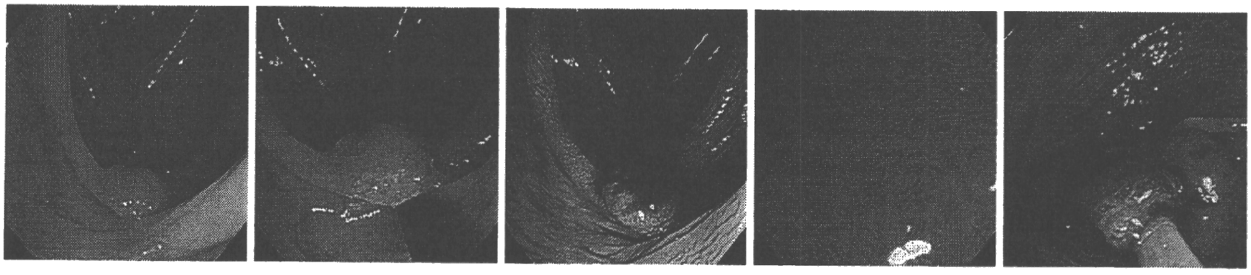

Figure 1 The lesion was located in the transverse colon. Endoscopic examination revealed a flat, elevated lesion with a central depression, which was macroscopically diagnosed as 0-Ⅱa+Ⅱc. The high-magnification view revealed a typical type Ⅵ pit (invasive) pattern on the depressed margin. The final endoscopic diagnosis was a 0-Ⅱa+Ⅱc type early colon cancer with submucosal deep invasion. However, patient strongly hoped EMR as an initial treatment. We performed EMR after injecting normal saline into the submucosa.

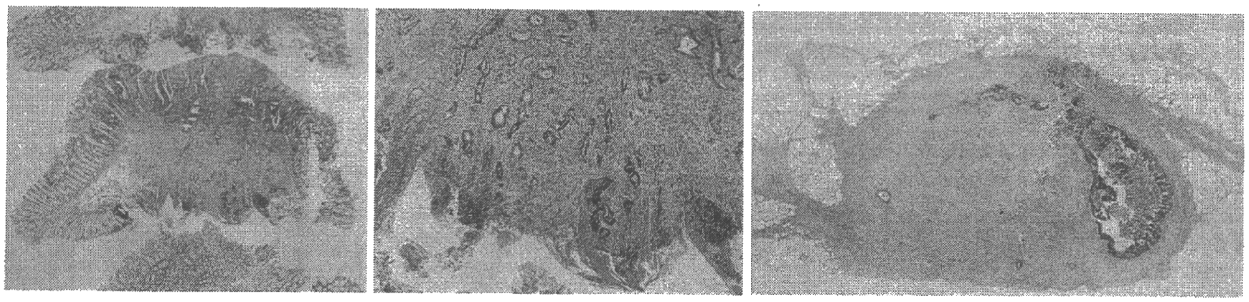

Figure 2 The final histopathological diagnosis was early invasive colon cancer, well-differentiated adenocarcinoma, sm-deep, NPG type, ly (-), v (-), cut end (+) (vertical margin positive). Since cancer was exposed in the vertical cut margin, additional surgical resection was performed and LNM was detected.

size[4,28-31]. Kurisu *et al*[20] have investigated the development and progression of EI-CRC. In that study, NPG lesions were significantly smaller in size (14.2 mm *vs* 24.2 mm) but showed deeper infiltration than PG types. They concluded that tumor development and the degree of invasion differed significantly between the two types of carcinoma. On the other hand, non-polypoid colorectal neoplasms (NP-CRNs) have been reported recently in the United States. Soetikno *et al*[31] have reported the prevalence of NP-CRNs in a veterans' hospital population. The overall prevalence of NP-CRNs and NP-CRNs with in situ or submucosal invasive carcinoma was 9.35% and 0.82%, respectively. They also concluded that NP-CRNs were more likely to contain carcinoma (OR: 9.78) than polypoid lesions, regardless of size. In the present study, small EI-CRCs ≤ 10 mm in diameter showed a significantly higher incidence of NPG type lesions than in the large lesion group ($P < 0.0001$). However, there was no significant difference in proportion of the macroscopic type between the groups ($P = 0.13$). Among the lesions diagnosed as Is type (sessile) in the small lesions group, 47% (14/30) were classified as NPG type histopathologically. From these results, we conclude that further investigation is required to confirm the growth pattern, especially for small sessile lesions diagnosed during colonoscopy.

In contrast, the rate of EMR as an initial treatment was 33% (195/583) in our study. In particular, it was significantly higher in the small lesion than the large lesion group (52% *vs* 29%, $P < 0.0001$). Among the 195 lesions removed by EMR as an initial treatment in both groups, 61 cases (32%) were sm-superficial cancers. On the other hand, there was no significant difference in the positive rate of cut margins between the small and large lesion groups (18% *vs* 20%). This result implies that EMR should not be performed readily for EI-CRC, from the viewpoint of no-touch isolation[32] and EMR complications. Intramucosal lesions (adenoma or intramucosal cancer) are usually well lifted by submucosal injection. In contrast, invasive cancer, especially sm-deep cancer, cannot be lifted because of the presence of submucosal fibrosis or desmoplastic reaction. Uno *et al*[33] have reported this phenomenon as the "non-lifting sign". Kobayashi *et al*[34] have reported, among 271 colorectal neoplastic lesions, that the non-lifting sign of deeper infiltration had a sensitivity of 61.5%, specificity of 98.4%, and accuracy of 94.8%. In contrast, endoscopic diagnosis had a sensitivity of 84.6%, specificity of 98.8%, and accuracy of 97.4%, with statistically significant differences in terms of sensitivity and accuracy. Furthermore, since submucosal injection varies depending on the expertise of the endoscopist, we consider that an endoscopic diagnosis is much more important and accurate when endoscopic resection is considered as the therapeutic option.

There are some limitations to this study. Firstly, this was a single-center study, and although the number of examined EI-CRCs was adequate, a multicenter analysis should be performed to clarify the clinical importance of small EI-CRCs. In addition, this study was carried out retrospectively between 1980 and 2004. In relation to endoscopic treatment for early CRC, endoscopic submucosal dissection (ESD) technique and Glycerol/Sodium hyaluronate as an injected solution during EMR has made progress recently[35,36]. In particular, ESD provides not only an *en bloc* large specimen but also

negative lateral and vertical cut margins.

In conclusion, with regard to the risk of LNM, small EI-CRCs demonstrate the same aggressiveness and malignant potential as large lesions. Moreover, from the perspective of the concept of no-touch isolation, therapeutic cost, and complications during EMR, special attention must be paid when treating even small early stage lesions, especially NPG type lesions.

COMMENTS

Background

In general, small colorectal lesions are suspected of having a lower malignant potential than large ones, and hence are easy to remove endoscopically. Several authors have reported that the malignant potential of early invasive colorectal cancer (EI-CRC) increases with lesion size.

Research frontiers

The aim of this retrospective study was to clarify the clinicopathological characteristics of small (≤ 10 mm) and large (> 10 mm) EI-CRCs.

Innovations and breakthroughs

A total of 583 EI-CRCs were evaluated retrospectively, with 120 (21%) small and 463 (79%) large lesions identified. With regard to the risk of lymph-node metastasis (LNM), small EI-CRCs demonstrate the same aggressiveness and malignant potential as large lesions.

Peer review

The authors examined retrospectively a large group of patients with EI-CRCs gathered over 20 years in a national cancer hospital, and demonstrated that small EI-CRCs (≤ 10 mm) had the same aggressiveness and malignant potential as large cancers. Special attention must be paid when treating even small lesions.

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SPECIAL ARTICLE

Pragmatic classification of superficial neoplastic colorectal lesions (CME)

René Lambert, MD, FRCP, Shin ei Kudo, MD, Michael Vieth, MD, PhD, John I. Allen, MD, Hiroaki Fujii, MD, Takahiro Fujii, MD, Hiroshi Kashida, MD, Takahisa Matsuda, MD, Masaki Mori, MD, PhD, FACS, Hiroshi Saito, MD, Tadakazu Shimoda, MD, Shinji Tanaka, MD, Hidenobu Watanabe, MD, Joseph J. Sung, MD, Andrew D. Feld, MD, John M. Inadomi, MD, Michael J. O'Brien, MD, David A. Lieberman, MD, David F. Ransohoff, MD, Roy M. Soetikno, MD, Ann Zauber, PhD, Claudio Rolim Teixeira, MD, Jean Francois Rey, MD, Edgar Jaramillo, MD, Carlos A. Rubio, MD, PhD, Andre Van Gossum, MD, Michael Jung, MD, Jeremy R. Jass, MD[+], George Triadafilopoulos, MD, DSc

Tokyo, Yokohama, Beppu, Hiroshima, Niigata, Japan, Shatin, Hong Kong, China, Minneapolis, Minnesota, Seattle, Washington, San Francisco, Palo Alto, Stanford, California, Boston, Massachusetts, Portland, Oregon, Chapel Hill, North Carolina, New York, New York, USA, Rio Grande do Sul, Brazil, Lyon, Saint Laurent du Var, France, Brussels, Belgium, Stockholm, Sweden, Bayreuth, Mainz, Germany, Harrow, England

Recently, the emerging role of nonpolypoid precursors of colorectal cancer has challenged the conventional polyp-cancer sequence. The impact of colonoscopy in cancer prevention depends on its reliability in the diagnosis of colorectal neoplasia when the lesion does not extend beyond the submucosa and is potentially curable. The estimation of the risk of progression is based on the prediction of histology from the morphological appearance of the lesion and includes (1) distinction between neoplastic and non-neoplastic lesions, (2) identification of different categories of nonserrated and serrated lesions, and (3) determination of the localization in the proximal or distal colon, which has an impact on the morphology and behavior of the lesion. The pragmatic classification of superficial neoplastic lesions proposed in this text takes into account these changes and is based on a 2-step strategy of endoscopic diagnosis with initial detection and characterization, followed by treatment implementation, such as endoscopic resection, ablation, and surgery.

INTRODUCTION

Neoplastic lesions in the esophagus, stomach, colon, and rectum are called superficial when invasion is limited to the mucosa or submucosa; their gross morphology is described as polypoid and nonpolypoid subtypes according to the Paris classification.[1] The specific role of nonpolypoid precursors in colorectal carcinogenesis has been analyzed by the same group of authors during the Kyoto workshop in February 2008.[2] Until recently, it was assumed that all neoplastic lesions of the colorectal mucosa developed through the unique adenoma-carcinoma sequence[3,4] and a sequence of mutations involving *APC* inactivation, K-*ras* mutation, and *TP53* inactivation.[5] These theories have now been challenged by the demonstration that serrated lesions provide an alternative pathway between neoplastic and non-neoplastic lesions.[6] New molecular approaches, based on microdissection and DNA sequencing with polymerase chain reaction, have complicated the framework of distinct colon cancer classes and genomic profiles. Furthermore, the ability to detect and classify the surface of neoplastic lesions, with or without the help of chromoendoscopy, has increased with high-resolution video colonoscopes[7] that offer not only magnification but also image enhancement, such as narrow-band imaging (NBI).

Good practice in endoscopic diagnosis and treatment of colorectal mucosal lesions relies on a comprehensive classification that integrates morphological features with lesion location (proximal or distal colon), surface microarchitecture, molecular markers, and histopathology. The objective of a pragmatic classification of the morphological appearance of lesions detected at endoscopy with prediction of histopathology is the estimation of the risk of progression and therefore the selection of an appropriate treatment. This pragmatic classification applies to neoplastic lesions arising from colonocytes unaltered by chronic inflammation and does not apply to specific situations such as neoplasia in inflammatory bowel disease or those arising from hamartomatous syndromes such as familial juvenile polyposis or Peutz-Jeghers syndrome.

Abbreviations: ACF, aberrant crypt foci; CIMP, CpG island methylator phenotype; CIN, chromosomal instability; FAP, familial adenomatous polyposis; HNPCC, hereditary nonpolyposis colon cancer; HP, hyperplastic polyp; IEN, intraepithelial neoplasia; LST, laterally spreading type; MGMT, methylguanine-DNA methyltransferase; MMR, mismatch repair gene; MSI, microsatellite instability; MSS, microsatellite stability; NBI, narrow-band imaging.

DISCLOSURE: *All authors disclosed no financial relationships relevant to this publication.*

[+]In memoriam.

See CME section; p. 1158.

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This study is based on our knowledge of genomic profiles, first steps in colorectal carcinogenesis, and distinct categories of lesions in the nonserrated and serrated pathways. A strategy of endoscopic diagnosis with prediction of histopathology and treatment for colorectal lesions with a superficial appearance is then proposed. The pragmatic classification takes into account for each category of nonserrated and serrated lesions the risk of progression to invasive cancer. The final part of this study recalls the prevalence of lesions in endoscopic series and the distinct characteristics of proximal and distal neoplastic lesions.

GENOMIC PROFILES IN COLORECTAL CARCINOGENESIS

Colorectal neoplastic lesions do not develop through a single molecular profile but instead from various types of genomic alterations involving gene transcription as well as epigenetic alterations.[8-10]

Genetic alterations

Two categories of instability are mutually exclusive. Chromosomal instability (CIN) develops after the inactivating mutation of the *APC* tumor suppressor gene with disruption of the Wnt signaling and affects whole or parts of chromosomes, resulting in aneuploidy and activation of oncogenes (*K-ras*, *BRAF*) or inactivation of suppressor genes (*TP53*). CIN is classified as present or absent (CIN positive or CIN negative, respectively). Microsatellite instability (MSI) develops after an inactivating mutation in the mismatch repair (MMR) genes (*MLH1*, *MSH2*) and results in multiple mutations and deletions. MSI is classified as absent (MSS), high (MSI high), or low (MSI low).

Epigenetic alterations

Epigenetic alterations are based on hypermethylation in the promoter region of multiple genes; this region is particularly rich in cytosine-guanine dinucleotides linked by a phosphodiester bond called CpG islands. Epigenetic hypermethylation characterizes the methylator phenotype called CpG island methylator phenotype (CIMP), which is linked to the initial mutation of the *BRAF* oncogene, expressing a protein with *BRAF* kinase activity. A high degree of aberrant promoter hypermethylation will cause silencing of multiple genes including the 6-0-methylguanine-DNA methyltransferase (MGMT) repair gene. The CIMP phenotype is classified as negative (CIMP negative), high (CIMP high), or low (CIMP low).

Genomic profiles

Several diseases have emerged, and they involve lesions developed in the nonserrated adenoma-carcinoma sequence and those developed through the serrated pathway.[8] This distinction also applies to the precursors of colorectal cancer (ie, superficial neoplastic and non-neoplastic lesions), given that molecular events occur early (Fig. 1). The genomic profile has an impact on clinical, pathological, and biological features and is described by the status of CIN, MSI, CIMP, and the initial mutations of K-*ras*, and *BRAF* oncogenes.[11-19] The clinical outcome of the CIMP-high status is associated with a better prognosis; the same also applies to the MSI-high status.[19] The profile CIMP high, MSI high, *BRAF* mutation suggests a serrated lesion. The profile CIMP-negative, MSS, CIN positive suggests a nonserrated lesion.

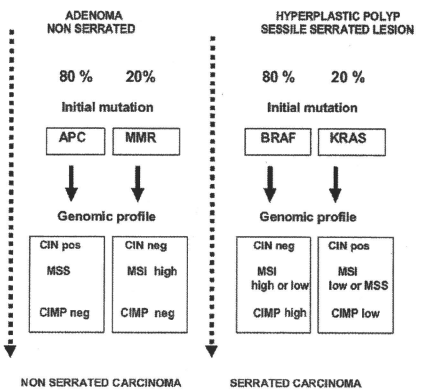

Figure 1. Initial mutations and genomic profiles in the progression to carcinoma in nonserrated and serrated neoplastic lesions. The genomic profile includes mutations of oncogenes and suppressor genes, chromosomal instability (CIN), microsatellite stability or instability (MSS and MSI), and CpG island methylator phenotype (CIMP). The degree high or low of MSI has relevance to prognosis.

EARLY CHANGES FOR NEOPLASIA

Altered homeostasis in the mucosa

Homeostasis of the intestinal crypts of the colorectal mucosa depends on the balance between cell multiplication in the basal segment, upward cell migration, and surface apoptosis (ie, a genetically programmed process of cell death). An imbalance follows the increased cell multiplication shown by the positive reaction to Ki-67 antibody MIB-1, and the progressive inhibition of surface apoptosis, controlled by the *Bcl-2* gene and the antiapoptosis protein survivin. Two mechanisms have been put forward for the progression from a monocryptal event to a macroscopically visible lesion: (a) the top-down theory of Shih and Vogelstein that proposes that the abnormal cells born at the base of one crypt migrate to the surface, expand laterally, and fill adjacent crypts from top to bottom and (b) the bottom-up theory of Tomlinson and Wright, that proposes that stem cells at the crypt base colonize in a second hit the entire crypt and that lateral expansion occurs by crypt fission.

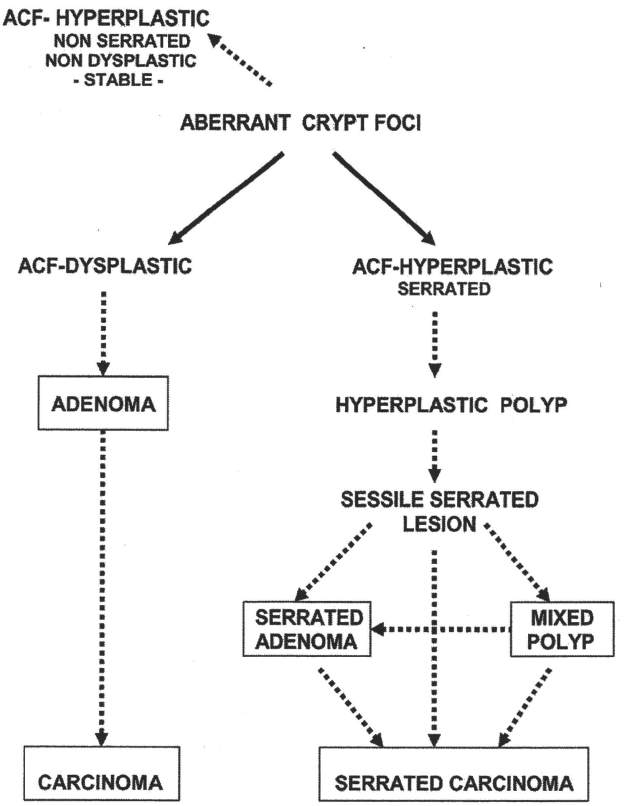

Figure 2. Progression from aberrant crypt foci (ACF) to carcinoma in the adenoma-carcinoma sequence and in the serrated pathway. The progression of non-neoplastic sessile serrated lesions to serrated carcinoma may occur directly or through serrated adenomas or mixed polyps.

Role of aberrant crypt foci

The disruption of homeostasis in the colonic mucosa preferentially occurs in small clusters of enlarged crypts that are called aberrant crypt foci (ACF). As shown in Figure 2, their structure may be metaplastic or dysplastic. Dysplastic ACF are precursors in the nonserrated pathway of neoplasia; metaplastic ACF are precursors in the serrated pathway of neoplasia. Their potential as a source of nonserrated neoplastic lesions is still controversial.[6]

Morphological development of a lesion

A neoplastic premalignant lesion associates structural changes with crypt crowding, lateral expansion of the basal segment, cytological alterations and cell atypia exhibiting loss of cell polarity, increased nuclear size, and cell stratification in multiple rows. The gross morphology of the lesion is determined by the predominant direction of growth; upward progression in polypoid or nonpolypoid and nondepressed lesions, downward progression in the case of nonpolypoid depressed lesions, and transverse progression for laterally spreading types (LSTs) of lesions. Progression in mixed directions leads to combined patterns.

Intraepithelial neoplasia

An adenoma is confined to the epithelial compartment of the mucosa, without invasion beyond the basal membrane. It is further classified as tubular, tubulovillous,

and villous by its architectural pattern and as low or high grade by the cytological atypia in tissue sections. This condition, formerly called dysplasia, is now called intraepithelial neoplasia (IEN) in the modified World Health Organization classification of GI tumors and was coined in reference to the absence of invasion into the lamina propria mucosae and/or submucosa (stroma). *APC* and K-*ras* mutations, which are frequent in polypoid lesions, are found less frequently in nonpolypoid and in depressed lesions.

NONSERRATED PATHWAY TO COLORECTAL CANCER

Intramucosal carcinoma

A carcinoma is characterized by (1) high-grade cell atypia, high nucleus-to-cytoplasm ratio, swollen nuclei with enlarged nucleoli, and loss of nuclear polarity; (2) altered cribriform architecture of the crypts with many branches and lateral expansion; and (3) invasion into the lamina propria (eg, junction between 2 neighboring tubules, sprouting of single neoplastic cells or small neoplastic cell nests). Breakthroughs across the epithelial basal membrane cannot be observed in well-differentiated lesions because these are capable of building their own basal membrane. Single tumor cells are mostly observed in more advanced tumors. When the alterations are restricted to the mucosa without crossing the muscularis mucosae, the lesion is classified as intramucosal carcinoma in the category 4-4 of the Vienna classification, as already introduced in the esophagus, stomach, and small bowel.

Submucosal carcinoma

When there is submucosal invasion, the risk of lymph node metastasis and/or progression to advanced cancer is estimated as low or high, depending on the degree of extension of the invasion. The assessment of invasion is reliable in surgical specimens involving the full thickness of the colonic wall. After endoscopic resection of stalked lesions, a semiquantitative estimation of submucosal invasion is possible by using the Haggitt levels from 1 (invasion of submucosa limited to head of polyp) to 4 (invasion of submucosa beyond the stalk). The Japanese school has worked particularly on the analysis of specimens after endoscopic resection of sessile and nonpolypoid neoplastic lesions.[20] The semiquantitative methods are based on 3 progressive levels (sm1, sm2, sm3) for depth of invasion and 3 progressive levels (sm1a, sm1b, sm1c) for lateral extension in the more superficial layer of the submucosa. Carcinomas classified as sm1a or sm1b are slightly invasive (sm-s). Carcinomas classified as sm1c, sm2, or sm3 are massively invasive (sm-m). The measure in micrometers of the depth of invasion in the submucosa from the lower part of the muscularis mucosae is a more precise quantitative method; a lesion is called low risk when the invasion is 1000 μm or less and high-risk when the invasion exceeds this limit. Additional criteria for high-risk lesions are the budding or tumor cell dissociation at the invasive front and the presence of lymphatic and venous involvement.

Grading of carcinoma

In the World Health Organization classification of colon cancer, the carcinoma is classified according to cytological and structural criteria in 4 categories: (1) well differentiated, (2) moderately differentiated, (3) poorly differentiated, and (4) undifferentiated. In addition to this classification, the Japanese school of neoplasia grading established for differentiated carcinoma only a subdivision based on the grade of cell atypia.[21] Differentiated carcinomas with low-grade cell atypia have a better prognosis than those with high-grade cell atypia, which tend to rapidly invade of the digestive wall.

De novo carcinoma

This corresponds to a flat and small (<1 cm) carcinoma, without residual adenoma; the terminology suggests that it did not pass through the stage of premalignant lesion. Such aggressive tumors have a rather specific genomic profile in which the low proportion of K-*ras* and *APC* mutations contrasts with a high proportion of *TP53* mutations.

Carcinoma in situ

The definition of a carcinoma in situ corresponds to a carcinoma that is restricted to the epithelial layer. For squamous cell neoplasia, the criteria are clearly described in the literature. Because of the single cell layer of the columnar epithelium, it is very difficult to identify a carcinoma in columnar epithelium that is solely restricted to the epithelial layer. Such a lesion should not be mistaken for high-grade IEN or intramucosal carcinoma. Because there are no clear-cut criteria at the moment, it is not recommended to use the term carcinoma in situ for columnar epithelium.

Genomic profiles in the nonserrated pathway to adenocarcinoma

There are 2 distinct profiles: (1) In 80% of cases, a somatic mutation of the *APC* gene is the initial event (Fig. 1). The profile of the tumor is CIN positive, MSS, CIMP negative, and there is no *BRAF* mutation. This applies to sporadic neoplasia and hereditary familial adenomatous polyposis (FAP), caused by a germline mutation of the *APC* gene. It also applies to familial polyposis, in which the autosomal recessive biallelic germline mutation of the base excision repair gene *MUTYH* (mutY homologue) results in G:C-T/A transversions in the *APC* and K-*ras* genes.[2] In the remaining 20% of cases, the initial event is a mutation in the MMR gene system. There is a somatic mutation of the *MLH1* gene in sporadic neoplasia

and germline mutations of the MMR genes *MLH1* and *MSH2* in hereditary nonpolyposis colon cancer (HNPCC). In this alternative sequence, the genomic profile is CIN negative, MSI high, CIMP negative, and there is no *BRAF* mutation.

SERRATED PATHWAY TO COLORECTAL CANCER

Hyperplastic polyps (HPs) are serrated lesions. They introduce an alternative pathway between neoplastic and non-neoplastic lesions because some of them do progress to neoplasia (Fig. 1). All serrated lesions share the same architecture in the upper part of epithelial crypts with a sawtooth lumen and a distinctive phenotype of somatic mutations of the *BRAF* gene.[19,21-27]

Non-neoplastic serrated lesions

Hyperplastic ACF. The metaplastic and serrated subtype of ACF is the monocryptal precursor of HPs and serrated lesions. Serrated ACF are characterized by crypts with enlarged and notched (sawtooth) lumen in the upper segment and a normal cell proliferation in the basal segment. Serration of the lumen is attributed to hypermaturation of epithelial cells during their progression toward the surface and inhibition of apoptosis by reduced expression of the Fas (CD 95) receptor, which is a surface transmembrane receptor of the tumor necrosis factor that activates apoptosis. Mutations of K-*ras* and *BRAF* genes are often present at this early stage without mutation of the *APC* gene.

HPs. The direction of predominant growth determines the morphology of the (metaplastic) HP as polypoid (pedunculated or sessile) or nonpolypoid (slightly elevated, flat, or depressed).[24,25] Most HPs are small, less than 10 mm in diameter, with serration in the proximal part of crypts, whereas cell multiplication is normal and without cellular atypia in the basal segment. Histological subtypes have been described, with poor interobserver variation, as microvesicular, goblet-rich, and mucin-poor variants. Large HPs are occur less frequently, and their architecture is characterized by increased serration, dilation of crypt lumen, and horizontal extension of crypts.

Hyperplastic polyposis. This diagnosis is accepted when more than 30 HPs are distributed throughout the colon, above the sigmoid, or in presence of some HPs larger than 10 mm in diameter or if first-degree relatives of patients with hyperplastic polyposis show HPs. An increased risk of cancer in hyperplastic polyposis is linked to the association of synchronous adenomas or to the presence of HPs with an atypical structure called sessile serrated lesions. In addition, a syndrome of familial cancer, with adenomatous polyposis, caused by biallelic mutations in the *MUTYH* gene, is associated with hyperplastic polyposis in nearly half of cases.[28] In this hereditary mixed polyposis, HPs maintain their distinct phenotype of serrated lesions.

Sessile serrated lesions. The term sessile serrated lesions is more acceptable than sessile serrated adenomas. The term adenoma is not justified for these lesions, which show structural changes but no IEN. Confusion also applies to the terminology sessile serrated polyp. Use of this term is not recommended because it has been used for lesions that cannot be subclassified for technical reasons into a precise category, and in the first studies, this ill-defined category included as many as 20% of all serrated lesions. In addition, the nonpolypoid pattern of sessile serrated lesions is more frequent than the polypoid sessile pattern. The morphological and histological features of sessile serrated lesions are very similar to those of large HPs with additional increased cell proliferation. The complex structural alterations include extension of serration to the basal segment of crypts, crypt branching with horizontal growth, and abundant mucus production. This leads in the majority of the lesions to a characteristic mucus cap. Sessile serrated lesions have a preferential proximal localization; the *BRAF* mutation[29] is more frequent than in serrated adenomas. Although they are not adenomas, sessile serrated lesions have a significant risk of progression to carcinoma and therefore should be completely removed rather than performing a biopsy.

Neoplastic serrated lesions

Fifteen percent to 20% of carcinomas located in the proximal colon arise from sessile serrated lesions and serrated adenomas. In contrast, the proportion of carcinomas in the distal colon that develop through the serrated pathway is much smaller.

Neoplasia in HPs. The neoplastic progression of small HPs, which are predominantly located in the distal colon, is extremely rare. Small HPs are classified as non-neoplastic. Conversely, large HPs, preferentially located in the proximal colon, behave as borderline lesions with a potential for neoplasia and malignancy.

Mixed hyperplastic and adenomatous polyps. These lesions represent an intermediate step in the evolution of serrated adenoma. The structure is that of an HP in some sectors and that of a serrated adenoma in others, suggesting a merger between 2 types of lesions.

Traditional serrated adenomas and serrated carcinomas. These lesions represent a complete mixture and combination of a serrated lesion and an adenoma because they associate serration in the upper segment of the crypts and adenoma in the lower segment, where there is high proliferative capacity, nuclear stratification, and cells with abundant eosinophilic cytoplasm. Typical serrated adenomas frequently progress to serrated carcinomas after a mucinous or trabecular growth pattern. The behavior of serrated carcinomas is more aggressive compared with carcinomas developed on sessile serrated lesions or on classic adenomas.

Genomic profiles in the serrated pathway to adenocarcinoma. The mutation of the *BRAF* oncogene, absent in nonserrated adenomas, is an initial event in serrated adenomas, independent of CIMP or MSI status.[24] Actually there are 2 distinct profiles in the serrated pathway (Fig. 1): (1) In approximately 80% of cases, the initial event is the mutation of the *BRAF* oncogene followed by progressive epigenetic methylation of multiple genes and inactivation of MMR genes with epigenetic silencing of the *MLH1* gene. It results in high MSI or silencing of the MGMT repair gene, leading to low MSI. The profile of the tumor is CIN negative, MSI high or MSI low, and CIMP high. It is suggested that the precursors of sporadic carcinomas with an MSI-high status are either a nonserrated adenoma developed from a somatic mutation of the MMR gene *MLH1* or a serrated lesion developed from a *BRAF* mutation.[30] (2) In approximately 20% of cases, the initial event is a mutation of the K-*ras* gene, followed by progressive epigenetic methylation of multiple genes concerning the DNA repair gene *MGMT* or tumor suppressor genes. The profile of the tumor is CIN positive at a late stage of progression with loss of heterozygosity and *p53* mutations, MSI low or MSS, CIMP low. This genomic profile is more frequent in serrated adenomas than in sessile serrated lesions and overlaps with the conventional adenoma-carcinoma nonserrated sequence.

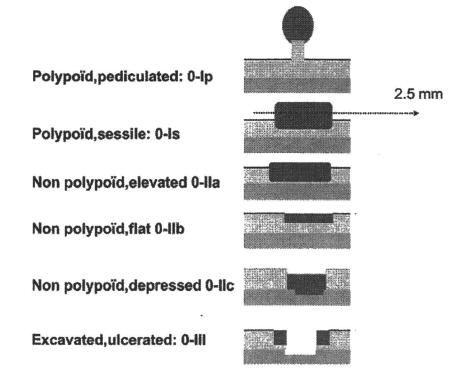

Figure 3. The Paris classification of superficial neoplastic lesions (1): polypoid type 0-I lesions are pedunculated or sessile. The elevation of sessile lesions above the surface of the mucosa is more than 2.5 mm. Nonpolypoid type 0-II lesions are slightly elevated, flat, or slightly depressed. The elevation of elevated lesions is less than 2.5 mm. Excavated or ulcerated type 0-III superficial neoplastic lesions do not occur in the colon.

STRATEGY FOR ENDOSCOPIC DIAGNOSIS AND TREATMENT OF NEOPLASTIC LESIONS

Endoscopic detection and characterization

Detection. An abnormal area at the surface of the mucosa is detected without magnification and chromoendoscopy by any of the following elements: (1) obvious elevation or depression, (2) mucosal discoloration, (3) interruption of the course of superficial capillaries. Special attention is required in the exploration of the cecum and ascending colon, searching for poorly visible and large nonpolypoid lesions, often covered by bile-stained mucus. Chromoendoscopy with indigo carmine solution helps to analyze the extent and morphology of the lesion. If the size is not measured with a graduated gauge, it should at least be classified as very small ($\leq$5 mm), small or intermediate (6-9 mm), or large ($\geq$10 mm). The morphology is described in subtypes of the category 0 of the Paris classification (1): type I polypoid with subtypes Ip and Is or type II nonpolypoid with subtypes IIa, IIb, and IIc (Fig. 3). The ulcerated type III occurs only in advanced cancer. Mixed polypoid and nonpolypoid patterns are frequent. Lesions larger than 10 mm spreading superficially on the surface of the mucosa have been first called nodule-aggregating tumors and, more recently, LST.

Characterization. This aims at classifying the endoscopic appearance of the lesion (Figs. 4-17) before pathological interpretation (Figs. 18-23) as non-neoplastic or neoplastic and at evaluating the risk of malignancy before treatment decision. Characterization relies on the analysis of the surface microarchitecture and the network of superficial capillaries. Magnification, using an optical zoom (×80 to ×100), an electronic zoom, or an objective with adaptive focal distance, is combined with dye chromoendoscopy or the NBI technique for the description of the surface microarchitecture or pit pattern (Figs. 24 and 25). Type I with small and regular pit openings suggests a normal mucosa. Type II with large and regular stellar pit openings suggests a non-neoplastic, hyperplastic lesion. Types IIIL, IIIS, IV, IV, Vi, and VN with sinus short, long, or branched crests suggest neoplasia and progression from a low to a high risk of malignancy. The mild or high degree of irregularity of the pit pattern Vi predicts the depth of invasion in the submucosa below or above the limit of 1000 μm.[31] Nonserrated and serrated lesions are shown before and after chromoendoscopy with some magnification in Figures 4 to 17. The network of superficial capillaries or vascular pattern is described in magnification without chromoendoscopy, either in transparency or with the NBI[32] or FICE (Fuji Intelligent Chromo Endoscopy) technology.[33] The successive categories (faint, network, dense, irregular, sparse) correspond to the transition from non-neoplastic to malignant neoplasia.

Treatment adapted to prediction of pathology

The next step after endoscopic detection of a colorectal lesion with a superficial appearance is the treatment decision. The options are as follow: no treatment, EMR, or

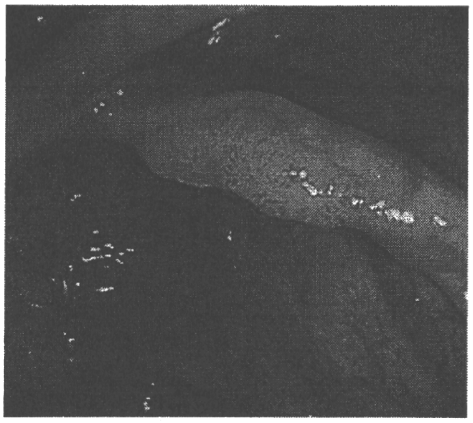

Figure 4. Adenomatous polyp, subtype IIa.

Figure 6. Hyperplastic polyp, subtype IIa.

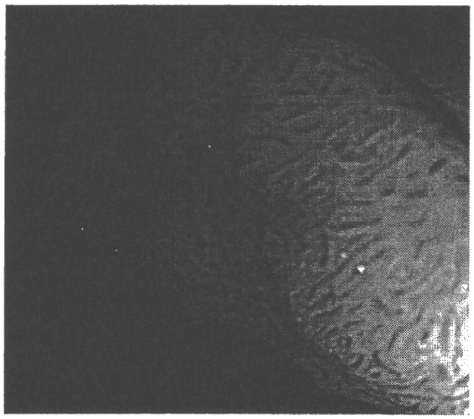

Figure 5. Pit pattern IIIL (same as in Figure 4 after chromoendoscopy with indigo carmine).

Figure 7. Pit pattern II (same as in Figure 6 after chromoendoscopy with indigo carmine).

surgery. EMR is limited by its inability to achieve en bloc resection of lesions larger than 25 mm. This limit is overcome in the new technique of endoscopic submucosal dissection; however, the procedure requires more time and technical skill and needs to be standardized for application in the colon.

The legitimacy of the treatment decision will be confirmed by the results of histopathology (Figs. 18-23), by using the Vienna classification of GI neoplasia into 5 categories adapted to the colon.[34] An in vivo reliable prediction of histopathology during endoscopy has been obtained with confocal laser endomicroscopy; however, the emerging technique with subcellular resolution is still not routinely available. Conversely, a strategy of endoscopic diagnosis with prediction of histology based on high resolution and magnification combined with chromoscopy or the NBI technique is accessible to most endoscopy units. The pragmatic correlation (Fig. 26) between the treatment options and estimated risk of progression of the tumor was shown during the Kyoto workshop,[2] and the following ranges of risk were proposed.

Non-neoplastic mucosal lesion: no risk. This corresponds to categories 1 and 2 in the Vienna classification and applies to normal epithelium, inflammation, and small HPs less than 10 mm in diameter. For these lesions, no treatment is justified and the decision for endoscopic surveillance is optional. There is an exception for large HPs and sessile serrated lesions for which endoscopic resection is recommended.

Low-grade neoplasia: low risk. This corresponds to categories 3 and 4-1 to 4-4 of the Vienna classification and applies to low-grade IEN, noninvasive high-grade IEN, suspected invasive carcinoma, and well-differentiated intramucosal carcinoma with low-grade cell atypia. The risk of lymph node metastasis is theoretically considered to be zero. Endoscopic resection of the lesion is proposed. Follow-up is required, with surveillance intervals adapted according to the histopathology.

Intermediate-grade neoplasia: intermediate risk. This corresponds to category 4-4 in the Vienna classification and partly to category 5. It involves 3 types of lesions: (1) differentiated intramucosal carcinoma with high-grade

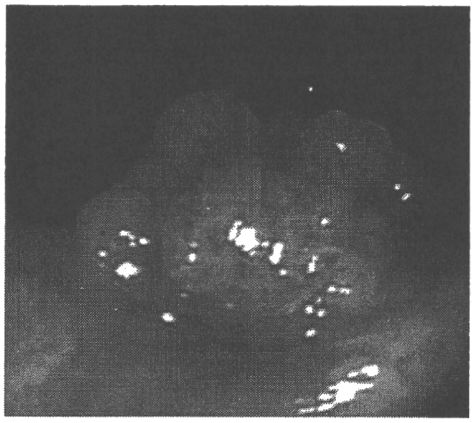

Figure 8. Sessile serrated lesion, subtype Is.

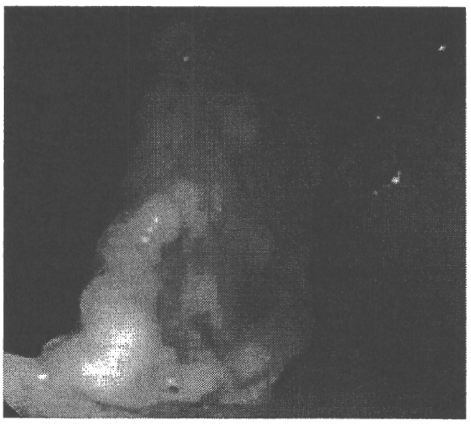

Figure 10. Sessile serrated lesion, IIa, granular surface, in the ascending colon.

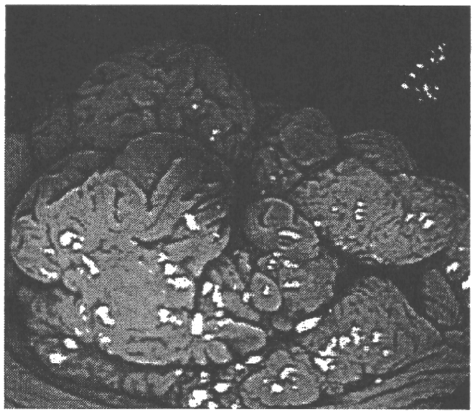

Figure 9. Mosaic pit pattern: II, IIIL, IV (same as in Figure 8 after chromoendoscopy with indigo carmine).

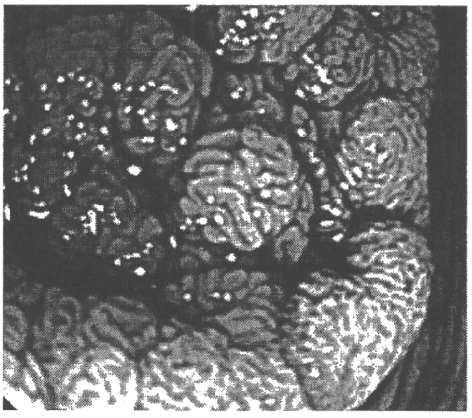

Figure 11. Pit pattern IV (same as in Figure 10 after chromoendoscopy with indigo carmine).

cellular atypia, (2) poorly differentiated intramucosal carcinoma with signet ring cells, (3) well-differentiated submucosal carcinoma with depth of invasion in the submucosa less than 1000 μm and with low-grade cell atypia. The risk of lymph node metastasis is low, being estimated at 1% to 4.8%. There is an option between endoscopic and surgical resection. Surveillance at short intervals is required after treatment. Surgery is recommended if histopathology reveals a high-risk lesion.

High-grade neoplasia: high risk. This corresponds to a subgroup of category 5 in the Vienna classification and applies to 2 types of lesions: (1) submucosal poorly differentiated carcinoma and (2) well-differentiated submucosal carcinoma with high-grade cell atypia or invasion deeper than 1000 μm. Surgical treatment with or without neoadjuvant therapy is required.

Pragmatic classification of nonserrated lesions

Polypoid adenomas. Pedunculated or sessile, these lesions are classified as subtypes Ip and Is of the Paris classification.[1] Their direction of growth upward increases their volume more than depth. The majority of polypoid adenomas are small or intermediate in size; larger adenomas ($\geq$10 mm) and those showing at least a 25% villous architecture or high-grade IEN are often called advanced. The frequency of malignant transformation increases in proportion to size and correlates with the progressive shift of the surface pit pattern from the category IIIL to VN. Their genomic profile includes a high proportion of *APC* and K-*ras* mutations.

Nonpolypoid and nondepressed adenomas. Elevated less than 2.5 mm above the level of the mucosa, they are classified as subtype IIa.[1] Rarely the adenoma is completely flat and classified as IIb. Small adenomas, less than 10 mm in diameter, are often missed at endoscopy; chromoendoscopy is more effective at detecting them. They are also called small flat adenomas or small depressed adenomas when their surface offers a smooth and central depression. A pit pattern in the category IIIL is frequent and correlates with a low risk of progression to an adenocarcinoma. Small adenomas may be stable, regress, extend laterally, or progress upward to a polypoid morphology.

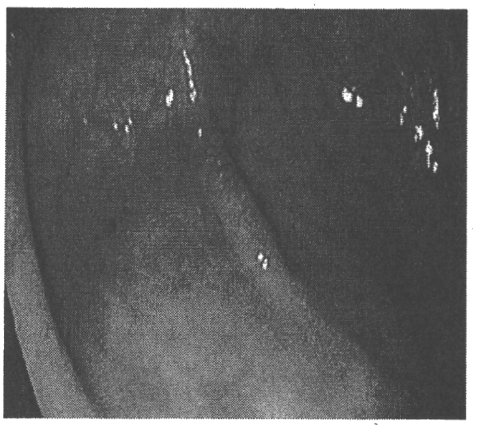

Figure 12. Sessile serrated lesion in hepatic flexure, IIb, after rinsing the covering mucus.

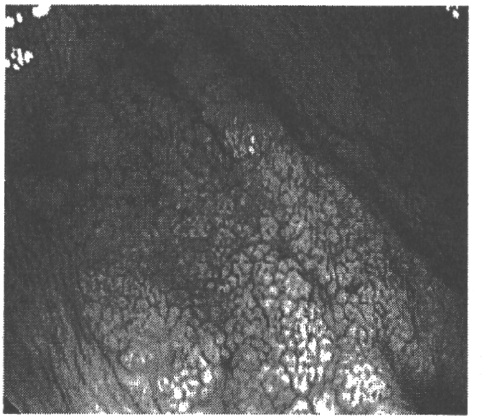

Figure 13. Pit pattern II, predominantly (same as in Figure 12 after chromoendoscopy with indigo carmine).

Figure 14. Serrated adenoma, subtype Is + IIa.

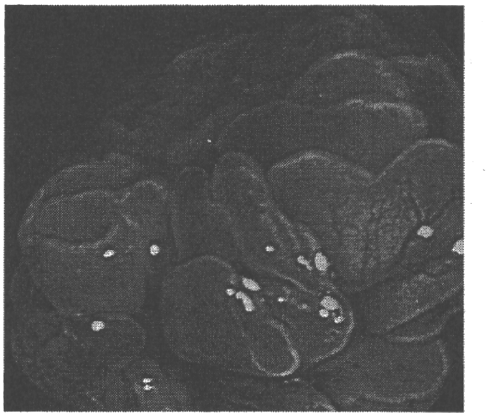

Figure 15. Large tufts on a sessile nodule (same as in Figure 14 after chromoendoscopy with indigo carmine).

LST adenomas. They are relatively rare and large, more than 10 mm in diameter. The growth pattern is more lateral than vertical; their global morphology is nonpolypoid, but mixed patterns with sessile elements are frequent. LST adenomas[2] are classified into 2 groups: (1) Granular LST adenomas are elevated and exhibit a homogeneous or nodular surface, classified as subtype IIa or IIa + Is. (2) Nongranular LST adenomas are elevated or pseudodepressed with an even surface, in contrast to the nodular type, and are classified as subtype IIa or IIa + IIc. The pit pattern, classified as category IIIL or IV, confirms a relatively low potential of progression to adenocarcinoma. A comparative study of molecular markers was conducted in LST adenomas (n = 28) and in slightly elevated IIa adenomas (n = 22)[35]: K-*ras* mutations and *p53* are more frequent in LST adenoma; this suggests that LST adenomas have a distinct genomic profile compared with nonpolypoid lesions. Another molecular analysis confirmed in LST adenoma a high proportion of *p53* and K-*ras* mutations, similar to that of polypoid tumors.[36]

Nonpolypoid and depressed adenomas. These are not frequent and account for not more than 5% of superficial neoplastic lesions. The growth pattern is mostly in depth, and they are classified as subtype IIc.[1] Combined patterns of depression with a slight marginal elevation are classified as IIc + IIa or IIa + IIc. In lesion type IIc + IIa, the structure of the elevation is not always adenomatous and may show the surface pit pattern of a hyperplastic lesion. Depressed IIc lesions differ from the so-called flat depressed adenomas by the abrupt edge of the central depression. The pit pattern in categories IIIS to VN correlates with frequent progression to adenocarcinoma. The malignant transformation, unrelated to size, is already frequent in lesions less than 10 mm. Depressed lesions may show a much higher proportion of submucosal invasion than other subtypes. In the very large Japanese series (n = 25,862) of superficial neoplastic lesions collected in the Akita and Yokohama Hospitals, submucosal invasion occurred in 35.9% of depressed lesions; proportions were 1.3% for polypoid lesions and 2.4% for nonpolypoid, nondepressed lesions.[2] In the Hiroshima University Hospital series (n = 12,811), the proportions of submucosal invasion

Figure 16. Serrated adenocarcinoma, subtype Is.

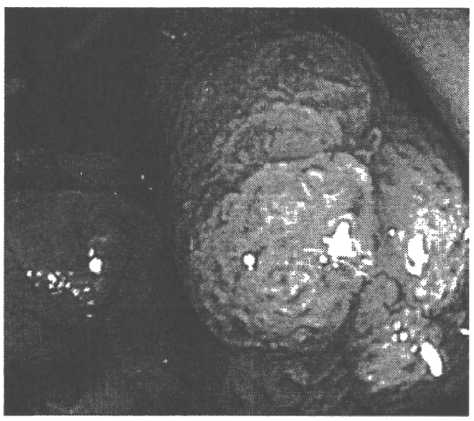

Figure 17. Heterogeneous pit pattern (same as in Figure 16 after chromoendoscopy with indigo carmine).

were 27% for depressed lesions, 0.7% for polypoid lesions, 2.1% for nonpolypoid and nondepressed lesions.[2] *APC* and K-*ras* mutations have a low frequency in these depressed or flat adenomas.[37] In a molecular analysis conducted in 56 flat adenomas and 81 polypoid adenomas, the proportion of K-*ras* mutations was low (23%) in flat and high (67%) in polypoid lesions.[38] The proportion of K-*ras* mutations at an early stage was low (8.6%) in 81 very small flat lesions exhibiting a central depression.[39]

De novo cancer. This lesion is small, less than 10 mm in diameter, with flat or depressed nonpolypoid morphology, and is classified into subtypes IIc, IIa, and IIb.[1] The pit pattern is classified into categories Vi to VN. Despite the small size, invasion in the submucosa is frequent, as is its progression to ulcerated advanced cancer. The frequency of de novo carcinoma among superficial malignant lesions is low, but it is a frequent precursor of advanced cancer because of its aggressive nature.

Pragmatic classification of serrated lesions

HPs. Small HPs are the most frequent; they are less than 10 mm in size, nonpolypoid, and slightly elevated

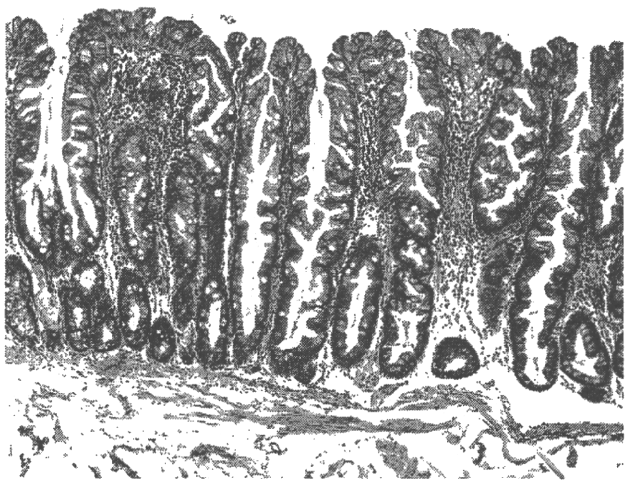

Figure 18. Hyperplastic polyp with notched lumen of crypts and normal cell pattern in its basal segment (H&E, orig. mag. ×100).

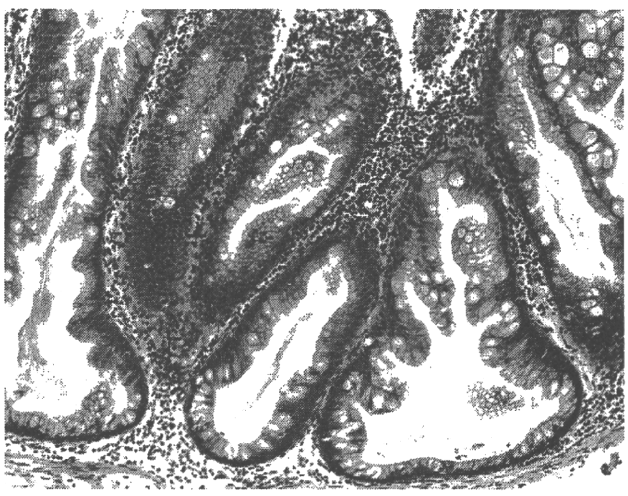

Figure 19. Sessile serrated lesion with enlarged basal segment of crypts, and nuclear crowding at the bottom (H&E, orig. mag. ×200).

or even flat and are classified as subtype IIa or IIb by the Paris classification. Their surface pit pattern is classified in category II, with large stellar pit openings. Small HPs are stable, non-neoplastic lesions. Large HPs (>10 mm) are much less frequent. When their growth pattern is predominantly lateral, the morphology is classified as subtype IIa. When their growth pattern is upward, the morphology is polypoid, classified as subtype Ip or Is by the Paris classification. The significant risk of malignancy in hyperplastic polyposis is linked to the presence of synchronous adenomas or sessile serrated lesions.

Sessile serrated lesions. Most of these lesions are large (>10 mm) and follow a predominantly lateral growth pattern. Their general morphology is nonpolypoid or a combination of nonpolypoid and sessile polypoid, resembling an LST, and they are therefore classified as IIa or IIa + Is. The surface of the lesion is homogeneous and

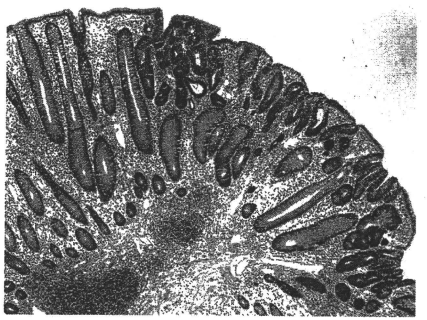

Figure 20. Nonserrated tubular adenoma, initial stage of development with typical top-down morphology and stratified and hyperchromatic nuclei in some crypts, whereas other crypts are still normal (H&E, orig. mag. ×40).

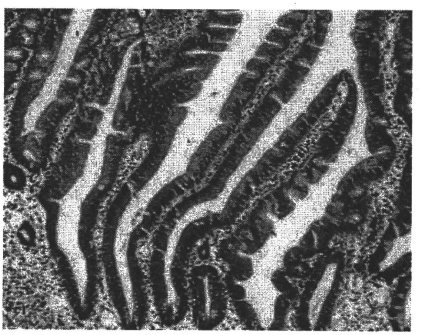

Figure 22. Traditional serrated adenoma, nuclear atypia, and stratified nuclei, predominant in basal segments of crypts with notched lumen, typical so-called micro acini. Low-grade IEN (H&E, orig. mag. ×100).

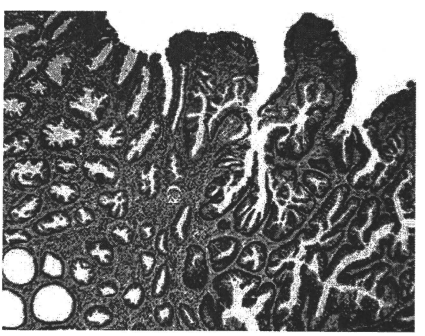

Figure 21. Mixed polyp. Serrated adenoma with stratified hyperchromatic nuclei and structural atypia (*right*). HP with notched lumen of crypts in both sectors (*left*) (H&E, orig. mag. ×100).

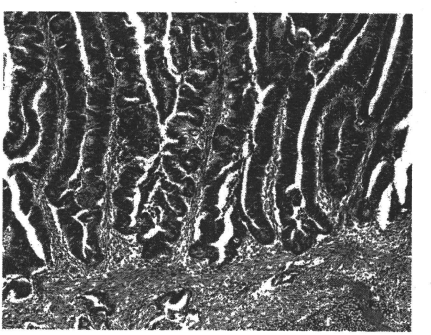

Figure 23. Well-differentiated serrated adenocarcinoma, nuclear atypia, and stratified nuclei along crypts with notched lumen. Invasion is noted in the submucosal layer (H&E, orig. mag. × 100).

often covered with a yellow mucus layer, which should be carefully washed as it masks the microarchitecture showing a preponderant type II pit pattern. Although they are not adenomatous, sessile serrated lesions have a significant risk of progression to serrated adenoma, and *BRAF* mutations are frequent.

Mixed hyperplastic and adenomatous polyps. The surface of the lesion is irregular with nodules and often covered with a yellow mucus layer. Microarchitectural assessment shows a mosaic of pit patterns with hyperplastic-like type II alternating with types IIIL and IV in adenomatous areas.

Traditional serrated adenomas/carcinomas. These lesions often reach a size of 10 mm. Their growth pattern is both upward and downward, but they also extend laterally. Their morphology is polypoid or nonpolypoid,[40] corresponding to subtypes Ip, Is, and IIa.[1] The surface pit pattern varies from type II in small serrated adenomas to types IIIL and IV in large adenomas and type Vi or VN in carcinomas. An endoscopic survey conducted with 52 serrated adenomas[41] classified their surface microarchitecture as hyperplastic in 17, cerebriform in 18, and mixed in 17. A histopathologic study of 178 traditional serrated adenomas[42] showed that high-risk intramucosal neoplasia was more frequent in nonpolypoid (25.2%) than in polypoid (9.2%) lesions. Serrated adenomas frequently progress to serrated carcinoma, and some have been described as adjacent to a carcinoma.[43] Serrated carcinomas show a serrated mucinous or trabecular growth pattern with abundant eosinophilic cytoplasm

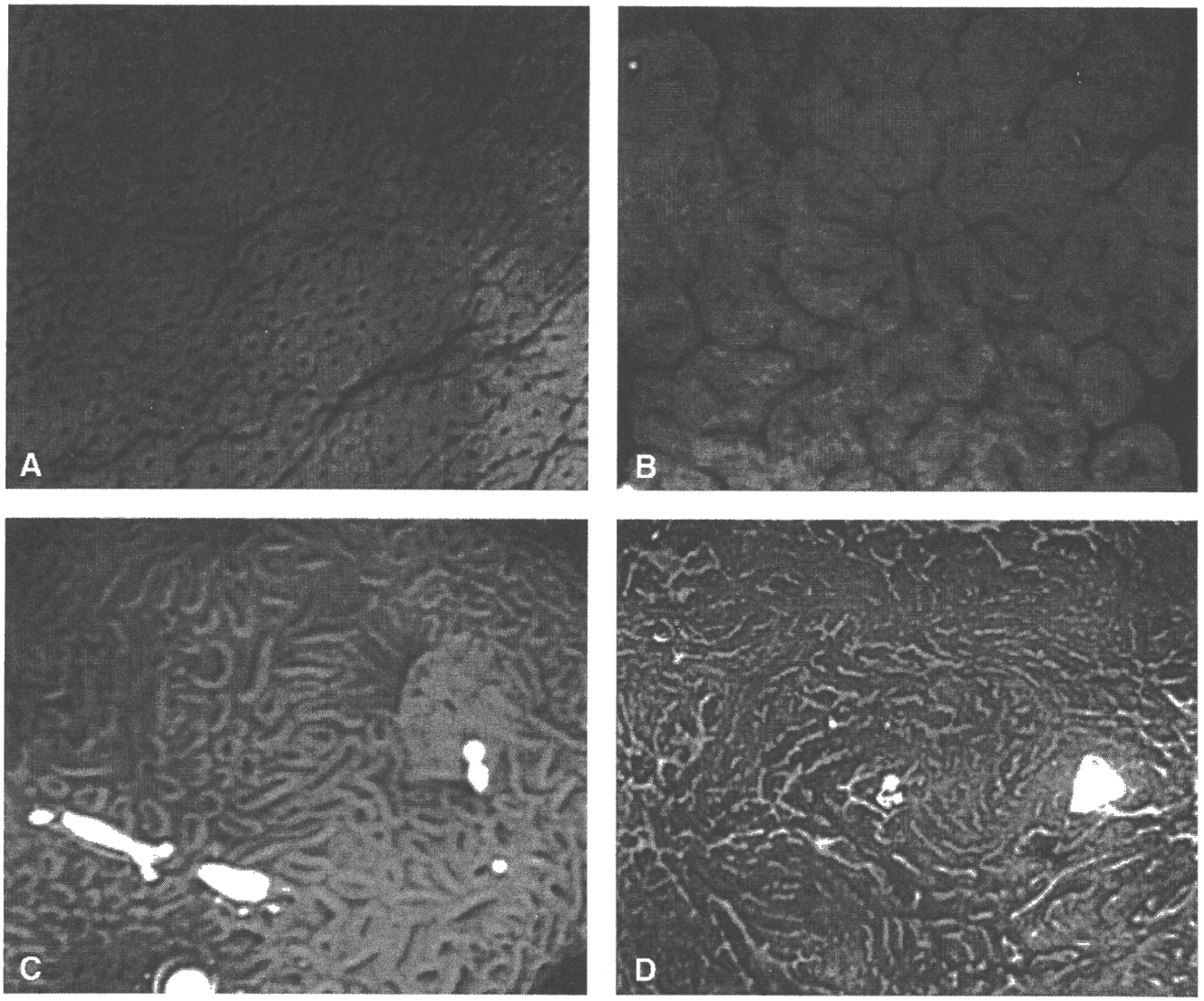

Figure 24. Pit pattern of the colonic mucosa in magnification after dye staining. **A,** Normal with small, round pits (Kudo type I). **B,** HP with stellar, enlarged pits (type II). **C,** Low-risk neoplasia with sinuses retaining the dye and elongated crests (type III L). **D,** High-risk neoplasia with irregular sinuses and crests (type Vi).

and absence of necrosis. A comparative analysis of MSI in 35 serrated and 75 nonserrated lesions[44] showed that serrated carcinoma is more likely to develop MSI. However, the biological background of serrated carcinoma is not directly linked to MSI, and there is still a large proportion with an MSS status. K-*ras* mutations are frequent in serrated adenomas.

PREVALENCE OF SUPERFICIAL COLORECTAL LESIONS

Several publications report on the yield of nonserrated and serrated lesions detected during screening or diagnostic colonoscopy and during surveillance in cohort studies after a colonoscopy with negative findings or a colonoscopy with endoscopic resection of adenomas. Additional data on the respective proportions of lesions in each category are also found in surgical series.

Global prevalence in endoscopy series

Reliable data from large endoscopy series require histology validation of the detected lesions. Worldwide variations in the prevalence of superficial lesions are linked to racial and environmental factors. In addition, prevalence increases with age. On average, superficial neoplastic or non-neoplastic lesions are detected in 30% to 40% of persons 50 years of age or older, but their prevalence can be as high as 70% when high-resolution endoscopy and magnification are combined with a careful detection of nonpolypoid and very small lesions. The respective prevalence of distinct categories of lesions found during colonoscopy has been analyzed in many countries. In the United States, the detection yield of colonoscopy

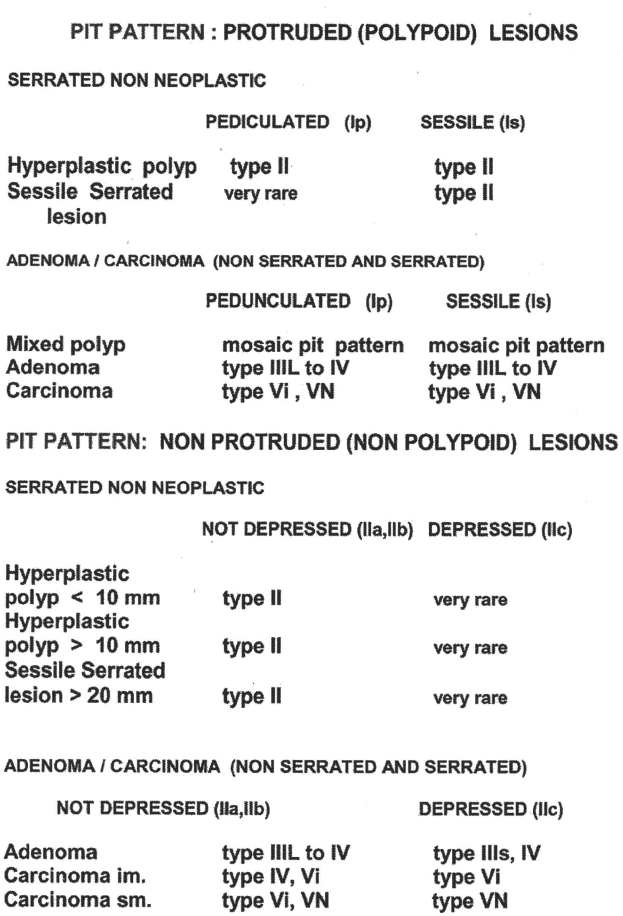

Figure 25. Endoscopic diagnosis of nonserrated and serrated superficial lesions of the colorectal mucosa. Characterization needs the help of chromoscopy and image-processing techniques. Microarchitecture of the surface is classified in categories of pit pattern. Type II pit pattern suggests a non-neoplastic lesion. Types III and IV correspond to the progression of premalignant neoplasia. Types Vi and VN suggest a carcinoma.

performed for screening in 3121 persons 50 to 75 years of age during the period 1994 to 1997 in a Veterans Affairs study was 37.5% for neoplastic lesions and 12.5% for HPs.[45] Another analysis of screening colonoscopy data was conducted by the same group in 2004 to 2005[46] in 13,992 persons: 26% had adenomas and 14.7% had HPs. The prevalence of HPs can be fairly high when their detection is systematic and includes very small lesions. In Japan, at the National Cancer Center Hospital East, Chiba,[47] HPs were detected with magnifying endoscopy in 86% of the examined persons, and most lesions (3020/3060) were less than 6 mm in diameter. The major role of the operator in the detection of non-neoplastic lesions was confirmed by a study conducted at Indiana University Hospital of 10,034 colonoscopies performed between 1999 and 2004 by 9 operators[48]: the prevalence of HPs varied with the operator and ranged from 11.8% to 34.9%.

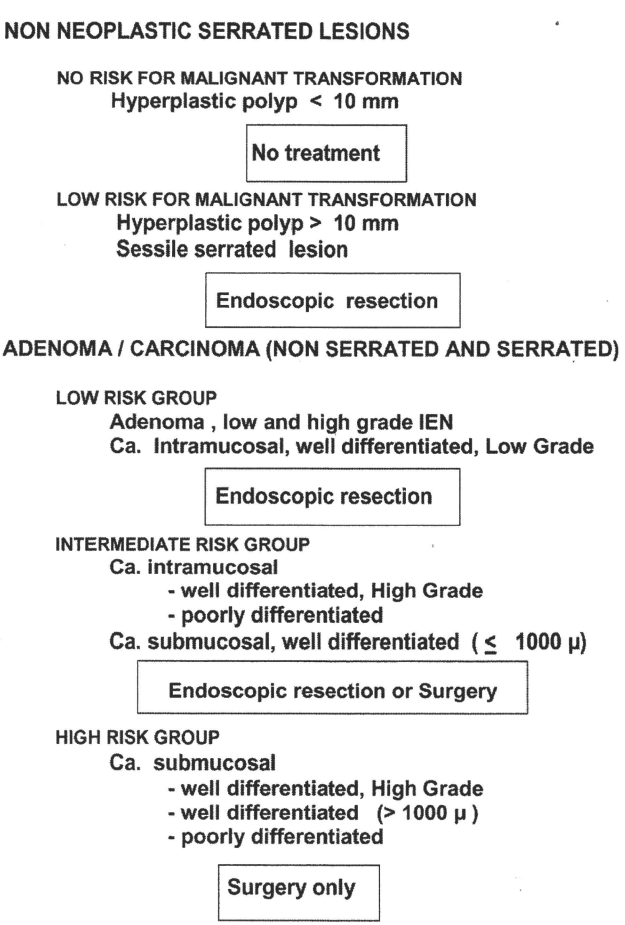

Figure 26. Treatment decision for nonserrated and serrated superficial lesions of the colorectal mucosa. Therapeutic option is based on the evaluation of the risk of malignancy during endoscopic diagnosis. A legitimate option is confirmed by pathology.

Other studies have addressed the proportions of distinct categories of lesions in pathology series. In Australia, in 414 superficial lesions, the proportions were 60% for adenomas, 29% for HPs, 9% for sessile serrated lesions, 0.7% for traditional serrated adenomas, and 1.7% for mixed lesions.[49] In Taiwan, among 400 superficial lesions, the respective proportions of adenomas and HPs were 73.7% and 11%.[50] In Korea, histopathological evaluation of 296 superficial lesions showed a proportion of adenomas of 60%,[51] whereas in Japan, in a large series of 20,129 superficial lesions removed at endoscopy at the National Cancer Center, Tokyo, during the period 1999 to 2008, the proportions were 83% for adenomas, 13% for carcinomas, 4% for HPs, and 0.7% for serrated adenomas.

Some studies only deal with neoplastic lesions. A Korean analysis estimated that 5.2% of small adenomas (6-7

mm) had a villous or tubulovillous architecture.[52] In Malaysia, superficial lesions, mostly adenomas, were detected in 14% of 3404 colonoscopies.[53] In the U.S. Veterans Affairs study, 52% of the persons with advanced neoplasia in the proximal colon had no distal adenoma and therefore it would not be detected by sigmoidoscopy.[45] In a U.S. screening study setting, the prevalence of advanced neoplasia was found to be higher in Asian American men (12%) than non-Asian (9%); for women, the respective figures were 8% and 7%.[54] Another study showed that superficial lesions larger than 9 mm were more frequent for either sex in American blacks (7.7%) than in whites (6.1%).[55]

Prevalence of nonserrated lesions

Nonserrated lesions' morphology is classified into 3 groups: (1) polypoid lesions, (2) nonpolypoid and nondepressed lesions, and (3) nonpolypoid and depressed lesions, which are not frequent and have a higher risk of progression to cancer. The best figures on their respective prevalence are reported in endoscopy series from Japan. In the Akita Red Cross Hospital, the morphology of neoplastic superficial lesions (n = 9530) was polypoid in 57%; nonpolypoid, nondepressed in 39%; and depressed in 4%.[1] The respective proportions were 61.1%, 36.4%, and 2.4% in a larger (n = 23,048) series from the same group between 1985 and 2007.[2] Another statistic from Japan confirms the low proportion of depressed lesions that represent 1.9% of 66,670 lesions in a multicenter study.[56] When similar criteria of detection were used in the West, the proportion of depressed lesions was 1.2% in a series from the United States.[57]

Prevalence of serrated lesions

HPs are the most frequent serrated lesions. Their prevalence ranges from 10% to 15% in large cohorts, but much higher figures are obtained when very small HPs are systematically sought. Most HPs are small (<10 mm in diameter) and have no potential for malignancy. Their preferential location (at least 80%) is in the distal colon and rectum. Large HPs, which are less frequent, may be associated with small HPs and are preferentially located in the proximal colon. A relationship between the presence of HPs and that of adenomas at colonoscopy is suggested by a study conducted in the United States on metachronous adenomas occurring after a colonoscopy with negative findings. In this study, a second exploration was performed 5 years after a colonoscopy that was negative for adenomas: metachronous adenomas were detected in 23.6% of the 199 subjects who had HPs on initial examination and in only 14.6% of the persons negative for HPs at the initial endoscopy.[58] A morphological and histopathological study was conducted in Japan on 891 adenomas and 359 serrated lesions.[59] The respective numbers in categories of serrated lesions were HPs in 298, sessile serrated lesions in 27, mixed polyps in 10, and traditional serrated adenomas in 24. In this series, the proportion of sessile serrated lesions with a proximal location was higher than for all other categories.

TOPOGRAPHY OF SUPERFICIAL COLORECTAL LESIONS

Definition of proximal and distal colon

The distinction between proximal and distal large bowel refers to the splenic flexure. Therefore, neoplastic lesions located in the cecum, ascending colon, and transverse colon are called proximal; lesions located in the descending colon, sigmoid, and rectum are called distal. The terminology right-sided versus left-sided colorectal neoplastic lesion is based on the same definition. This distinction relies on differences in anatomy, biology, and metabolism.[60] The proximal colon is perfused by the superior mesenteric artery, whereas the distal colon is perfused by the inferior mesenteric artery. Blood group A and B antigens are expressed only by cells of the proximal colon. Furthermore, the intraluminal fermentation and its impact on the metabolism of bile acids and the production of short-chain fatty acids and the bacterial enzymes involved in the generation of mutagenic metabolites are confined to the proximal colon. Environmental factors may have a distinct impact on the incidence of proximal and distal tumors.

Nonserrated neoplasia: proximal versus distal location

The temporal trend for the increasing incidence of colorectal cancer in developed countries only applies to proximal tumors. In developing countries, the increased incidence applies only to distal tumors.

The location of adenomas progressing to carcinoma differs in the 2 major categories of hereditary colorectal cancer, FAP and HNPCC. In FAP, the whole colonic mucosa is covered by a dense network of small adenomas, but most of them are stable; progression to cancer occurs in the distal colon. In HNPCC, adenomas are few but less stable, and progression to cancer occurs in the proximal colon.

The distinction between proximal and distal tumors is confirmed in genomic profiles: proximal tumors are mostly diploid, with a low proportion of *TP53* mutations and a frequent MSI-high and CIMP-high status; distal tumors are aneuploid, with a high proportion of *K-ras* and *p53* mutations and a frequent MSI-low and CIMP-low status.[61,62] The majority of sporadic tumors with MSI-high status occur in the proximal colon, whereas most sporadic tumors with a CIN-positive status are distributed in the distal colon.[63] Proximal tumors that exhibit a frequent MSI-high status have a better prognosis than distal tumors and show a higher sensitivity to 5-fluorouracil–based chemotherapy.[64]

Serrated neoplasia: proximal versus distal locations

The distinction in location also applies to serrated lesions. Proximal HPs present with more crypt dilation and extension of serration to the basal segment of crypts than distal HPs.[65] An endoscopic study of the morphology of 68 traditional serrated adenomas[66] showed that polypoid lesions have a preferential distal location and were more frequent (n = 53) than nonpolypoid lesions, which had a predominantly proximal location (n = 15). Traditional serrated adenomas that are often polypoid occur more frequently in men and have a poor prognosis after progression to carcinoma. Proximal serrated lesions are frequently classified as sessile serrated lesions, whereas distal lesions correspond to serrated adenomas.[66] Proximal serrated carcinoma has a better prognosis than distal carcinoma[27,43]: the 5-year survival rate is higher (70%) than that of distal serrated lesions (30%).

The distinction between proximal and distal tumors is confirmed by genomic profiles: most proximal serrated adenomas that developed after a *BRAF* mutation are CIN negative, MSI high, CIMP high. Most distal tumors develop after a K-*ras* mutation and are CIN positive, MSS, CIMP low. This was confirmed in a recent study of the genomic profile of 110 serrated lesions conducted in the United States[30]; the CIMP-high status is more frequent in proximal (62%) than in distal (22%) serrated tumors that have a more frequent CIN-positive status.

Missed diagnosis of neoplasia in the proximal colon

The proximal colon, including the cecum and ascending colon, is the preferential site of large and nonpolypoid, nonserrated or serrated lesions. This heterogeneous group includes nonserrated LSTs, large HPs, and sessile serrated lesions, which occur more frequently in women and in old age; they have better prognosis than left-sided lesions when they progress to carcinoma. Those large but poorly visible lesions are often missed and give rise to interval cancer after a screening colonoscopy. A population-based, case-control study conducted in the state of Ontario, Canada confirmed that there was no protection afforded by colonoscopy for proximal cancer.[67] The occurrence of a previous complete colonoscopy was compared in the history of persons who died of cancer and of controls having no cancer. Colonoscopy was strongly associated with fewer deaths from left-sided colorectal cancer, with an odds ratio of 0.33. There was no effect on death from right-sided colorectal cancer with an odds ratio of 0.99. The difference was attributed to poor detection of nonpolypoid lesions in the proximal colon. Interval cancers were revealed a few years after a colonoscopy with negative findings; they corresponded either to missed lesions during the initial examination or to fast-developing lesions. In a study conducted in the United States,[68] the site of 51 interval cancers that developed within 5 years after complete colonoscopy was compared with that of 112 noninterval colorectal cancer: the interval cancers were 3 times more likely to occur in the proximal colon. Concerning the genomic profile, MSI was more frequent in interval cancers (30.4%) than in noninterval cancers (10.3%). After adjusting for age, the frequency of MSI was 79% in proximal cancers and 21% in distal ones.

CONCLUSION

The pragmatic classification of the endoscopic appearance of superficial neoplastic and non-neoplastic lesions of the colorectal mucosa aims to classify the risk of progression to advanced neoplasia in 3 degrees (low, intermediate, high) and facilitate appropriate treatment and surveillance. The privileged position of colonoscopy results from its double impact on the prevention of colorectal cancer: (1) reduction in incidence after early detection and eradication of precursors and (2) reduction of mortality after detection and treatment of cancer at an early and curable stage. However, its efficacy in diagnosis is still far less than optimal and will require improvement and quality control on the following points: (1) technology, with a generalized use of the recently introduced high-resolution endoscopes; (2) diagnosis of poorly visible nonpolypoid precursors, which applies to small depressed lesions and large, slightly elevated or sessile serrated and nonserrated precursors, particularly in the proximal colon; and (3) treatment and training in therapeutic endoscopy, which applies to the most recent techniques of mucosal resection of nonpolypoid lesions.

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