 2.5-3:1). Nearly all patients present with obstruction, abdominal pain, a sudden deterioration in symptoms or weight loss.^{52,54} The lesions occur in inflamed intestinal segments corresponding to the distribution of CD, 75% in the distal ileum and 20% in the jejunum,⁵⁵ by contrast with sporadic small bowel cancers which occur most frequently in the duodenum.

Grossly, the lesions are usually flat and stricturing, mimicking the typical inflammatory strictures of CD. Histologically, most are poorly differentiated adenocarcinomas with intestinal⁵⁶ or signet ring features.^{53,54} Adjacent dysplasia has been reported in ~75% of cases.⁵⁶ Because cases are so rare, follow-up data have been based on small numbers of cases and short follow-up periods. A recent Mayo Clinic series reported mortality rates of 42% at 1 year and 61% at 2y.⁵⁴

Adenocarcinoma following diversionary surgery in CD

Surgical bypass of diseased intestinal segments, a practice once advocated in the surgical management of CD but now largely abandoned, has been implicated in the long-term development of cancers within excluded segments. The lesions typically are clinically silent, advanced at discovery and rapidly fatal. They usually occur in sites of previous active inflammation.⁵⁷ It is debatable whether excluded segments are inherently cancer prone or merely surrogate markers of longstanding CD.⁵² Patients with excluded segments are part of a shrinking patient pool. CT imaging and prophylactic revision have been suggested as means of averting this rare but lethal complication.⁶

Appendiceal cystadenoma and adenocarcinoma

Microscopic chronic appendicitis occurs in >50% of colectomy specimens from patients with UC and CD. Given the small area of mucosa at risk, any associated risk of appendiceal neoplasia would probably be low and difficult to distinguish from the baseline incidence of sporadic neoplasia. Of 8 cases of appendiceal mucinous neoplasms hitherto described in IBD patients, including 6 cancers,⁵⁸ only one reported synchronous colonic neoplasia, implicating the lesion as a complication of IBD rather than a fortuitous occurrence.⁵⁹ In a recent study of incidental appendiceal neoplasms in colectomy specimens at the Mount Sinai Hospital, IBD patients with synchronous colonic dysplasia had a significant 8-fold increased prevalence of cystadenomas compared with IBD patients without dysplasia and a 15-fold increased prevalence compared with patients without IBD.⁵⁸ The implications for the risk of developing appendiceal cancer are unclear and would probably be best addressed by means of population-based studies.

Gastrointestinal carcinoid tumors

There is little evidence to indicate that IBD predisposes to classical intestinal carcinoids despite that mucosal neuroendocrine cell hyperplasia is relatively common in IBD and other chronic inflammatory GI diseases and that patients with UC account for most case reports of large intestinal microcarcinoids. A total 65 GI carcinoids have been reported in patients with IBD including 19 carcinoids of the appendix (5 in UC, 14 in CD). The largest case series, which was based on a 1997 review of the records of 2284 patients at The Mount Sinai Hospital, reported the prevalence of appendiceal carcinoids as 0.26%, nearly identical to the rate of 0.27% reported in an earlier population-based study of non-IBD patients, suggesting that any reported association between IBD and carcinoid tumors is probably fortuitous.⁶⁰ A more recent case-control study at Mount Sinai reported no increase in the prevalence of incidental appendiceal carcinoids in the colectomy specimens of 705 patients with IBD.⁵⁸

Cholangiocarcinoma

Several hospital and population-based studies,^{8,61-64} have reported an increased risk for cholangiocarcinoma⁸ and hepatocellular carcinoma⁶¹ in patients with UC. PSC has been implicated as a predisposing factor in most cases,⁶¹ though not all.⁶²

Hematological malignancies

There has been longstanding concern CD might confer an increased risk for lymphomas as a result either of underlying immune defects, immunomodulatory therapies or both. Three population studies from different countries found no excess cases of lymphoma but another reported a 4-fold incidence in males⁶² and a large Swedish study reported a marginal increase in young patients.⁶⁵ A recent meta-analysis concluded that IBD patients treated with purine analogs incur a 4-fold risk of lymphoma, but left the issue of its etiology, i.e., the disease *vs.* its treatment, unresolved.⁶⁶

The availability of monoclonal anti-TNF agents such as infliximab has revolutionized the management of patients with refractory IBD. However, there has been concern stemming from reports of 10 cases of hepatosplenic T cell lymphoma, a rare but invariably fatal disease, in children who received combined therapy with infliximab and 6-MP.⁶⁷

A suspected link between IBD and myelodysplastic syndromes was confirmed in a population-based Mayo Clinic study which found a much higher than expected prevalence of MDS in a referral cohort of patients with UC and CD. The onset of CD occurred at an older age than expected, and few of the patients had received purine analogs.⁶⁸

Following several anecdotal reports of myelogenous leukemia in patients with UC and divergent findings in small population-based studies, a large Swedish population-based study recently confirmed a small but significant increased risk of acute and chronic leukemia cases in this population.⁶⁵

Other cancers

Some studies have reported increased risks for bladder and squamous skin carcinoma in CD and for soft tissue sarcomas, brain tumors, nonmelanoma skin cancers and endometrial carcinomas in UC. There are no readily apparent explanations for these associations, and in some cases they may merely reflect better medical attention.⁶²

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