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## Crohn's Disease and Colorectal Cancer

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### 1. Introduction

The etiology of Crohn's disease is still unknown. The most likely hypothesis is the alteration of the intestinal immune system with abnormal response to environmental factors and/or intrinsic factors in genetically predisposed individuals, with tissue destruction, chronic inflammation and fibrosis. There are many factors that could contribute to the onset of the disease, modulate clinical manifestations and influence the occurrence of complications also post-operative: cigarette smoking is often associated with a more aggressive disease. The pathophysiological mechanism of this association is not yet clear. Crohn's disease is difficult to cure and even on the basis of this evidence, the therapeutic approach to patient can not be other than multidisciplinary. The most common complications of Crohn's disease are represented by stenosis, fistulas and abscesses that generally need a surgical therapy, despite drug treatment, newly with biological drugs have proved effective. Neoplastic degeneration is a terrible and feared complication in the long term. Although there is a substantial evidence that patients with ulcerative colitis are at increased risk of developing colorectal cancer, the prevalence of cancer in patients with Crohn's disease is also not so well defined even if it's now accepted that the risk of colorectal cancer is equivalent in both conditions. From a review of the literature it can be assumed that the number of cancer cases of large and small intestine associated with inflammatory bowel disease has increased both in patients with ulcerative colitis as well as in patients with Crohn's disease. The rectum, interested only in a small percentage of cases by Crohn's disease, does not seem to be subject to this consideration. Beside it the risk of developing extraintestinal tumors and lymphomas in patients with Crohn's disease appears to have increased in relation to the general population, but, at present, evidences to establish secure real causal link between these disorders are still lacking. The role of immunosuppressive therapies, often carried out on patients with Crohn's disease, also remains unclear. Cancer is often preceded by dysplasia in both patients with ulcerative colitis and in patients with Crohn's disease affection. Young patients who have severe Crohn's disease of long standing, with extensive colonic involvement may benefit from endoscopic surveillance for cancer, especially those affecting the large intestine. We're waiting for good screening methods more sensitive, less invasive and less costly in terms of economic cost and discomfort for the patient. An attitude of alertness may be stated as good: the onset of new symptoms in a patient with up till now stable disease should always be investigated.

## 2. Crohn's disease and cancer: History

For many years after the description of a chronic granulomatous intestinal disease by Dalziel in 1913 (Dalziel, 1913) and, more fully, by Crohn, Ginzburg and Oppenheimer in 1931 (Crohn et al., 1932), it was considered that there was no relationship between Crohn's disease and cancer. The risk of developing cancer in patients with Crohn's disease, in fact, was subject of controversy since 1948, when Warren and Sommers reported the case of a colorectal carcinoma arising in a patient with Crohn's disease (Warren & Sommers, 1948). The testimony of some association between Crohn's disease and cancer remained for many years related to description of single case reports (Ginzburg et al., 1956; Buchanan et al., 1959; Zisk et al., 1960; Hoffert et al., 1963; Berman et al., 1964; Cantwell et al., 1968), until in 1973 Weedon et al. published an epidemiological study on the risk of cancer in patients with Crohn's disease compared with that of the general population (Weedon et al., 1973). While the evidence of an increased risk of colorectal cancer in patients with ulcerative colitis is yet another further confirmation in recent study (Eaden JA. et al., 2001; Freeman, 2008; Viennot et al., 2009; Lukas, 2010; Affendi et al., 2011), the risk of cancer in Crohn's disease on the other side is not so well defined, despite several investigations in this direction from 1973 to present. Based on the literature, however, it seems reasonable to assume that there is an association between Crohn's disease and cancer of the large intestine (Greenstein, 2000; Zisman & Rubin, 2008; Xie & Itzkowitz, 2008; Kraus & Arber, 2009; Kiran et al., 2010; Katsanos et al., 2011). Eaden's meta-analysis has shown that the risk of colorectal cancer in ulcerative colitis increases more with long-standing disease (Lukas, 2010). The risk of developing colorectal cancer in patients with ulcerative colitis is 2% at 10 years, 8% at 20 years and 18% at 30 years of disease duration and this seems to happen also in Crohn's disease (Lukas, 2010; Kiran et al., 2010). The risk of developing cancer appears to be higher in patients with long-standing Crohn's disease particularly if diagnosed before 25 years of age with extensive colonic involvement. Extent of disease, in fact, is another major risk factor (Lukas, 2010). Most cancer arise in patients with extensive disease, which is generally defined as extension of inflammation beyond the hepatic flexure but it was demonstrated that proctitis and proctosigmoiditis posed no increased risk for patients with ulcerative colitis (Lukas, 2010). Recent data from numerous studies suggests that a degree between colonoscopic and histologically active inflammation are associated with an increased risk of cancer. The risk of lymphomas and extraintestinal neoplasms appears to be increased (Von Roon et al., 2007). Patients with Crohn's disease have a higher risk of gastrointestinal tract and hematopoietic system cancers compared with that of the general population. Identify the most vulnerable groups of subjects may be useful for planning appropriate methods of surveillance and early detection. New clinical studies, basic, genetic and molecular research are needed in order to shed light on the complex pathogenetic mechanisms involved in cancer in patients with Crohn's disease.

### 2.1 Risk factors

The presence of an inflammatory bowel disease, especially if long standing, is in itself a risk factor for the development of malignancies (Eaden JA. et al., 2001; Jess et al., 2004; Jess T et al., 2005). Generally cancer develops through chronic inflammation leading to dysplasia, and then cancer but unlike sporadic colorectal cancer in the general population, the development of carcinogenesis in Crohn's disease does not always follow this sequential progression from low-grade dysplasia to high-grade dysplasia and finally cancer. In fact

cancer can arise in patients with no prior dysplasia or without first progression from low-grade dysplasia to high-grade dysplasia even if they are therefore usually located in the region of the bowel affected by colitis and often, but not always, as the cancer grows in an exophytic sporadically, forming a "polyp", cancer that occurs on the mucosa affected by a chronic inflammatory process results in flat lesions that can affect the entire wall with circumferential stenosis (Ullman et al., 2009). Dysplasia is defined as the unequivocal neoplastic alteration of the epithelium without invasion into the lamina propria and macroscopically dysplastic lesions can range from flat lesions to plaque-like lesions even to raised localized or multifocal lesions. The onset of cancer is one of the most serious complications of inflammatory bowel disease and, moreover, the cause of 1/6 of deaths in patients with ulcerative colitis and 1/12 in patients with Crohn's disease (Jess et al., 2002). It is not easy to determine the potential role of the many factors involved in the development of cancer in patients with Crohn's disease. The risk estimates vary greatly in different studies, and this is due to differences in patient population, the statistical methods used and possibly to the different therapeutic approach to the disease. In this regard it should be noted the greater tendency in the Scandinavian countries to perform colectomy or proctocolectomy: this could justify a lower incidence of colorectal cancer in these regions than the United States or the United Kingdom (Von Roon et al., 2007). Nor should we forget the possible misinterpretation of the real incidence of cancer if you are referring only to studies in reference centers, which flow into the categories of patients at increased risk per se. The duration and the extent of anatomic disease (Von Roon et al., 2007), with a strong correlation between the intestinal segment affected by chronic inflammation and increased risk of cancer (Gyde et al., 1980; Greenstein et al., 1981; Ekbom et al., 1990; Gillen et al., 1994; Jess et al., 2004), younger age at diagnosis of Crohn's disease (Von Roon et al., 2007), a positive family history for colorectal cancer (Askling et al., 2001), the Lynch syndrome (HNPCC) (Caruso et al., 1997), the presence of primary sclerosing cholangitis (Broomè et al., 2006), a positive drug history with immunomodulatory or immunosuppressive therapy (Bickston et al., 1999; Farrell et al., 2000; Bouhnik et al., 1996; Lewis et al., 2001; Bernstein et al., 2001), a history of oral contraceptive use (Lakatos et al., 2007), the habit of cigarette smoking at diagnosis of Crohn's disease and the persistence of this in subsequent years (Johnson et al., 2005; Von Roon et al., 2007; Jess et al., 2007), and, ultimately, a less than optimal surgical approach to the disease (Greenstein et al., 1978; Greenstein, 2000), are all factors that can contribute also independently to the development of cancer in patients with Crohn's disease. Some studies testify the possibility that other factors may play a preventive action against the onset of cancer in patients with Crohn's disease. In this regard find space sporadic follow-up colonoscopy or through office visits or hospital admissions (Jess et al., 2007), treatment with 5-aminosalicylates (Eaden J., 2003; Velayos et al., 2005; Jess et al., 2007), non steroidal anti-inflammatory drugs, folic acid and ursodeoxycholic acid (Itzkowitz, 2002), and finally cessation of cigarette smoking, labeled as the first step towards the possible therapeutic effects in the development of a cancer (Jess et al., 2007) and against the disease itself (Johnson et al., 2005). An appropriate surgical approach also plays an important role. A careful study of the role played by these factors could lead to the identification of groups of individuals at high risk of developing cancer, allowing you to plan methods of prevention or early detection practice.

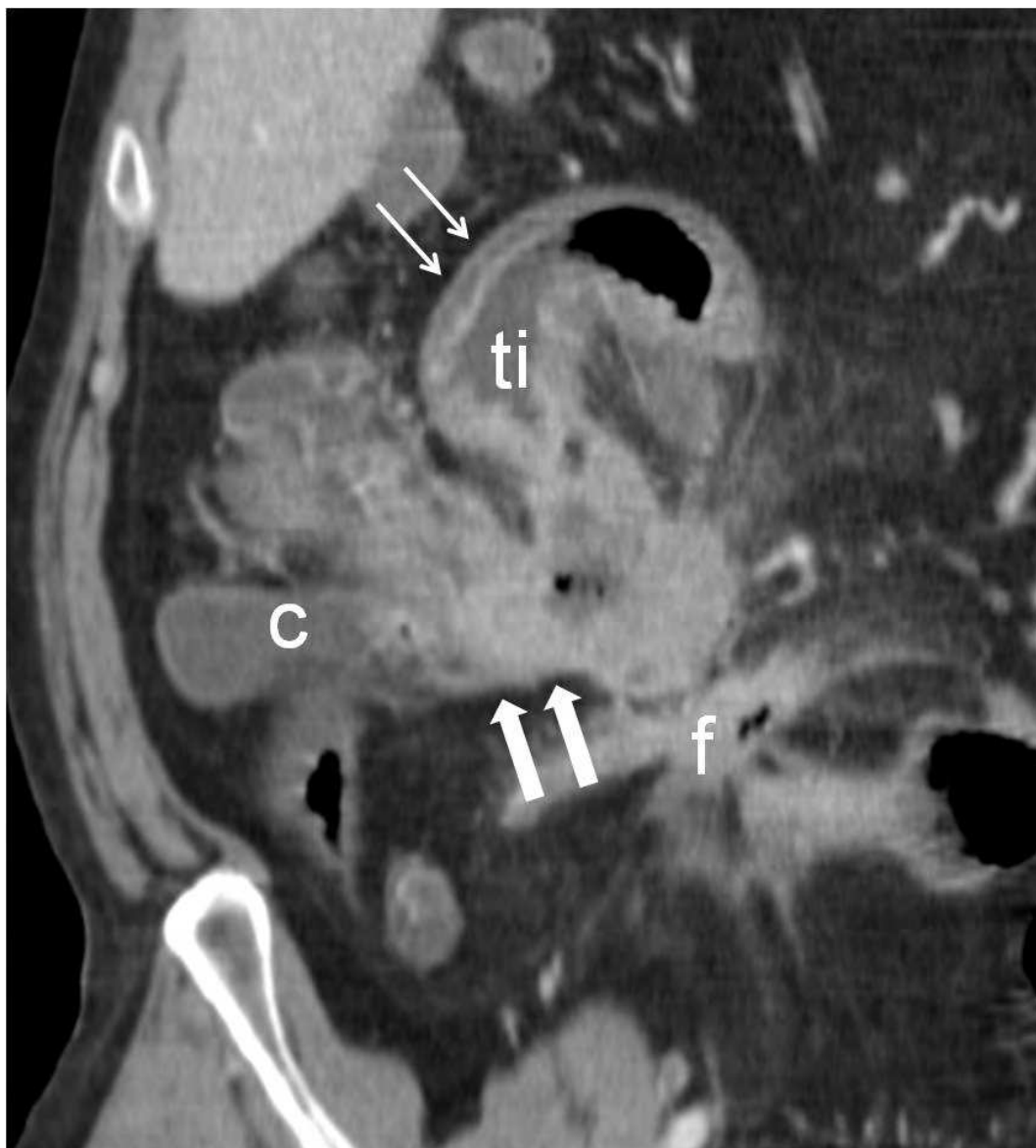
The known association of dysplasia and colorectal cancer in Crohn's disease has been the basis for defining endoscopic screening and surveillance strategies. Surveillance strategy

consists in the systematic search for dysplasia on endoscopic biopsies following a defined calendar. During endoscopic examination it is essential to examine the whole colon in search for all visible lesions preferably during the quiescent period of the disease to avoid histological confusion between dysplastic and regenerative lesions. In this case medical therapy is essential to reduce active inflammation and, once got it, plan short-term repeat colonoscopy (Viennot et al., 2009). More numerous are the biopsies performed higher is the probability of detecting dysplasia. However this strategy is difficult, costs and involves a rate of morbidity which reduce its long-term observance. The ideal solution would be find other risk markers for neoplastic degeneration, cheaper and better tolerated by patients. Chemoendoscopy is a new technique that involves the application of dye during colonoscopy. Indigo carmine is a contrast dye that augments subtle mucosal alterations whereas methylene blue is an absorptive dye that is avidly taken up by mucosa but does not stain areas of inflammation or dysplasia, thereby creating a contrast gradient that enhances visualization. Chemoendoscopy seems to improve the sensitivity of detecting neoplasia and in addition to this offers potential to improve specificity as well, by facilitating enhanced endoscopic characterization of lesions. This allow the endoscopist to perform fewer biopsies more targeted. The combination of chemoendoscopy with magnification permits a detailed analysis of the mucosal helping to differentiate between benign and malignant lesions. Despite the promising information about this technique chemoendoscopy is not yet considered a standard of care approach to surveillance because of its cost and lack of training (Zisman & Rubin, 2008). 5-aminosalicylates are currently the most acknowledged treatment for colorectal cancer prevention in patients with Crohn's disease and the evidence of this protective role for 5-aminosalicylates against colitis-associated colorectal cancer is known since several years (Pinczowski et al., 1994; Viennot et al., 2009). Several recent studies confirmed this evidence (Van Staa et al., 2005; Velayos et al., 2005) even if not all authors are agree on this protective effect, because there is an important heterogeneity of individual study results and the best available data interpretation appears to be that of published meta-analysis (Viennot et al., 2009). Similar roles are played by non-steroidal antiinflammatory drugs and ursodeoxycholic acid (Itzkowitz, 2002). Is now generally accepted that Crohn's disease is associated with an increased risk of cancer. An increased risk of cancer in the intestinal tract is in fact detectable in patients with Crohn's disease, although not specifically have seen increases in incidence or relative risk of oropharynx, esophagus and stomach cancer than the general population; an upward trend has been documented for anus cancer. The risk of developing lymphoma is also increased. Controversial and difficult to interpret are the data on the association between Crohn's disease and other cancers.

### **2.1.1 Cancer of colon and rectum**

The colorectal cancer in patients with Crohn's disease has particular characteristics that set it apart from sporadic cancer. Generally diffuse, with multiple characters, it may not be obvious macroscopic observation or involve the entire bowel wall with stricture formation, remaining silent with regard to the symptoms until an advanced stage: at this point is generally manifested by obstructive type symptoms, weight loss and presence of abdominal mass. Sometimes it can occur in association with fistulas or may occur in loops. The colorectal cancer in Crohn's disease frequently affects younger patients (48 vs. 70 years) and is localized preferably in the right colon (45% vs. 20% of cases), compared with the cancers arose de novo (Figure 1).

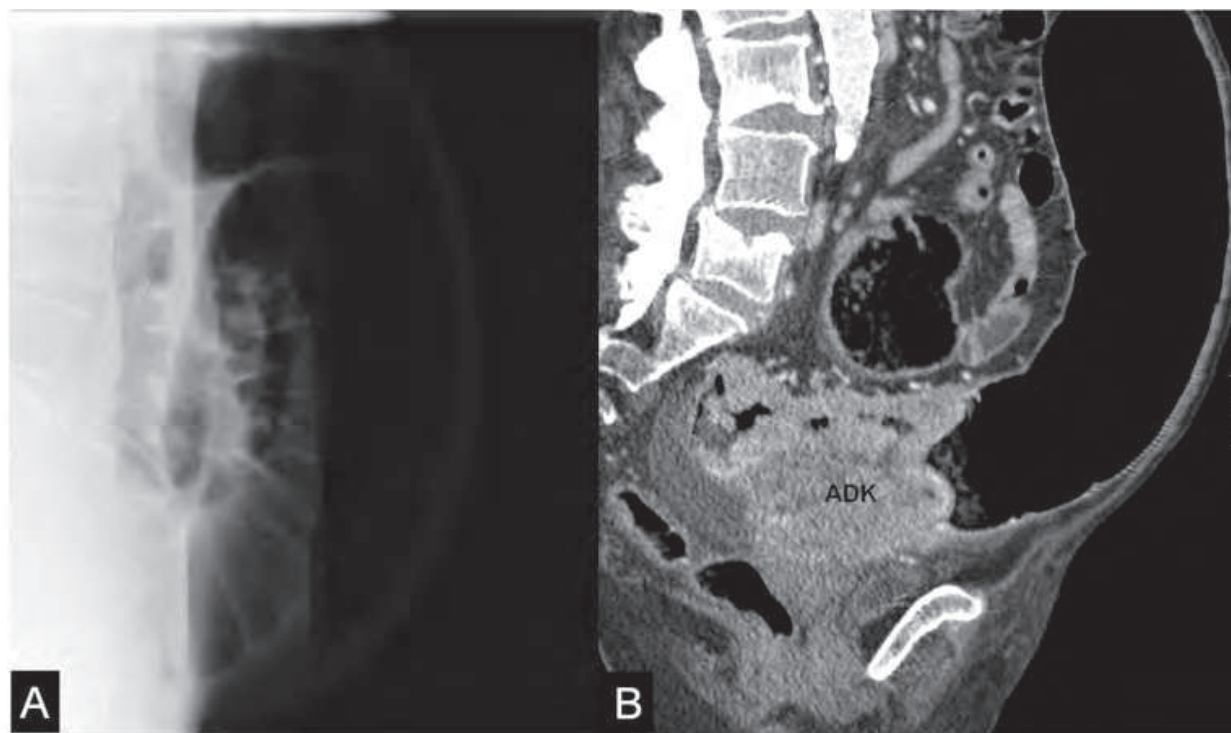




Coronal CT enterography reconstruction showing a severe stricture form involving the ileocecal area in a 58 year-old male patient. Histological analysis of endoscopic biopsies demonstrated the presence of an invasive mucinous adenocarcinoma of the ileocecal valve. Legend: c = cecum; ti = terminal ileum; large arrows = ileocecal stricture; f = extra-enteric fistulous tract with internal air bubbles.

Fig. 1. Neoplasm of ileocecal valve

The risk of developing a colorectal cancer in patients with Crohn's disease is thus increased (Von Roon et al., 2007): this increased incidence is due to an increased incidence of only colon cancer, with regard to the rectum cancer; in fact, there are significant differences in risk than the general population (Von Roon et al., 2007; Figure 2).



83 year-old female patient with a 40-year history of Crohn's disease and low intestinal obstruction signs. Supine trans-lateral radiography of the abdomen (A) demonstrates significant large bowel distension. The sagittal CT reconstruction (B) reveals the presence of a neoplastic stricture (ADK) which appears on CT images as a discrete circumferential thickening with inhomogeneous contrast enhancement of the sigmoid colon wall.

Fig. 2. Sigmoid colon tumor

This assumption could be attributed to the fact that Crohn's disease affects the rectum in a small percentage of cases. Intestinal segments affected by the disease are at increased risk (Gyde et al., 1980; Greenstein et al., 1981; Ekbom et al., 1990; Gillen et al., 1994; Jess et al., 2004;). While the risk of developing a colorectal cancer in patients with Crohn's disease confined to the small intestine appears to be similar to that of the general population (Von Roon et al., 2007), location of the large bowel disease is associated, however, a significant increase in the risk of cancer in this seat (Von Roon et al., 2007). The exact mechanism by which chronic inflammation results in carcinogenesis is unclear but it is believed that persistent inflammation result in increased cell proliferation as well as oxidative stress ending with the development of dysplasia (Itzkowitz & Yio, 2004). Probably the similar genetic mutations that result in sporadic colorectal cancer in the general population are also responsible for its development in Crohn's disease, but the sequence of events and frequency are altered (Ullman et al., 2009). These events include microsatellite instability, inhibition of regulatory genes and loss of adenomatous polyposis coli, p53 and k-ras tumor specific suppressor function (Itzkowitz & Yio, 2004). For example in sporadic colorectal cancer loss of adenomatous polyposis coli gene function generally occur early and is frequent whereas p53 mutations occur late and are less frequent while in Crohn's disease associated colorectal cancer loss of adenomatous polyposis coli gene function generally occur late and is infrequent whereas p53 mutations occur early and are more frequent. Further studies are needed to explain this complex process (Ahmadi et al., 2009; Figure 3).

A diagnosis of Crohn’s disease prior to age 25 is associated with an increased risk of cancer (Weedon et al., 1973; Greenstein et al., 1981), as well as a long-standing Crohn’s disease (Fireman et al., 1989). Patients with severe Crohn’s disease with extensive involvement of the large intestine and diagnosed before 25 years of age, not previously subjected to an intervention of prophylactic colectomy are at high risk for the development of a colorectal

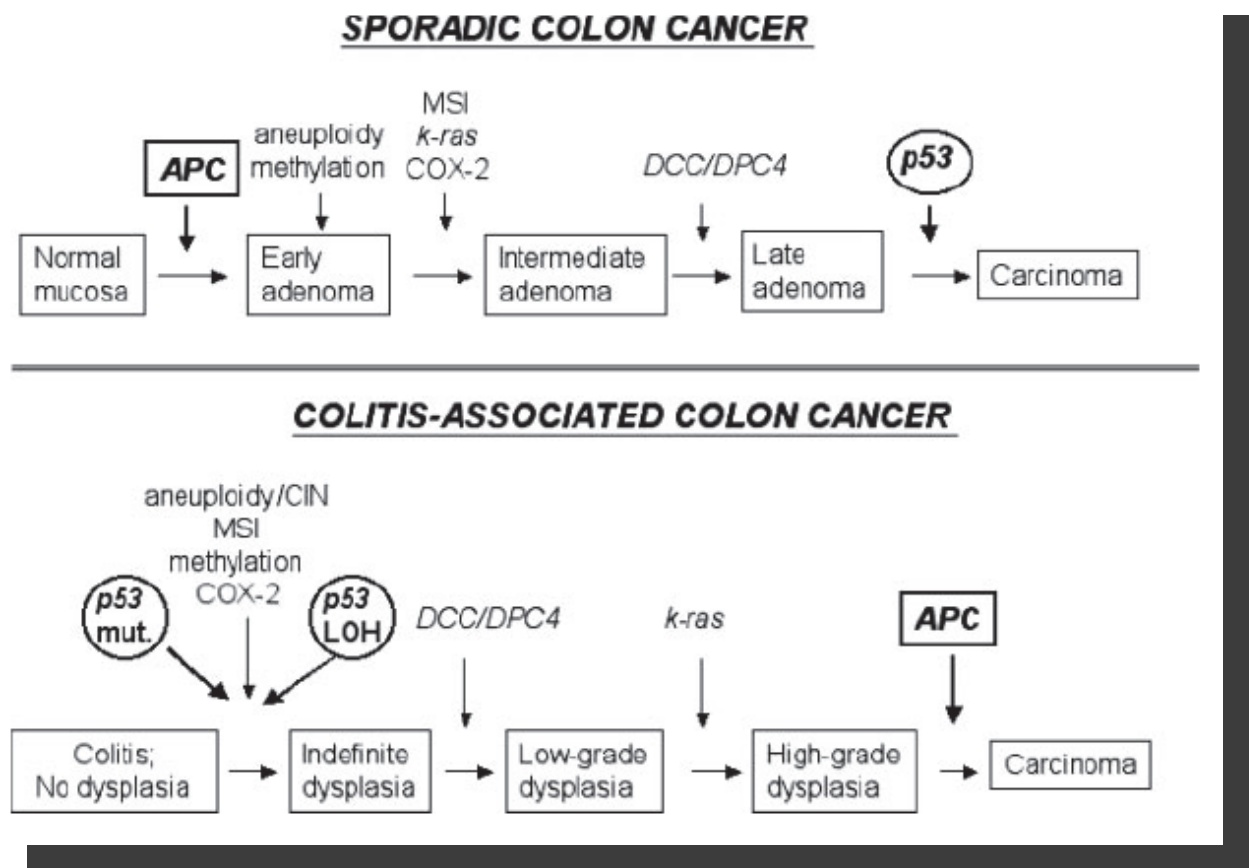


Fig. 3. Cancer in Crohn’s disease: the role of k-ras, p53 and APC (Itzkowits & Yio, 2004).

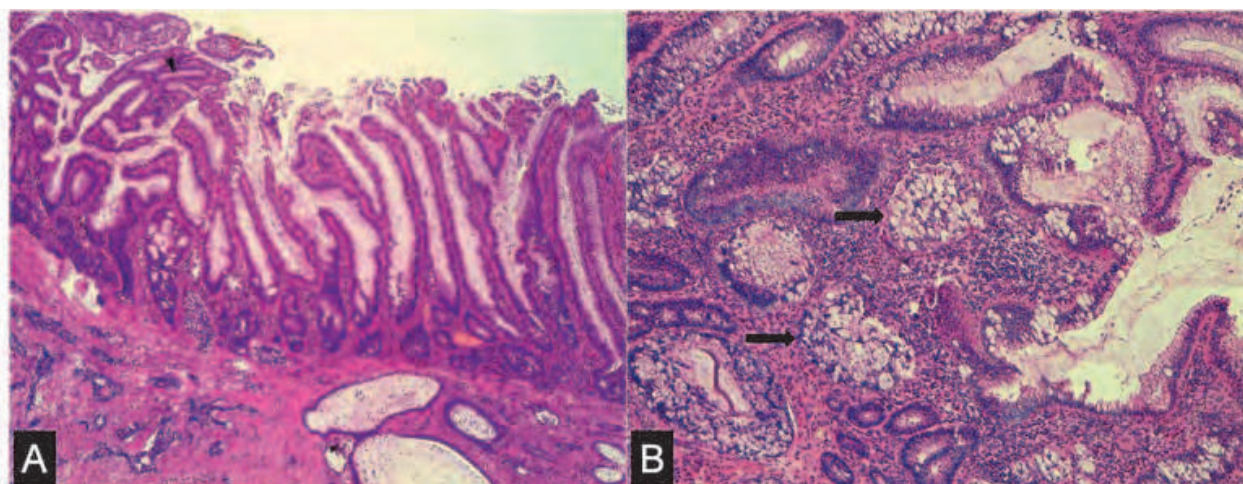
cancer (Gillen et al., 1994; Sachar, 1994), these are precisely the patients who may benefit from an adequate surveillance program by endoscopy (Hamilton, 1985; Von Roon et al., 2007). The attitude of the surgeon facing a patient with Crohn’s disease, which undergoes neoplastic transformation is borrowed from cancer surgery. Resection with wide margins on disease-free anastomosis accompanied by lymphadenectomy and possibly enlargement of the intervention in case of inflamed bowel in these cases are the primary target (Greenstein, 2000). In Crohn's colitis, unless you are facing a severe and extensive disease or the presence of perianal involvement, we prefer to perform, especially in young patients, segmental resection with immediate restoration of intestinal continuity with or without ileostomy possibly temporary. Other surgical procedures that are used in these patients: subtotal colectomy, the total proctocolectomy with end ileostomy or packaging of a J-pouch and palliative procedures (Fornaro et al., 2006; Fornaro et al., 2008; Fornaro et al., 2009). Contraindicated on the basis of the frequent recurrences reported in the literature, seems to be the ileoanal pouch (Greenstein, 2000). Screening colonoscopy should be performed in patients with Crohn’s disease after 8-10 years of disease and the interval between



surveillance examinations is dependent on each individual's personal risk factors. In patients with a previous history of primary sclerosing cholangitis, active inflammation, dysplasia or stenosis, family history of bowel cancer annual surveillance is recommended (Kiran et al., 2010). Colectomy is strictly recommended for patients who were diagnosed with flat high-grade dysplasia or colorectal cancer and where diagnosis was confirmed by expert gastrointestinal pathologists. In patients with a biopsy indefinite for dysplasia, guidelines suggest colonoscopy between 3 and 12 months. Multifocal low grade dysplasia is a stronger indication for colectomy. The optimal colonoscopic surveillance interval for patients who were diagnosed with a flat low grade dysplasia is still unknown, but 3-6 months is often recommended (Lukas, 2010). Although guidelines currently exist, limitations of these guidelines indicate the need to continue research into the molecular pathogenesis of Crohn's disease associated colorectal cancer with the hope to identify targets for prevention. Advances in endoscopic imaging are already underway and may potentially aid in detection of dysplasia and improve surveillance. Management of dysplasia depends above all on the focality of dysplasia itself with the mainstay of involving proctocolectomy or continue endoscopic surveillance. Continued research on additional chemopreventive agents may reduce the incidence of Crohn's disease colorectal cancer but further studies are necessary to get this goal (Ahmadi et al., 2009).

### 2.1.2 Cancer of the small intestine

Most tumors of the small intestine in patients with Crohn's disease are composed of adenocarcinoma of the jejunum and terminal ileum, rarely diagnosed at an early stage likely to cure (Fornaro et al., 1994, Figure 4).



Histological microphotographs (A, B) of endoscopic biopsies taken from the proximal small bowel loop of an ileocolic anastomosis in a patient with Crohn's disease recurrence. Image A demonstrates superficial adenomatous transformation of small bowel mucosa, which was adjacent to an area of invasive mucinous adenocarcinoma. Image B shows neoplastic nests of small bowel mucinous adenocarcinoma (black arrows).

Fig. 4. Dysplasia-carcinoma sequence in the small bowel.

The most common clinical presentation of small bowel cancer is intestinal obstruction (Greenstein et al., 1978). Other important symptoms are diarrhea, weight loss and fistulae. They, too, such as colorectal cancer, differ from the adenocarcinomas occurred *de novo* in several respects. The mean age of patients is generally lower (45 vs. 60 years), the cancer occurs more often distally with multiple characters (76% vs. 20% of cases) or in loops (Greenstein et al., 1978), attributable to the postoperative life even reduced to 8 months (Greenstein, 2000). Sarcomas are rarely seen in the small intestine in patients with Crohn's disease: these rather represent a third of cancers arose *de novo*. Risk factors for developing carcinoma in small bowel segments of involved mucosa in patients with Crohn's disease are poorly defined but numerous case reports document them in strictured mucosa and fistulae. Surgery must be considered if it's difficult to examine fistulae and strictures or if symptoms worsen (Xie & Itzkowitz, 2008). A long-standing history of Crohn's disease is most frequently associated with the appearance of small intestine tumors. Small intestine cancers occurs, as told above, in two thirds of cases with symptoms of obstructive (Greenstein et al., 1978; Greenstein, 2000); diarrhea, weight loss, fistulas, abdominal masses, may also be present. A delay in diagnosis may be partly justified by a non-specific accompanying symptoms and the presence of such symptoms in patients with quiescent Crohn's disease for a long time, however, must lead early on the implementation of appropriate diagnostic tests. The prognosis of small intestine cancer in patients with Crohn's disease is poor (Crohn et al., 1932). The relative risk of developing small intestine cancer in Crohn's disease patients is higher than in the general population (Von Roon et al., 2007), increasing in relation to the anatomical segment affected by chronic inflammation (Greenstein et al., 1981; Jess et al., 2004). Patients with Crohn's disease exclusively localized to the ileum only have a higher risk of developing a small intestine cancer (Von Roon et al., 2007). Although the risk of developing small intestine cancer is higher in patients with Crohn's disease compared with that found in the general population, it remains, in absolute terms, rather than restricted. In fact the absolute number of cases of small bowel adenocarcinoma is low because of the rarity of this cancer in the general population but in patients with Crohn's disease the risk is greater than in the general population. This risk vary in the different studies reported in literature. Based on the stated, hypothesis of a correlation between a chronic inflammation and cancer seems reasonable (Itzkowitz & Yio 2004). The different modes of clinical presentation, with symptoms often generic and nonspecific, and the difficulties of endoscopic evaluation of the small intestine, now partly overcome by modern techniques videocapsulo-tele-endoscopy, the difficult exploration of strokes or bypassed affected by stenosis or possibility of an occult malignancy are important limitations to the surveillance of these patients. Outpatient visits, with particular emphasis on examination of the abdomen and the perineal skin, accompanied by a careful anamnestic investigation aims to investigate the occurrence or the modification of old and new symptoms, especially if it occurred after a long period of quiescence of the disease, could be a viable alternative to more cumbersome methods of surveillance. Segmental resection is preferable to surgery in patients with Crohn's disease complicated by small intestine carcinoma (Greenstein, 2000).

### 2.1.3 Other intestinal tumors

The risk of developing squamous cell carcinoma of the anus is increased (Von Roon et al., 2007). Worsening perianal symptoms in these patients should warrant vigilance for this tumor which often requires examination under anesthesia for adequate tissue diagnosis. An increased risk for hepatobiliary cancers in patients with primary sclerosing cholangitis (Xie

& Itzkowitz, 2008). There is nothing, however, statistically significant increases with regard to the oropharynx, esophagus and stomach cancer. These data find ample confirmation in the literature (Mellekjaer et al., 2000; Von Roon et al. 2007). There is also an association between Crohn's disease and carcinoid tumors, found primarily in the appendix (Fornaro et al. 1998; Szabo et al. 1999; Fornaro et al., 2007). The onset of cancer in loops is described in the literature (Greenstein et al., 1978): This complication has led to the abandonment of the internal bypass interventions, largely carried out until the 60s, now played only in exceptional cases, urgently. Patients with perianal Crohn's disease out to meet the development of squamous cell carcinoma of the anus are usually treated with an abdominal-perineal resection (Greenstein, 2000; Sjødahl et al., 2003), or alternatively can be treated with local excision surgery preceded by radiotherapy and chemotherapy, especially if they are in early stage squamous cell carcinoma (Greenstein, 2000).

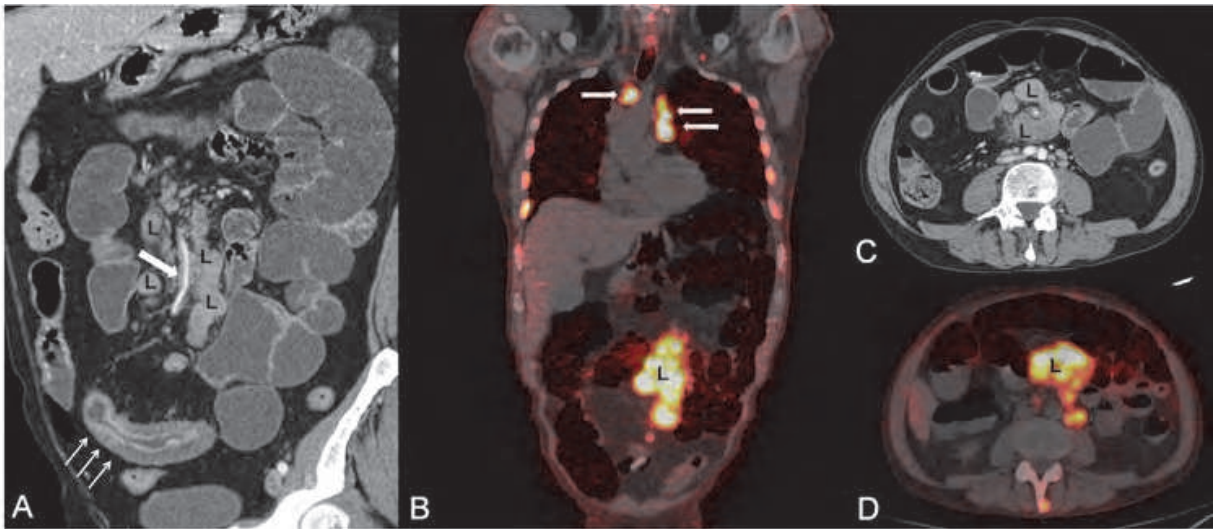
#### **2.1.4 Lymphomas and leukemias**

The risk of lymphoma in patients with Crohn's disease is increased compared with that of the general population (Mellekjaer et al., 2000; Arsenau et al., 2001; Von Roon et al., 2007), particularly in patients who undergo immunosuppressive therapy with corticosteroids or other immunomodulatory agents (Bernstein et al., 2001; Lakatos L. & Lakatos PL., 2007). The risk of hematopoietic cancer in patients with Crohn's disease has been a growing concern. In Crohn's disease, in fact, there is an increased risk of lymphoma specially in the first years of follow-up. Immunosuppressive therapy, which are often carried out on patients with Crohn's disease, influence the occurrence of hematopoietic disorders (Bouhnik et al., 1996; Bickston et al., 1999; Farrell et al., 2000). Following the introduction of tumors necrosis factor inhibitors in the treatment of Crohn's disease, subsequent reports indicated an excess of malignant lymphoma among treated patients with a raised fear of iatrogenic lymphoma. Studies examining the risk of lymphoma associated with azathioprine and 6-mercaptopurine reported variable results. Heterogeneity in the type, the dose and duration of immunomodulatory therapy may be responsible for this discrepancy (Xie & Itzkowitz, 2008). The association between Crohn's disease and lymphoma is confirmed by numerous case reports (Perosio et al., 1992; Brown et al., 1992; Vazquez et al., 1993; Vanbockrijck et al., 1993; Larvol et al., 1994; Veldman et al., 1996; Kelly et al., 1997; Woodley et al., 1997; Charlotte et al., 1998; Kashyap et al., 1998; Parasher et al., 1999; Musso et al., 2000; Li et al., 2001; Martinez Tirado et al., 2001; Calvo-Villas et al., 2003; Hall et al., 2003; Sivarajasingham et al., 2003; Losco et al., 2004; Garcia-Sanchez et al., 2006). In 60% of cases, lymphomas occur in the small and large intestine (Figure 5, 6). An association between Crohn's disease and leukemia has been described in literature (Caspi et al., 1995), but the data do not reach statistical significance. It seems difficult to implement methods of monitoring the patients at high risk of developing cancer: hospital visits, set carefully on history of symptoms and physical examination, could be a viable alternative to costly and unnecessary diagnostic tests. For intestinal lymphomas is primarily surgical excision (Greenstein, 2000). Surgery may be followed by radiation therapy when indicated, or chemotherapy, which is the definitive therapeutic approach for this type of cancer.

#### **2.1.5 Extraintestinal malignancies**

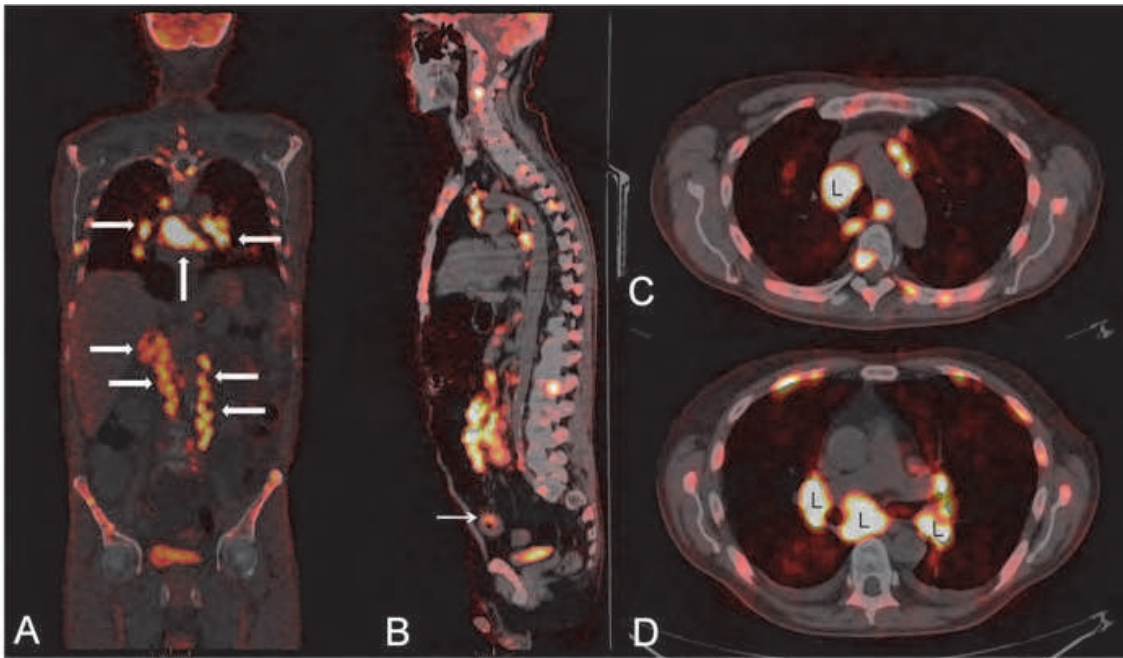
The risk of extraintestinal malignancy in patients with Crohn's disease is slightly increased compared with that of the general population (Von Roon et al., 2007; Figure 7). Hardly,





Imaging findings in a 60 year old man with lymphoma and long standing Crohn's disease. Coronal CT enterography reconstructed image (A) showing multiple, large mesenteric adenopathies (L) along the course of the superior mesenteric artery (large white arrow) and a small bowel inflamed segment with the typical bilaminar stratification of Crohn's disease (white arrows). Coronal PET-CT (fused) reconstructed image (B) which demonstrates 18F-FDG-glucose uptake of mesenteric adenopathies (L) and the presence of concomitant mediastinal adenopathies characterized by an high SUV (standard uptake value) (large white arrows). Axial CT enterography image (C) and corresponding PET-CT fused image (D) showing the mesenteric lymphadenopathies (L) surrounding the superior mesenteric artery.

Fig. 5. Lymphoma



Coronal PET-CT reconstructed image (A) which demonstrates the presence of several lymphadenopathies in mediastinal and abdominal para-aortic nodal stations (large arrows). In the sagittal PET-CT reconstructed (fused) image (B) a moderate 18F-FDG-glucose uptake is appreciable on a small bowel loop with signs of inflammation (white arrow). Two axial PET-CT fused images focused on the mediastinal lymphadenopathies (L).

Fig. 6. Same patient of Figure 5

however, studies reported in this sense in literature don't reached statistical significance and the association-Crohn's disease tumor may be entirely random (Mellemkjaer et al., 2000). Cases are reported in the literature of malignancies arising on fistula, stricture or stoma (Grenstein 2000), and also for this reason, actions of palliation are to be preferred to resection (Askling et al., 2001). Monitoring of cancer in these patients is very complex and a screening is not feasible. Attention is directed to the symptoms: a history and physical examination can direct accurately to the most appropriate diagnostic methods.



Two sagittal reconstructed CT enterography images (A, B) and two axial CT enterography images (C, D) in a 75 year old woman with a long standing Crohn's disease. Image A reveals the presence of a solid nodular lesion on the upper pole of the right kidney with unhomogeneous contrast enhancement (T), and a small bowel loop affected by Crohn's disease (white arrows), which is characterized by typical bilaminar stratification of its wall.

In the same patient a large left ovarian dermoid cyst (DC), with a prominent fat component, is well appreciable in image B. Image C shows the solid nodular lesion of the right kidney which demonstrated to be a clear cell carcinoma at histological analysis. An inflamed small bowel loop (white arrows) can be seen adjacent to the right lateral aspect of the ovarian lesion in image D. Legend: T = renal tumor; C = renal cyst; white arrows = small bowel loop affected by Crohn disease; u = uterus; DC = dermoid cyst.

Fig. 7. Kidney tumor in long-standing Crohn's disease

### 3. Conclusion

Patients with Crohn's disease are at increased risk of colon, small bowel and hematopoietic cancers with and increased risk of lymphoma or extraintestinal malignancies (although lower). The risk of developing a colorectal cancer is mainly increased in patients with diffuse and severe colic, especially if arose at a young age, with a Crohn's disease diagnosis made before 25 years of age. These patients appear to be at particularly high risk of developing a colorectal cancer and are therefore ideal candidates for surveillance with repeated colonoscopies. In particular young patients could benefit from regular endoscopic screening. However, since only one study in literature has stratified patients for extent of disease (Gillen et al., 1994), you can not make recommendations or determine a cut-off extension of disease above which it is legitimate to begin screening for colorectal cancer even if there are now guidelines that recommend a screening after 8-10 years of Crohn's



disease. Little can be done at present with regard to screening and prevention of cancer in the small intestine, but recommended an attitude of alert because of the risk to which patients with Crohn's disease are exposed. In therapeutic management of Crohn's disease a similar attitude of vigilance should be taken towards the possible development of lymphoma: further studies are needed to accurately determine the value of the association between the use of immunosuppressive drugs and the risk of developing lymphoma. Some sort of protection against the development of a colorectal cancer seems to be exerted by aminosalicylates (Greenstein et al., 1985; Pinczowski et al., 1994; Bansal & Sonnenberg, 1996; Moody et al., 1996; Eaden J., 2003; Binder, 2004; Van Staa et al., 2005), but a possible preventive role of salicylates in relation to cancer in patients with Crohn's disease should be supported by further studies. The survival of patients with Crohn's disease operated on for cancer seems to be better in colorectal cancer compared with small intestine cancer. The survival of patients with colorectal cancer on insurgent intestine affected by Crohn's disease did not differ significantly from that of ulcerative colitis patients and even from that of the general population that meets the development of a colorectal cancer with no background colitis (Greenstein, 2000; Von Roon et al., 2007). According to Greenstein, the 5-year survival of patients with Crohn's disease with colorectal cancer is around 45%, but seems to be worse than that of patients with small intestine cancer, estimated around 23% at 3 years after surgery. In conclusion, although by many reported a higher incidence of tumors in patients with Crohn's disease, it should be noted how much the felt need for additional new studies on large numbers to better define the real risk of cancer in Crohn's disease. The future looks promising with respect to new development in the management of cancer risk for these patients. Chemoendoscopy, a technique that involves the application of dye during colonoscopy to highlight subtle mucosal changes that cannot be appreciated by standard white light, is likely to be used more for the management. Beside it much remains to be studied in the field of dysplasia and the natural history of the disease. In the modern era of molecular diagnosis tissue and even stool sample of patients with Crohn's disease can be investigated for molecular alterations. University of Washington investigators have demonstrated that because there is widespread genomic instability throughout the colon of patients with Crohn's disease it may be possible to analyze rectal biopsies by DNA fingerprinting or fluorescence in situ hybridization methods to identify patients at particularly high risk (Brentall, 2003). The advent of technology to extract human DNA from stool and look for specific DNA mutations associated with sporadic colon carcinogenesis implies that a similar approach may also be worth in these patients. Further studies plan to refine our knowledge of cancer biology, clinical practice, and molecular discovery will bring a new level of management of patients with long-standing disease and maybe lower incidence of cancer in this high-risk population (Xie & Itzkowitz, 2008).

#### 4. Acknowledgment

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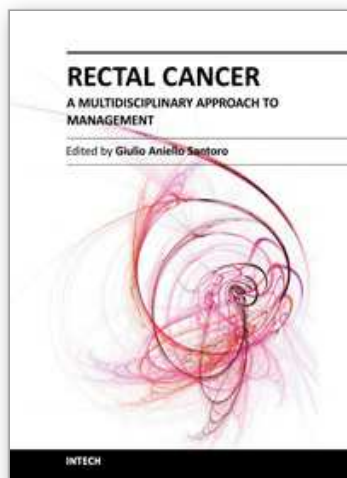
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## **Rectal Cancer - A Multidisciplinary Approach to Management**

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Dramatic improvements in medicine over the last few years have resulted in more reliable and accessible diagnostics and treatment of rectal cancer. Given the complex physiopathology of this tumor, the approach should not be limited to a single specialty but should involve a number of specialties (surgery, gastroenterology, radiology, biology, oncology, radiotherapy, nuclear medicine, physiotherapy) in an integrated fashion. The subtitle of this book "A Multidisciplinary Approach to Management" encompasses this concept. We have endeavored, with the help of an international group of contributors, to provide an up-to-date and authoritative account of the management of rectal tumor.

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