Dysplasia in ulcerative colitis: still a challenge

Ann. Ital. Chir., 2010 81: 5-10

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Dysplasia in ulcerative colitis: still a challenge

As duration of inflammatory bowel disease (IBD), in particular ulcerative colitis (UC), is a major risk factor for the development of colorectal cancer (CRC), it is rational to propose a screening colonoscopy when the risk starts to increase, i.e. after 8-10 years from the onset of disease. If low-grade dysplasia is detected, the 9-fold increased risk of developing CRC reported in the most recent meta-analysis could reasonably be viewed as justification for colectomy even if some follow-up studies have shown a lower rate of CRC. A reasonable compromise could be to continue surveillance with extensive biopsy sampling at shorter (perhaps 3-6 month) intervals. If high grade dysplasia is present, the decision is easier, because the risk of concomitant CRC may be as high as one third, assuming that the biopsies were indeed obtained from flat mucosa and not from an adenoma. Total proctocolectomy with ileal pouch anal anastomosis (IPAA) has become the most commonly performed procedure for patients with ulcerative colitis requiring elective surgery for dysplasia. Nevertheless, a recent systematic review alerted that the risk of dysplasia in anal transition zone and rectal cuff in patients undergone to restorative proctocolectomy was remarkable, mainly in patients operated on for dysplasia or colorectal cancer.

KEY WORDS: Colonoscopy surveillance, Colorectal cancer, Dysplasia, Ileal-pouch anastomosis, Restorative proctolcolectomy, Ulcerative colitis.

Epidemiology

Inflammatory bowel diseases (IBD), in particular ulcerative colitis (UC), are notorious precancerous conditions [1-8]. In the largest report of surveillance colonoscopy in a population of patients with extensive UC to date (600 patients followed over a 30 year period), the cumulative incidence of colorectal cancer (CRC) by UC duration was 2.5% at 20 years, 7.6% at 30 years, and 10.8% at 40 years, being the rectum and the sigmoid colon the zones mainly involved by cancer [9]. The mean age of patients who develop CRC in the setting of IBD is lower than for sporadic CRC, 40 to 50 versus 60 years. Moreover, the mortality in these patients is higher than patients with sporadic CRC [11].

Several studies pointed out the conditions associated with an elevated risk of developing a CRC in patients with UC. The risk of CRC onset in UC resulted mainly related to the duration and anatomic extent of the disease, while in Crohn's colitis it appeared not linearly related to disease duration [12]. There is no uniform definition of the duration of disease, although onset of symptoms has generally been used in the studies that have identified this parameter as a risk factor [13]. In a review of 19 practice and population-based studies, Eaden confirmed that the CRC risk appears to increase 8–10 years after the onset of UC related symptoms and subsequently accelerate in later decades of the disease; the risk was increased in patients with less than 20 years of age at the time of UC diagnosis [14]. In one series, the absolute risk of CRC in patients with pancolitis was 30 percent after 35 years of disease [5]. However, in other reports, the age of onset of colitis was not related to the risk of

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CRC after adjusting for the longer period of time and the extent of the disease [1] and, in the 600-patient study from St Mark's Hospital, there was no difference in median age at onset of colitis for those with or without CRC [9].
Most studies have found that the risk of CRC increases after 15 to 20 years (approximately one decade later than in pancolitis) in patients with colitis confined to the left colon (i.e, distal to the splenic flexure) [15]. However, in these patients, rates of CRC and dysplasia similar to those seen in patients with pancolitis have been described [16]. Finally, patients with ulcerative proctitis and proctosigmoiditis are probably not at increased risk for CRC. The extent of mucosal inflammation (including backwash ileitis) has been correlated with the risk of CRC in several studies, as well as in a systematic review [17-22], but the presence of "backwash ileitis" has not been confirmed in other studies [19,23].
Other features have also been individuated as risk factors for CRC in ulcerative colitis. In fact the presence of primary sclerosing cholangitis (PSC) is associated with a high risk of CRC in UC [24]. Cancer in patients with PSC was more likely to be in the right colon, suggesting a possible role of bile acids in oncogenesis (a hypothesis supported by studies showing a protective effect of ursodeoxycholic acid). The persistence of mucosal inflammation [19,20,25] or a family history of CRC [26] may also contribute to an increased risk, but the association has been less consistent across the studies. Some possible protective factors are use of anti-inflammatory agents (aspirin, non-steroidal anti-inflammatory drugs and 5-aminosalycilicc acid agents) and surveillance colonoscopy [12,27].

Endoscopic management and indication for surgery

Unlike in sporadic CRC in which dysplastic adenomas begin as raised polypoid lesions, dysplasia in IBD can arise in mucosa that is indistinct from surrounding mucosa, making it "invisible" to the endoscopist. Consequently many lesions may be missed. The current approach to surveillance is based on the concept of an inflammation-dysplasia-carcinoma sequence, with dysplasia representing a premalignant phase during which intervention can prevent or minimize the complications associated with the onset and progression of an invasive cancer. An understanding of the definition, diagnostic challenges and natural history of dysplasia in IBD is, therefore, essential when contemplating complex clinical management decisions [28]. So endoscopic surveillance is important to detect dysplasia in patients with UC. As duration of disease is a major risk factor for the development of CRC in UC patients, it is rational to propose a screening colonoscopy when the risk starts to increase, i.e. after 8-10 years from the onset of disease. This initial colonoscopy also is aimed to reassess the extent of disease, since this parameter also impacts on the risk of CRC [13].
In extensive colitis, surveillance should start after screening colonoscopy and be performed every other year up to year 20 of disease, then annually. Surveillance should start 15 years after onset of disease in left-sided or distal UC. Proctitis does not require further surveillance [13]. Several studies suggests that at least 33 biopsies should be obtained from the various segments of the colon to achieve 90-95% sensitivity for the detection of dyspla-

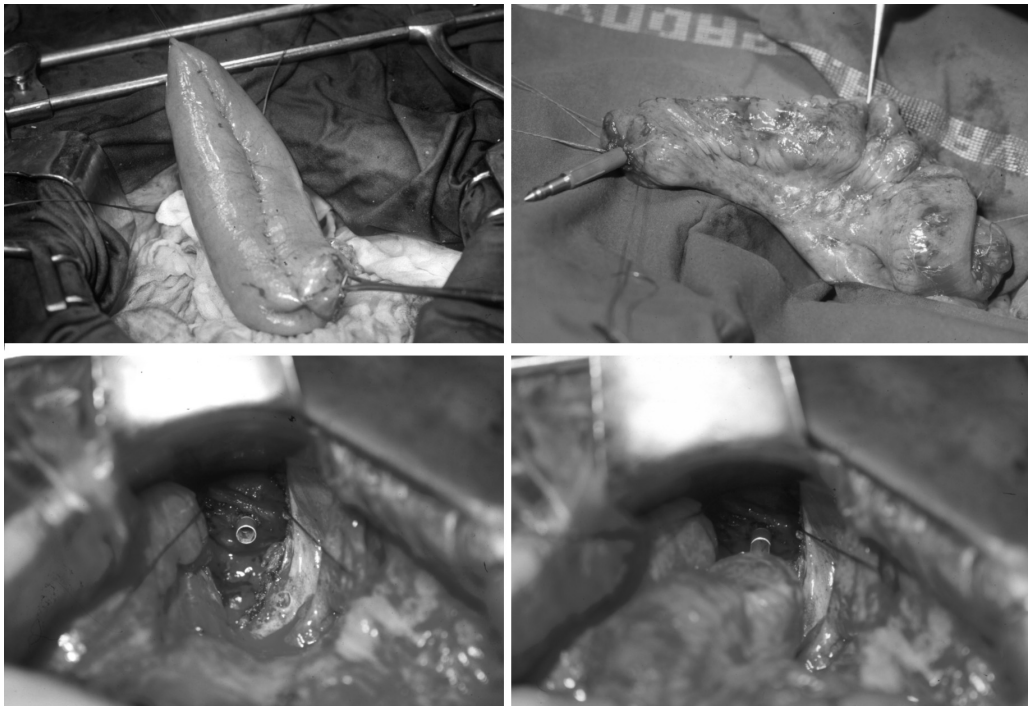

Fig. 1: Restorative proctocolectomy: ileal J pouch and mechanical anal anastomosis.

sia. A reasonable approach would therefore to perform 4 random biopsies every 10 cm around the circumference of the colonic lumen. Extra biopsies should be obtained from strictured or raised areas and from other abnormal areas in the colon [13,30-33].

If biopsies are indefinite for dysplasia and this is confirmed by an experienced pathologist, then follow-up surveillance colonoscopy within 3 to 6 months is recommended, with intensification of UC therapy in the meantime [13]. The finding of low-grade dysplasia carries a substantial risk: such a finding has important prognostic implications. For this reason, dysplasia should be confirmed by an experienced pathologist, because interobserver variation for the detection of dysplasia is high [34-36]. If high grade dysplasia is present, the decision is easier, because the risk of concomitant CRC may be as high as 32% [34], assuming that the biopsies were indeed obtained from flat mucosa and not from an adenoma. If low-grade dysplasia is detected, the 9-fold increased risk of developing CRC reported in the most recent meta-analysis could reasonably be viewed as justification for colectomy as well, and this option should be discussed with the patient [37]. However, because some follow-up studies of patients with low-grade dysplasia have shown a low rate of CRC development [38,39] it seems a reasonable compromise to continue surveillance with extensive biopsy sampling at shorter (perhaps 3-6 month) intervals in those who will adhere strictly to the surveillance program [17,40].

Raised lesions on a background of UC have been traditionally referred to as "Dysplasia Associated Lesion or Mass" or DALM. Until recently this finding has been considered an absolute indication for colectomy. It is increasingly recognised, however, that some of these raised lesions may resemble sporadic adenomas and that they may be amenable to complete endoscopic resection [41-44]. If the polypectomy is confirmed complete by histology and if biopsies obtained from the flat mucosa immediately adjacent to the polypectomy site show no dysplasia and if, in addition, no dysplasia is found elsewhere in the colon, then colectomy may be safely deferred. Careful follow-up, preferably with surveillance colonoscopy at 3 months and then 6 months, is needed if this strategy is followed, because at least half of such patients in the four studies quoted developed further raised lesions. If the lesion does not resemble typical adenoma, is not resectable, or it is associated with dysplasia in the adjacent mucosa, then colectomy is indicated due to the high risk of concomitant CRC [30].

Surgery

Proctocolectomy with ileostomy has been the conventional operative approach for patients with ulcerative colitis and may be considered a benchmark procedure to which all other operations are compared [44,45]. It has been established as a safe, curative operation that permits most patients to live a full, active lifestyle [46,47]. Although restorative proctocolectomy with ileal pouch anal anastomosis (IPAA, Fig. 1) has become increasingly popular during the past two decades, proctocolectomy with ileostomy can still be considered the first-line procedure for patients who choose not to undergo a restorative proctocolectomy and for those at significant risk for pouch failure, such as patients with impaired anal sphincter muscles, previous anoperineal disease, or limited physiologic reserve secondary to comorbid conditions [48].

Total proctocolectomy with IPAA has become the most commonly performed procedure for patients with ulcerative colitis requiring elective surgery. The operation is relatively safe and durable [49,50], associated with an acceptable morbidity rate (19 to 27 percent) and an extremely low mortality rate (0.2-0.4 percent) [51,52], and a quality of life that in some series seems to approach that of the normal population [53-55]. However, studies from of our group that used a quality of life questionnaire for inflammatory bowel disease (PIBDQL) patients found that the quality of life in patients undergone to restorative proctocolectomy was similar to that of patients with mild ulcerative colitis [56-58].

The complications of the procedure include those of any major abdominal operation: risks arising from the pelvic dissection, such as infertility or sexual dysfunction, and pouch specific complications, such as pouchitis [59-67]. Furthermore, a recent systematic review alerted that the risk of dysplasia in ileal pouch, anal transition zone and rectal cuff in patients undergone to restorative proctocolectomy was remarkable, mainly in patients operated on for dysplasia or colorectal cancer [68]. Nevertheless, total proctocolectomy with IPAA may be appropriately offered to selected ulcerative colitis patients with concomitant colorectal cancer. Studies examining the use of IPAA in patients with invasive cancers of the colon or upper rectum without distant metastases have yielded somewhat conflicting findings. In several series, ulcerative colitis patients with a concomitant carcinoma had a rate of postoperative complications and functional results comparable to colitis patients without cancer; metastatic disease developed in a small number of patients [68-72]. In contrast, a separate study revealed that nearly 20 percent of ulcerative colitis patients with cancer who underwent an IPAA subsequently died of metastatic disease [73].

A more conservative management approach has been also advocated by someone who recommend an abdominal colectomy with ileostomy followed by a restorative proctectomy after an observation period of at least 12 months to better assure that no recurrent disease had developed [74]. Metastatic disease is generally considered a contraindication to IPAA. These patients should usually be managed with segmental colectomy or abdominal colectomy with anastomosis to facilitate early discharge and allow them to spend the rest of their lives relatively free of complications. Another group of patients who may

not be eligible for IPAA are those with invasive carcinomas of the mid or low rectum, because basic principles of cancer surgery may be compromised. Adjuvant radiotherapy, if indicated, should be performed preoperatively whenever possible, because postoperative radiotherapy is associated with a high incidence of pouch loss secondary to radiation enteritis and poor pouch function [70]. Ulcerative colitis patients with cecal cancers represent another unique subgroup of patients. If a long segment of adjacent distal ileum with its mesenteric vessels must be sacrificed, difficulties with positioning of the reservoir into the pelvis may ensue, and an ileostomy may be necessary if a tension-free anastomosis cannot be attained.

Riassunto

Poiché la lunga durata della malattia infiammatoria intestinale (IBD), in particolare della colite ulcerosa (UC), rappresenta un fattore di rischio maggiore di evoluzione verso un cancro colorettale (CRC), è ragionevole proporre l'esecuzione di una colonscopia di screening quando il rischio comincia ad accrescersi, cioè dopo 8-10 anni dall'insorgenza della malattia. Se si individua una displasia di basso grado, il rischio nove volte maggiore di sviluppare un cancro riconosciuto dalla maggior parte delle recenti meta-analisi rappresenta una altrettanto ragionevole giustificazione all'esecuzione di una colectomia, anche se alcuni studi di follow-up hanno dimostrato un'incidenza minore di insorgenza di CRC. Un accettabile compromesso potrebbe essere quello di una continua sorveglianza con adeguati prelievi bioptici ad intervalli ravvicinati (proposti 3-6 mesi).
Se è presente una displasia di grado elevato la decisione è più facile, perché il rischio di un concomitante CRC raggiunge addirittura un terzo dei casi, considerando che le biopsie vengono prelevate da una zona di mucosa piatta e non da un adenoma.
La proctocolectomia totale con la confezione di una pouch ileo-anale (IPAA) è divenuta la procedura più spesso adottata per pazienti con colite ulcerosa sottoposti a chirurgia di elezione proprio per la displasia. Ciononostante una recente revisione sistematica ha lanciato l'allarme che il rischio delle displasia localizzata nella zona transizionale dell'ano e nel moncone rettale dei pazienti sottoposti ad una proctocolectomia restaurativa è significativo, specialmente nei pazienti operati per displasia o per cancro colo-rettale.

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