Dysplasia in inflammatory bowel disease

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Abstract

Ulcerative colitis and Crohn's diseases are relapsing longstanding inflammatory bowel diseases, associated with an increased risk of developing colorectal cancer. Continuous surveillance is necessary to detect the preneoplastic lesions in an early stage. New endoscopic techniques have improved the diagnostic accuracy and have resulted in a new and more simplified classification system of the dysplastic lesions in the bowel. Histopathologically these lesions are very heterogenous, consisting of adenomatous, villous and the more recently discovered serrated dysplasia. Its diagnosis may be hampered by the inflamed mucosa, resulting in a high interobserver variability in the categories of indefinite for dysplasia and low-grade dysplasia. Therefore the ECCO guidelines recommend to confirm the diagnosis of dysplasia by a pathologist with expertise in gastrointestinal pathology.

In this article we give an overview of colitis-associated dysplasia from the point of view of the endoscopist and the pathologist. (Acta gastroenterol. belg., **2017,** 80, **299-308**).

Introduction

Ulcerative colitis and Crohn's diseases are relapsing longstanding inflammatory bowel diseases (IBD) with an early onset, occurring in approximately 0.4% of the European and North-American population (1). IBD patients have a higher risk of developing colorectal cancer than the general population, as persistent inflammation may in time cause a malignant transformation of the mucosa. Colitis-associated colorectal cancer in ulcerative colitis has been reported for the first time by Crohn and Rosberg in 1925, and in Crohn's disease in 1948 by Warren and Sommers (2, 3). It is responsible for 10 to 15% of the mortalities among IBD patients and one of the main causes of death (4).

The appearance of dysplastic lesions in association with inflammatory bowel disease is very heterogeneous. In the past the terminology to describe these lesions has been very confusing. For example, the obsolete term DALM (dysplasia associated lesion or mass) refers to an endoscopically visible lesion in a background of an inflamed mucosa, whereas according to some gastro-enterologists the term only means a lesion suspicious for high grade dysplasia or invasive carcinoma (5). The improvement of the endoscopic techniques however has resulted in a new and more simplified classification system of the dysplastic lesions in the bowel (6, 7). Histopathologically, things have changed too, as dysplasia does not only correspond to adenomatous lesions, but also to the more recently discovered serrated lesions, and the increased risk to progress to cancer (8).

Risk factors

Epidemiological studies have shown that there is an overall trend towards a decrease in the incidence of colorectal cancer in ulcerative colitis patients. Whereas the meta-analysis of Eaden et al. has shown that ulcerative colitis patients are at risk with an incidence of respectively 1.6 per 1000 patient-years at 10 yrs, 8.3 per 1000 patient-years at 20 yrs, and 18.4 per 1000 patient-years at 30 yrs after the onset of the inflammatory process (9). A recent meta-analysis by Castano-Milla et al. revealed that the relative risk of colorectal cancer is only slightly elevated (RR 1.21) as compared to the general population. The incidence is significantly lower, namely 0.91 in the first decade, 4.07 in the second decade and 4.55 in the third decade (10). A possible explanation for the different outcome in these meta-analyses is the patient selection : in the past the study population mainly consisted of patients deriving from tertiary referral centers, presenting with more severe and extensive colitis. Other factors, which may explain the decrease in risk of colorectal cancer is the improvement in therapy, resulting in a better control of the inflammation, the meticulous surveillance of the patients, and the increased implementation of colectomy at an earlier stage of tumor development, namely dysplasia. The risk in ulcerative colitis patients is however determined by several risk factors such as the extent of disease, increasing from a proctitis (RR 1.7), left-sided colitis (RR 2.8) to a pancolitis (RR 14.8), the duration and the severity (RR 4.7) of the colitis with presence of post-inflammatory polyps (RR 2.1) and colonic stricture (RR 4.62), the coexistence with primary sclerosing cholangitis (RR 4.8) (9, 11-13). Liver transplantation in IBD patients with primary sclerosing cholangitis does not reduce the risk of colorectal cancer (14). Other risk factors are age at onset of disease, gender, family history of colorectal cancer (RR 2.5), first degree relative with colorectal cancer at an age before 50 years (RR 9.2), risk factors which are also found in sporadic colon cancer (11, 15, 16). Although the risk of colitis-

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Submission date : 07/12/2016
Acceptance date : 19/02/2017

associated cancer in ulcerative colitis patients is not as significant as originally shown in several epidemiological studies, the occurrence of cancer at an earlier age and the poorer prognosis in advanced stage compared to sporadic cancer justifies the meticulous surveillance of these IBD patients (9, 17).

The relative risk of colitis-associated cancer in Crohn's disease varies from 0.5 to 7.73 (18, 19). In contrast to ulcerative colitis, contradictory results have been published concerning the change in colorectal cancer risk in patients with Crohn's disease (20, 21). Some risk factors are similar to those in ulcerative colitis, namely the duration, extent and severity of the colitis, young age at onset of colitis, family history of sporadic colorectal cancer, first degree relative with colorectal cancer before 50 years (16, 22-25). A risk factor specific for CD patients is the association between anal fistula and the development of anal cancer (26). Small intestinal adenocarcinoma is an uncommon cancer of the gastrointestinal tract, but Crohn's disease patients are at risk to develop this type of cancer in inflamed small bowel segments (up to RR 31.2) (20).

Etiopathogenes

The microenvironment in its continuous state of inflammation plays an essential role in the carcinogenesis of colitis-associated cancer, which consists of three different phases, namely the initiation phase, the promotion phase and the progression phase. In the initiation phase the epithelial cells acquire precancerous molecular changes without overt alterations in their phenotype. In the promotion phase the genetically altered cells proliferate, and in the progression phase, the cells become tumor cells with invasive and metastatic properties due to activation of oncogenic pathways (27). The innate as well as the adaptive immune system is involved in the tumor development by the release of reactive oxygen and nitrogen species, and by cytokines such as TNF-α, IL-1β and IL-6. TNF-α is not only a pro-inflammatory cytokine, but it is also involved in the initiation and promotion phase by stimulation the production of reactive oxygen species, inducing oxidative stress, and activation of different oncogenic pathways such as the *NF-ϰB* activation pathway (28). Oxidative stress promotes tumor development in IBD patients by inactivation of tumor suppressor genes, such as *p53* mutations, and inactivation of the DNA mismatch repair system, resulting in microsatellite instability, both observed in the inflamed non-neoplastic colon mucosa in approximately 50% of the ulcerative colitis patients (29, 30). It also induces telomere shortening, facilitating chromosomal instability and tumor progression in ulcerative colitis patients (31). Chromosomal instability in colitis-associated cancer is as common as in sporadic colon cancer, but in contrast it is not restricted to tumor tissues as it also can be found in non-neoplastic colon mucosa (32). In non-neoplastic colon mucosa of ulcerative colitis molecular analysis reveals epigenetic changes, such as DNA hypermethylation and microRNA alterations. Hypermethylation of CpG islands in several genes is an early feature, not only detectable in dysplastic mucosa but also in inflamed mucosa (33). The genes most commonly hypermethylated in colitis-associated cancer are *hMLH1* (up to 46%), causing micro-satellite instability, the cell cycle inhibitor *p16INK4a* (up to 100%) and *p14 ARF* (33-64%) (34). Different types of microRNAs (miRNAs), which are small non-coding RNA, involved in cell proliferation, differentiation and apoptosis, are studied in inflammatory bowel disease. They are upregulated in the inflamed mucosa of ulcerative colitis and Crohn's disease patients and may play an essential role in colitis-associated cancer, as they promote cell proliferation, inhibit apoptosis, induce invasion and metastasis by interaction with tumor suppressor genes (35). *MiRNA214* e.g. is detected in inflamed mucosa and colitis-associated cancer in ulcerative colitis patients. It acts as an oncogene through the *NFϰB1* and *PTEN-Akt* pathway (36).

On the molecular level there are major differences between sporadic colon cancer and colitis-associated cancer. Whereas in sporadic colon cancer the *APC* gene is involved in the initiation phase of the tumor development, and *p53* in the progression phase with transition from adenoma to invasive carcinoma, the opposite is true in colitis-associated cancer. In non-neoplastic inflamed colon mucosa *p53* deletions and *p53* mutations can be found, increasing in frequency with the degree of dysplasia, whereas the *APC* gene is involved in the late stages of colitis-associated cancer carcinogenesis at the transition from high grade dysplasia to carcinoma, where *APC* mutations are present in respectively 27.3%, 50% of cases (30, 37, 38). Similar to sporadic colon cancer, *KRAS* mutation plays an essential role in the late stages of colitis-associated carcinogenesis, be it that it is less frequent (39). Colitis-associated cancer may also develop through the serrated neoplasia pathway, in which sessile serrated adenomas/polyps and traditional serrated polyps are associated with *BRAF* mutations and *KRAS* mutations (8, 40).

Dysplasia

Endoscopic classification of dysplasia

The improvement of the endoscopic techniques has resulted in a new classification of the dysplastic lesions in inflammatory bowel disease. In order to obtain uniformity in communication, a new endoscopic terminology is proposed, in which the old terminology such as adenoma-like previously named ALM and non-adenoma like previously named DALM should be abandoned (Table 1). This new classification is based on two major criteria namely the endoscopic visibility and resectability of the lesions (6). According to the SCENIC

Table 1. — **Correlation between the old and new terminology of IBD-related dysplasia (5-7)**

Old terminology	New terminology
Elevated-type dysplasia (DALM)	Visible dysplasia
Non-adenoma-like dysplasia	Non-polypoid dysplasia
Adenoma-like dysplasia	Polypoid dysplasia
Flat type dysplasia	Invisible dysplasia

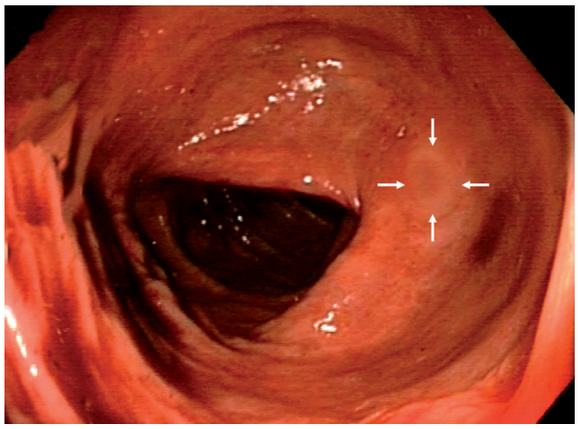

Fig. 1. — Colitis-associated dysplasia: Endoscopic picture of a non-polypoid dysplasia in the sigmoid in a patient with ulcerative colitis, which on target biopsy corresponded to a low-grade dysplasia.

guidelines nowadays distinction is made between visible and invisible dysplasia (6, 7). Based on its appearance visible dysplasia can be categorized, in parallel with the Paris-classification, into a non-polypoid and a polypoid dysplasia. Non-polypoid dysplasia is differentiated into a superficially elevated lesion (less than 2.5 mm in height), a flat (no protrusion into the lumen) or depressed (partially/totally below the level of the mucosa) lesion (Fig. 1).

Polypoid dysplasia, which is higher than 2.5 mm and extending into the gut lumen, is subtyped into a sessile or pedunculated lesion (Fig. 2). The main features, determining the therapeutic approach, are however nowadays its endoscopic resectability and the appearance of the surrounding mucosa. Hence the endoscopic report should describe the morphology of the lesion, if it is well-circumscribed and the nature of the surrounding mucosa (6).

Histological classification of dysplasia

Colitis-associated dysplasia is differentiated based on the architectural and cytological features of the epithelium. According to the architecture three different types of dysplasia are distinguished, namely adenomatous, villous or serrated, of which the last one is the most recently discovered type of dysplasia.

Adenomatous dysplasia

Based on the morphological appearance of the epithelium, adenomatous dysplasia was originally subtyped

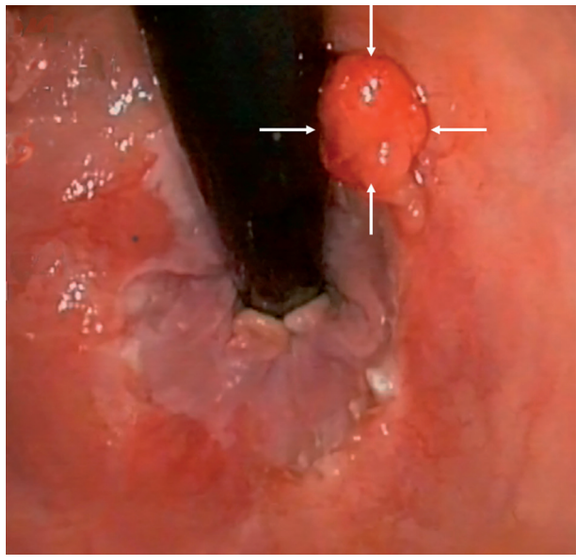

Fig. 2. — Colitis-associated dysplasia: Endoscopic picture of a polypoid dysplasia in the neighborhood of the anorectal junction, corresponding to an intramucosal adenocarcinoma on surgical specimen.

into negative for dysplasia, indefinite for dysplasia and positive for dysplasia (low and high grade dysplasia) (Fig. 3a) (41). In contrast to this early classification, the Vienna classification grades dysplasia in to four categories : 1. Negative for neoplasia/dysplasia ; 2. Indefinite for neoplasia/dysplasia ; 3. Non-invasive low grade neoplasia and 4. Non-invasive high grade neoplasia (42). The term indefinite for dysplasia is applied in case no distinction can be made between regenerative epithelium and low grade dysplasia because of the degree of inflammation or because of technical reasons such as inadequate sampling or poor orientation of the biopsy. The distinction between both conditions is based on architectural and cytological features, the presence of surface maturation and inflammation (43). Several studies however have shown that the diagnosis of indefinite for dysplasia ($\varkappa$ 0.25-0.27) and low grade dysplasia ($\varkappa$ 0.23-0.51) is associated with a high interobserver variability (44, 45). This problem may eventually be solved by performing immunohistochemical analysis with p53 or A-Methylacyl-CoA Racemase (AMACR), showing an increased expression in function of the degree of dysplasia. However expression of these markers in normal or reactive mucosa limits their diagnostic utility (46-48). Hence the ECCO guidelines recommend to confirm the diagnosis of dysplasia by an independent expert GI pathologist (49). Confirmation of the diagnosis of low grade dysplasia by an expert panel of gastrointestinal pathologists may impact the risk of development of high grade dysplasia and colorectal cancer (50).

The diagnosis of low grade dysplasia is based on cytological features, involving the epithelium of the surface and the basis of the crypts (Fig. 3b). The pseudostratified epithelium has basally situated enlarged and hyperchromatic nuclei, maintaining normal polarity.

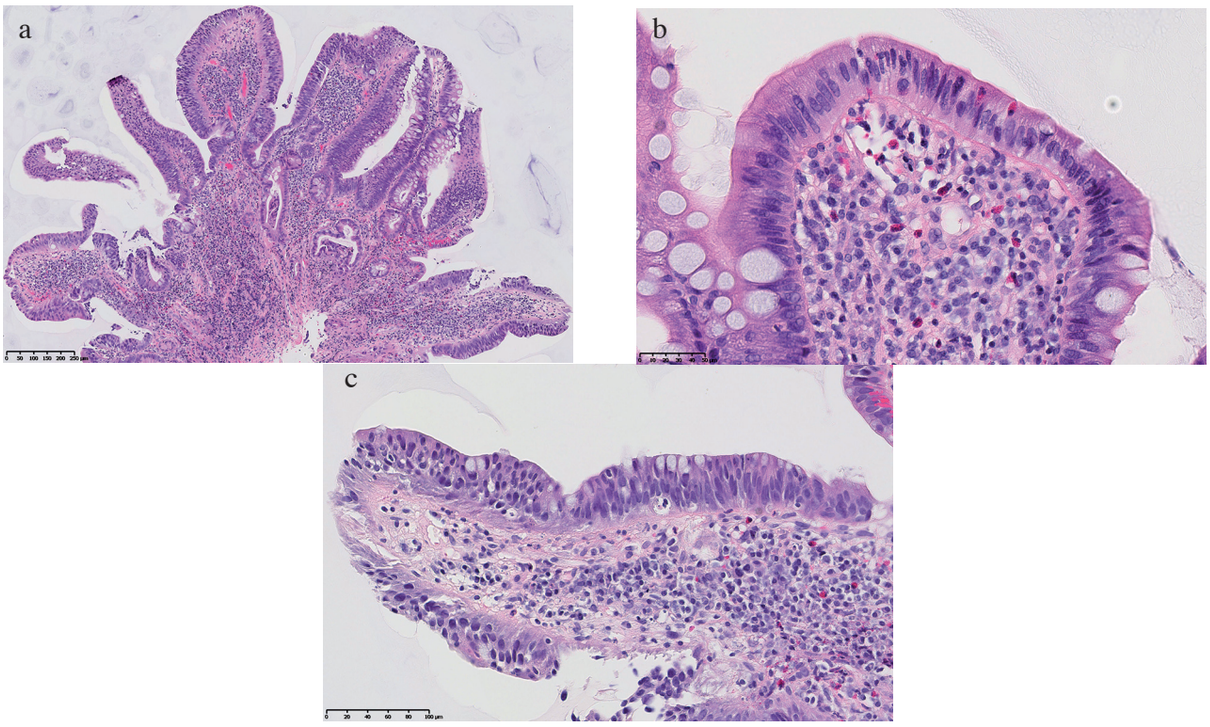

Fig. 3. — Colitis-associated dysplasia: Polypoid dysplasia (a, HE, 8.3X) with an adenomatous type of dysplasia, consisting of areas of low grade dysplasia, showing a pseudostratified epithelium with mild cytologic atypia (b, HE, 40X) and high grade dysplasia, characterized by a pseudostratified epithelium with nuclear polymorphisme (c, HE, 31X), in stead of original text.

In contrast to the normal situation the atypical epithelium loses its nuclear maturation at the surface.

In high grade dysplasia the epithelium shows pseudostratification with nuclear polymorphism. Elongated nuclei are not only present basally but also apically in the epithelial cells. The enlarged nuclei have prominent nucleoli and atypical mitotic figures (Fig. 3c). Besides cytological atypia high grade dysplasia is characterized by an abnormal architecture with a cribriform pattern. Similar to low grade dysplasia the surface epithelium shows no maturation. The cytological and architectural features are so obvious that the diagnosis of high grade dysplasia for pathologists is in general not a problem, resulting in a low interobserver variability (51). In biopsies it is commonly accepted that at least three crypts should be affected to confirm the diagnosis of high grade dysplasia (41).

Adenomatous dysplasia, occurring in the background of inflamed mucosa, shows some resemblance with sporadic adenoma but in contrast there is more glandular disarray. The irregular glands vary in size and diameter and are surrounded by a variable amount of loose stroma, infiltrated by inflammatory cells. The glands have a stratified epithelium, but in contrast to the sporadic adenoma, this epithelium has a bottom-up appearance : dysplasia starts from the basis of the crypt, extending upwards to the surface. Hence at the surface there is an admixture of normal and dysplastic glands. The epithelium is characterized by pleiomorphic and hyperchromatic nuclei. The mucus differentiation may vary with sometimes presence of dystrophic goblet cells (52-55). In contrast to sporadic adenomas these lesions may have a more tubulovillous or villous appearance (53).

Whereas adenomatous dysplasia is the most common type of cytologic dysplasia, there are other extremely rare types of cytologic dysplasia, such as oncocytic dysplasia and clear cell dysplasia. Whereas oncocytic dysplasia is characterized by an eosinophilic appearance of the atypical cells, in case of clear cell dysplasia the atypical cells have a mucus-poor vacuolized cytoplasm. Both types of dysplasia are uncommon in inflammatory bowel disease and have been described in other conditions such as colon polyps, gastric and colon cancer (52, 56-59).

Villous dysplastic lesions

Villous dysplastic lesions are found in the neighborhood of colitis-associated cancer (60). The study of Andersen et al. has shown that mucosal lesions with a villous, hypermucinous appearance are associated with a high number of *KRAS* mutations (61). Villous dysplasia is an ominous sign as it can be associated with a coexistent carcinoma. Hence in the past the finding of villous dysplasia has been an indication to perform proctocolectomy (62).

Serrated changes

In contrast to adenomatous and villous dysplasia, serrated dysplasia is even more common. The study of

Rubio et al. has shown that serrated adenomatous changes are more prevalent in patients with colitis-associated cancer (29%) than in the control population (3%) (60).

Serrated adenomatous changes can be found in the neighborhood of the colitis-associated cancer. They are a precursor, associated with an increased risk to develop malignancy (8, 60, 63). Colitis-associated cancer is more prevalent in association with a serrated polyp with low grade dysplasia, resembling a traditional serrated adenoma and associated with *KRAS* mutations, than in case of serrated polyp without dysplasia, resembling a serrated polyp/adenoma and harboring *BRAF* mutations (8). The study of Jackson et al. has confirmed these results showing that IBD patients with a sessile serrated adenoma have an increased risk for synchronous multifocal visible dysplasia as well as early metachronous visible dysplasia (64). In contrast to the serrated polyps, the significance of serrated epithelial changes, observed in the mucosa of IBD patients, is less clear. Serrated epithelial changes are hyperplastic mucinous or flat serrated alterations. Although they can be associated with subsequent development of colorectal cancer, further studies are needed to evaluate if serrated epithelial changes should be considered as precancerous lesions (65,66)

Surveillance

Because of the risk to develop colorectal cancer, regular endoscopic surveillance is recommended in ulcerative colitis and Crohn patients. Despite this surveillance patients are at risk to develop interval colorectal cancers, defined as a tumor developed in the time between a negative colonoscopy and before the date of the next recommended colonoscopy (67). Interval colorectal cancers account for 30 to 50% of the tumors, detected by coincidence in IBD patients (68, 69). Although endoscopist-related factors such as missing the lesion or incomplete resection of the lesion, may be an explanation of the high prevalence of interval colorectal cancers, the biological behavior of the tumors differs from sporadic tumors with an accelerated progression from inflammation to invasive tumor. Moreover the endoscopic detection of early lesions is hampered as dysplasia frequently presents as a flat lesion. Hence international guidelines are published in which a regular endoscopic surveillance with adequate mucosal sampling of the intestine is recommended (70). The aim of surveillance is to detect the neoplastic lesions at an early stage in order to reduce the morbidity and mortality secondary to colorectal cancer and to improve the prognosis of IBD patients. The study of Lutgens et al. has shown that colonoscopic surveillance is associated with an improved survival by detection of colorectal cancer at an earlier tumor stage compared to the non-surveillance group (71). Duration of the colitis is a major risk factor for development of colorectal cancer. Hence the ECCO guidelines recommend to perform screening colonoscopy 6 to 8 years after initiation of the disease in order to determine the risk profile of the patient (72). Despite this recommendation with a well-delineated interval between initiation of the disease and the first screening colonoscopy 17 to 28% of the IBD patients develop cancer in this period (73). In contrast to the European guidelines, the American guidelines make a distinction based on the time of first screening colonoscopy in function of the extent of the colitis : as in pancolitis the risk of malignancy is higher, screening surveillance is recommended after 8 years in contrast to left-sided colitis, where the first screening should be performed not earlier than 15 years after the first symptoms (74). In the ECCO guidelines no screening colonoscopy is recommended in case the inflammation is restricted to the rectum (72). During follow-up the interval between successive screening colonoscopies will vary in function of the risk factors. High risk factors, such as primary sclerosing cholangitis and a family history of colorectal cancer, are associated with a one or two-yearly interval (72).

The pathway towards invasive carcinoma is however not straight forward, as patients without prior diagnosis of dysplasia or without progression from low grade to high grade dysplasia may present with cancer (75, 76). Colorectal cancer may even arise directly from indefinite for dysplasia with 5 year-progression of 9% (77). The study of Lai et al. has shown that in patients with a diagnosis indefinite for dysplasia, the colectomy specimen revealed dysplasia in 27.3%, mainly high grade dysplasia (83%), within 6 months after diagnosis. During follow-up, dysplasia was found in 25.3%, of which nearly half of the cases advanced neoplasia (44%) (78). In these biopsies molecular analysis revealed DNA aneuploidy, which is a predictor for detection of neoplasia (79). Based on these observations the distinction between indefinite for dysplasia, probably negative and indefinite for dysplasia, probably positive, as recommended by Riddell et al., may be an aid in the therapeutic management of the patients (41). Accurate diagnosis of low grade dysplasia is essential, as it is a strong predictor of progression towards advanced neoplasia with a 54% rate of progression towards high grade dysplasia or colorectal cancer (80). Patients with low-grade dysplasia carry a 12-fold increased risk to develop high grade dysplasia or colorectal cancer, compared to those patients without dysplasia during surveillance (81). Synchronous high grade dysplasia or colorectal cancer is observed in 20% to 27% of the patients undergoing a colectomy immediately or within 6 months after diagnosis of low grade dysplasia (75, 80). Studies have shown that the location of low grade dysplasia is important as distal low grade dysplasia, which is more common, progresses more rapidly to cancer than proximal low grade dysplasia (82, 83). A pooled analysis by Choi et al. demonstrated a distal predominance for ulcerative colitis-associated colorectal cancers (84). A recent study confirmed that the frequency of progression of low grade to high grade dysplasia or cancer is low (4.9%) but flat low grade dysplasia located

in the distal colon is associated with a greater risk of progression to high grade dysplasia or cancer. Distal colonic low grade dysplasia showed an incidence rate for high grade dysplasia or cancer of 2.1 cases per 100 person years at risk while proximal low grade dysplasia had an incidence of 0.5 cases per 100 person years (85). Consequently, it is recommended that more biopsy specimens should be taken from the rectosigmoid colon during follow-up colonoscopy (86). In contrast to the significance of distal low grade dysplasia, contradictory results have been published about the association between multifocal low grade dysplasia and the risk of advanced neoplasia (75,87).

How to improve the detection of dysplasia?

Optimal detection of pre-neoplastic lesions in inflammatory bowel disease is dependent on an adequate bowel preparation, a meticulous inspection with a slow withdrawal and the application of advanced endoscopic imaging techniques (88, 89). Whereas polypoid lesions are easily visible with standard white-light endoscopy, non-polypoid lesions are easily missed, as these lesions can present as a red spot or granular lesion in the inflamed mucosa. Detection and characterisation of these lesions may be improved by performing more advanced endoscopic imaging techniques, such as chromoendoscopy, high-resolution magnification endoscopy or confocal endomicroscopy.

Before the discovery of advanced endoscopic imaging techniques numerous random biopsies had to be taken during surveillance colonoscopy. The study of Rubin et al. has shown that at least 33 random biopsies should be taken in order to exclude or diagnose dysplasia with a 90% confidence, and in case a 95% confidence is aimed even 56 biopsies should be sampled during each control colonoscopy (90). As dysplasia is frequently multifocal the ECCO-guidelines recommend to take 4 biopsies every 10 cm of the entire colon and additional biopsies from macroscopically visible lesions, if white light endoscopy is performed (49, 72). However despite the fact that neoplasia may be visible during colonoscopy, the diagnostic yield of random biopsies is low. In the retrospective study of Van den Broek et al., in 88 of 466 conventional colonoscopies, performed during surveillance of longstanding UC patients, intraepithelial neoplasia has been detected. The diagnostic yield is however significantly higher in targeted biopsies (75 colonoscopies, 85%), than in random biopsies (5 colonoscopies, 5.7%) or a combination of both random and target biopsies (8 colonoscopies, 9.1%)(91). Despite the detection rate is higher in case of white light endoscopy combined with targeted biopsies, more advanced endoscopic methods, in particular chromoendoscopy, may be superior to detect dysplasia (92). Hence the ECCO-guidelines recommend the use of chromoendoscopy with targeted biopsies by a well-trained endoscopist during the surveillance for dysplasia in IBD patients (72).

Chromoendoscopy is a dye-based enhanced endoscopic technique, in which dyes such as indigo carmine and methylene blue are sprayed into the intestine. Studies have shown that chromoendoscopy is superior to conventional white light endoscopy in the detection of dysplasia in ulcerative colitis patients (93). A recent meta-analysis, performed on 6 studies, has demonstrated that chromoendoscopy has a medium to high sensitivity and a high diagnostic accuracy in the detection of dysplasia in ulcerative colitis patients (94). Hence the application of this endoscopic technique is incorporated in the European surveillance guidelines (88). However this technique has some disadvantages as its accuracy depends on adequate bowel cleaning and the equal spreading of the dye. It is a time- and cost intensive method requiring some experience of the endoscopist. Moreover the ab-sorbed dyes are potentially genotoxic. Therefore a dye-less technique has been developed, namely digital virtual chromoendoscopy or electronic-based, imaging-enhanced endoscopic techniques such as narrow band imaging (NBI, Olympus), i-scan (Pentax) or Fujinon Intelligent Colour Enhancement (FICE, Fujinon). The aim of these enhancements-methods is to pronounce the vascular changes and superficial changes to the mucosal surface either by using a filter reducing the white light to the blue and green spectrum during the endoscopy, or by applying postprocessing spectrumanalysis software to enhance the image features. The diagnostic accuracy of these imaging-enhanced endoscopic techniques has only been assessed for narrow band imaging, showing that this method has no advantage in the detection of neoplasia compared to white light endoscopy (95).

High-definition endoscopes have a significant higher resolution and a wider field of view than standard endoscopes (96). Compared to white light endoscopy the study of Subramanian et al. has shown that high definition endoscopy has a 3-fold higher detection rate in IBD patients under surveillance (97). Its higher resolution leads to comparable detection rate of dysplastic lesions as chromoendoscopy, with a better delineation of the border of the lesions.

Confocal laser endomicroscopy (CLE) is a new method used for in vivo imaging of mucosal abnormalities at a subcellular level. It has a high diagnostic accuracy to detect neoplastic changes in ulcerative colitis patients as the study of Kiesslich et al. has shown that in combination with chromoendoscopy the detection rate shows a nearly 5-fold increase despite fewer biopsies were taken (98). It differentiates non adenoma like dysplastic lesions from true adenomas in UC with a high accuracy (97%) and shows an excellent diagnostic agreement with histology (99). This method helps to characterise visible lesions, but is too detailed and time consuming to be used as a screening method throughout the entire colon. The results of these studies need to be reconfirmed, as these studies are based on the use of an endoscope- based CLE, which is however no longer commercially available. The application of CLE is nowadays restricted to single,

most often academic centres, because it is a very costly, time-consuming method. Moreover its use is restricted to research and not indicated for routine clinical use (100).

Treatment

The improvement of endoscopic techniques has increased the adequacy to remove dysplastic lesions in the colon. Treatment is determined by the endoscopic visibility of the lesion, its endoscopic resectability and the appearance of the surrounding mucosa (Fig. 4).

An endoscopic resectable lesion is a well-delineated lesion, which after resection seems completely removed during endoscopic inspection and confirmed by histological examination of the resection specimen (lateral and deep margins). Biopsies are taken from the surrounding mucosa of the dysplastic lesion to exclude the presence of a residual dysplastic lesion or an associated non visible dysplasia, which is endoscopically more difficult to diagnose. Important is that these biopsies are free of dysplasia on histological examination. Therefore a polypoid lesion without dysplasia in the surrounding mucosa can be treated by endoscopic polypectomy, even if high grade dysplasia is diagnosed in the lesion. Follow-up studies have shown that polypectomy of a polypoid lesion is an appropriate treatment on condition that the lesion is completely resected (55, 101-103).

Since many years, the treatment of a high grade non-polypoid dysplasia consisted only of a proctocolectomy because of the high risk of a synchronous colorectal cancer, present in 42 to 67% of the cases (86). Now, the treatment is more elaborate. If the high-grade non-polypoid dysplasia is a solitary lesion, endoscopic resection, either mucosal or submucosal, of which the latter is done in specialized centres, can be performed on condition that the lesion is completely removed with negative deep and lateral section margins (104).

The choice of therapy in case of low grade non-polypoid dysplasia is determined by the same conditions, namely completeness of resection and unifocal versus multifocal disease. A proctocolectomy is recommended in case of multifocal disease or if complete resection is not feasible (105). Surveillance should consist of a meticulous follow-up with colonoscopies with biopsies on a regular base. The frequency of surveillance is determined by the size of the lesion (≥ 1 cm), the presence of villous dysplasia and high-grade dysplasia, and family history of colorectal cancer, in which it should be scheduled within 3 years after complete resection of the lesion (105). Patients should however be aware of the risk : in case of low grade dysplasia they have a nine-fold increased risk for colorectal cancer and a twelve-fold risk for advanced neoplasia (invasive tumor and high grade dysplasia) (81). A proctocolectomy is warranted in a young patient with primary sclerosing cholangitis and multifocal low grade dysplasia because of the higher risk to develop cancer (106).

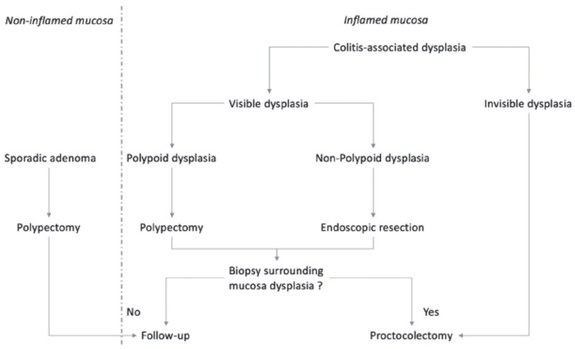

Fig. 4. — Treatment scheme adapted in function of the new endoscopic approach of colitis-associated dysplasia.

In case of endoscopically invisible dysplasia, even low grade dysplasia, detected by coincidence in random biopsies, a proctocolectomy is the only therapy of choice, to be discussed with the patient.

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