The Paris endoscopic classification of superficial neoplastic lesions: esophagus, stomach, and colon

November 30 to December 1, 2002

Participants in the Paris Workshop

Paris, France

An international group of endoscopists, surgeons, and pathologists gathered in Paris for an intensive workshop designed to explore the utility and clinical relevance of the Japanese endoscopic classification of superficial neoplastic lesions of the GI tract. This report summarizes the conclusions of the workshop and proposes a general framework for the endoscopic classification of superficial lesions of the esophagus, stomach, and colon. The clinical relevance of this classification is demonstrated in tables that show the relative proportion of each subtype in the esophagus, stomach, and colon, assessing the risk of submucosal invasion and the risk of lymph node metastases.

In the esophagus, stomach, and colon, neoplastic lesions of the digestive tract are called "superficial" at endoscopy when the endoscopic appearance suggests either a small cancer or a noninvasive neoplastic lesion (dysplasia/adenoma). If invasive, "superficial" tumors correspond to the T1 stage of the TNM classification, in which invasion is limited to the mucosa and submucosa. "Superficial" tumors are nonobstructive, usually are asymptomatic, and often are detected as an incidental finding or by screening.

In Japan, neoplastic lesions of the stomach with a "superficial" endoscopic appearance are classified as subtypes of *"type 0."*[1,2] The term *"type 0"* was chosen to distinguish the classification of "superficial" lesions from the Borrmann classification, proposed in 1926 for "advanced" gastric tumors, which included *types 1 to 4*.[3] Within *type 0*, there are polypoid and non-polypoid subtypes. The non-polypoid subtypes include lesions with a small variation of the surface (slightly elevated, flat, and slightly depressed) and excavated lesions. The Japanese Gastric Cancer Association (JGCA) also added a *type 5* for unclassifiable advanced tumors. The complete modification for gastric tumors becomes:

type 0 - superficial polypoid, flat/depressed, or excavated tumors
type 1 - polypoid carcinomas, usually attached on a wide base
type 2 - ulcerated carcinomas with sharply demarcated and raised margins
type 3 - ulcerated, infiltrating carcinomas without definite limits
type 4 - nonulcerated, diffusely infiltrating carcinomas
type 5 - unclassifiable advanced carcinomas

In summary, the macroscopic appearance of gastric cancer is distributed in 6 types (0-5) in the JGCA classification. *Type 0* with its subtypes adapted to endoscopic appearance includes both noninvasive neoplasia and cancer, which can be confirmed by pathologic analysis. The classification of gastric "superficial" neoplasia was promptly applied to esophageal tumors,[4] and later, when the incidence of colorectal cancer increased in Japan, to large bowel tumors as well.

Many endoscopists, particularly in the West, considered the Japanese classification, with its numerous divisions for esophagus, stomach, and colon, to be a "botanical hobby," too complex for practical use. Western endoscopists tend to base treatment decisions largely on the size and the location of the tumor and on the histology of biopsy specimens. However, Japanese endoscopists have found that the endoscopic classification of a lesion can be an important determinant of when endoscopic therapy should be applied. In choosing therapy, endoscopic appearance may be supplemented by other endoscopic criteria, including EUS and EMR, to evaluate lifting of the lesion during endoscopy and to obtain a large pathology specimen. In patients at increased risk for surgery, EMR may be the primary treatment, supplemented as needed by ablation treatments, such as electrocoagulation or photodynamic therapy.

Skepticism of the value of endoscopic classification of superficial neoplastic lesions has been further encouraged by East/West differences in pathology classification of intramucosal neoplasia. The recent Vienna classification[5] has, to some extent, resolved

0016-5107/2003/$30.00 + 0
PII: S0016-5107(03)02159-X

Table 1. Revised Vienna classification of epithelial neoplasia for esophagus, stomach, and colon[5,13]

Negative for IEN	
Indefinite for IEN	
Low-grade IEN	
Adenoma/dysplasia	
High-grade neoplasia (intraepithelial or intramucosal)	
Adenoma/dysplasia	(4-1)
Noninvasive carcinoma	(4-2)
Suspicious for invasive carcinoma	(4-3)
Intramucosal carcinoma (lamina propria invasion)	(4-4)
Submucosal carcinoma	

IEN, Intraepithelial neoplasia.

these differences in the use of the terminology of dysplasia, adenoma, early cancer, and advanced cancer. Feedback from the analysis of the pathology specimen is critical to teaching endoscopic diagnosis in Japan and leads to continuing education that helps move endoscopists along the learning curve. From a Japanese perspective, Western endoscopists tend to lack attention to endoscopic detail in obtaining images and descriptions of superficial lesions. While this may be, in part, because of differences in endoscopes and ancillary techniques such as chromoendoscopy, there is the sense that Western endoscopists do not appreciate and underuse precise endoscopic description, which can be of great value in assessing depth of invasion and in deciding treatment.

The distinct East and West points of view on the importance of endoscopic description developed during the second half of the twentieth century. In Japan, the high burden of gastric cancer encouraged early detection, at first with endoscopy and then with double contrast radiology. Because flat precursors play an almost exclusive role in gastric carcinogenesis, early endoscopic detection required extreme rigor during the endoscopic procedure. Additional techniques, such as chromoendoscopy and magnification, also were developed to help identify subtle lesions. Meanwhile, improved gastroscopes were made in Japan. These instruments, with improved optics, were initially tested at leading Japanese medical centers.

In Japan, the approach to early detection of neoplastic lesions in the esophagus and later in the colon continued along similar lines to those of gastric cancer. Some highly skilled endoscopists limit their practice to a single organ. At the same time the Japanese were concentrating on gastric carcinoma, many other countries were emphasizing the prevention of colorectal cancer. Polypoid precursors play a much greater role in large bowel neoplasia, and the polyp-cancer sequence established by Muto, Bussey, and Morson in 1975[6] is still valid. Chromoendoscopy is much less useful for polypoid than for non-polypoid lesions, and detailed endoscopic analyses of the morphology of a polyp are less helpful in the prediction of invasive malignancy than is the gross evaluation of size or expansion of the stalk. Therefore, routine chromoendoscopy at colonoscopy carried out to detect adenomas often is considered to have little value in the West.[7] Consequently, small non-polypoid (flat) adenomas (noninvasive neoplasia) or even carcinomas may go undetected.

The East and West points of view are now much closer. Asian, European, and American pathologists[5,8-10] proposed a consensus histopathologic classification in 3 major groups for intramucosal neoplasia: noninvasive low grade, noninvasive high grade, and cancer with invasion of the lamina propria (Table 1). This consensus, adopted in Vienna, has been published in a recent supplement of *Gastrointestinal Endoscopy*.[11] Merging endoscopic and pathologic terminologies will use the potential advantages of each of them. The Vienna classification, adopted (in part) in the recent World Health Organization (WHO) classification of digestive tumors,[12] has been slightly modified, with improved agreement scores and therapeutic relevance.[13-15]

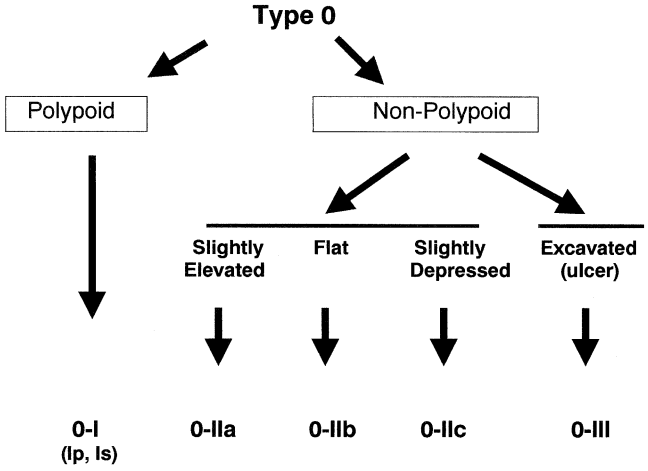
With respect to macroscopic morphology, the existence of small, but potentially malignant, non-polypoid lesions in the large bowel is now acknowledged; however, the importance of their role as precursors of advanced cancer is still unclear in Western populations.[7,16,17] Last, but not least, the increasing incidence of neoplasia in Barrett's esophagus (where non-polypoid precursors play a major role) has stimulated the interest of Western specialists in improving the detection, description, and classification of non-polypoid dysplastic lesions.

TERMINOLOGY AND DEFINITIONS

Superficial neoplasia at endoscopy

A neoplastic lesion is called "superficial" when its endoscopic appearance suggests that the depth of penetration in the digestive wall is not more than into the submucosa, i.e., there is no infiltration of the muscularis propria. In the esophagus, neoplasia develops in the stratified squamous epithelium or in a metaplastic columnar mucosa (Barrett's esophagus). Distal to the esophagus, neoplasia develops in the columnar mucosa in the stomach. A distinction is made between tumors located at the cardia and tumors distal to the cardia (sub-cardiac tumors). Tumors at the esophagogastric junction include adenocarcinoma in the distal esophagus and at the

Table 2. Neoplastic lesions with "superficial" morphology



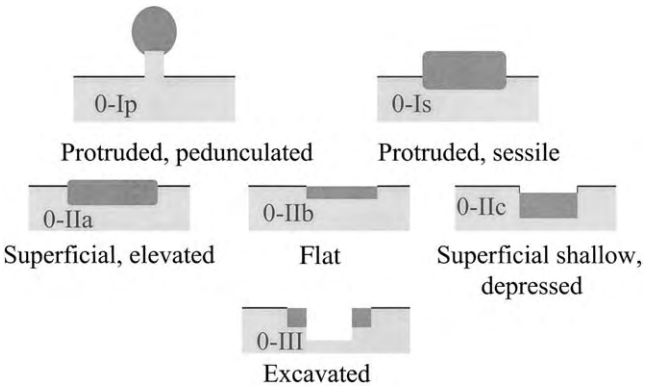


Diagram 1. Schematic representation of the major variants of *type 0* neoplastic lesions of the digestive tract: polypoid *(Ip and Is)*, non-polypoid *(IIa, IIb, and II c)*, non-polypoid and excavated *(III)*. Terminology as proposed in a consensus macroscopic description of superficial neoplastic lesions.[15]

cardia. Tumors of the large bowel (colon and rectum) are described in a single group.

"Superficial" neoplasia includes neoplastic lesions with no invasion in the lamina propria and carcinoma with invasion of the lamina propria and a depth of penetration limited to the mucosa (stomach and esophagus) or the submucosa (large bowel). The name "early cancer" suggests a localized tumor with potential for complete cure after complete resection, i.e., a low risk for lymph node metastases. Non-neoplastic lesions of the columnar epithelium (juvenile or, in the large bowel, hyperplastic polyps) also have a "superficial" morphology. Hyperplastic polyps have little or no potential for transformation to neoplastic lesions, but serrated adenomas are uncommon, noninvasive neoplastic lesions, combining neoplastic cells and a serrated structure.

Polypoid and non-polypoid neoplastic lesions

The distinctive characters of polypoid and non-polypoid lesions are summarized in Table 2 and Diagram 1, and illustrated in Diagrams 2 to 11.

A polypoid neoplastic lesion protrudes above the surrounding surface at endoscopy. In the operative specimen, the height of the lesion is more than double the thickness of the adjacent mucosa. In pedunculated polyps, the base is narrow; in sessile polyps, the base and the top of the lesion have the same diameter. Intermediate and broad-based forms are called semi-pedunculated *(Isp);* they should be managed just as sessile polyps.

Non-protruding or non-polypoid neoplastic lesions include ulcers and the so-called flat lesions. In the latter situation, the lesion, compared with the adjacent mucosa, is either slightly elevated, or completely flat, or depressed (absolutely depressed). At endoscopy, slightly elevated lesions are easily misclassified as sessile (polypoid subtype). This distinction is more reliable on pathologic examination of an operative specimen, in which it is possible to compare the height of the lesion with the full thickness of the normal mucosa. Some elevated lesions may reach a large (>10 mm) lateral diameter without increasing their height or protrusion above the mucosa. In the colon, these are called "lateral spreading type." In the case of depressed lesions, the entire thickness of the mucosa in the lesion is often less than that of the adjacent mucosa. Some elevated lesions have a central depression. When there is a shallow depression at the top of an elevated lesion, which is still more elevated than the surrounding normal mucosa, the depressed portion of the lesion is called "relatively depressed."

Metaplasia

Metaplasia is the transformation of an epithelium to another type of epithelium with distinct morphology and function. Intestinal metaplasia in the esophagus and stomach is classified as complete (type I) or incomplete (type II or III). Intestinal metaplasia type I is largely composed of absorptive cells with a well-defined brush border, some goblet cells, and occasional Paneth cells. Intestinal metaplasia type II and III are characterized by columnar intermediate cells and goblet cells that secrete sialomucin (type II) or sulfomucin (type III). In the distal esophagus, metaplasia is composed of 3 distinct types of epithelium, distributed in a patchwork or mosaic pattern: cardiac or junctional-type epithelium, where glands are composed almost entirely of mucus-secreting cells; oxyntic-type epithelium, where parietal and chief cells are present;

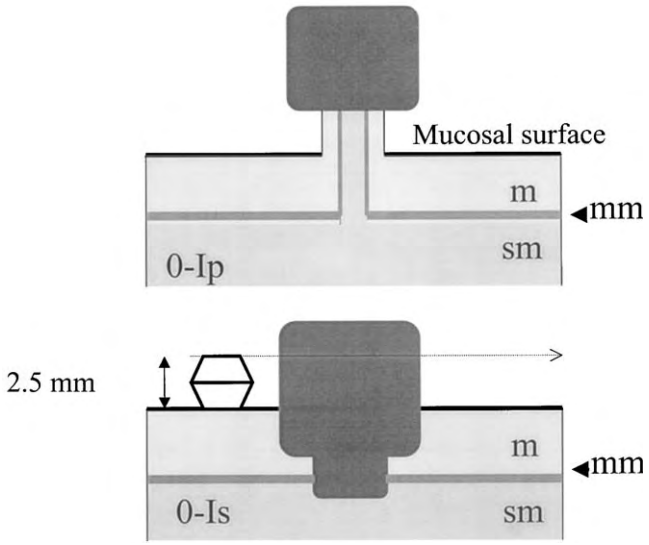


Diagram 2. Neoplasia in the columnar epithelium (Barrett's esophagus, stomach, colon, and rectum): *types 0-I*: pedunculated *(Ip)* or sessile *(Is)* in transverse section. In *0-Is* the protrusion of the lesion *(dark)* is compared with the height of the closed cups of a biopsy forceps (2.5 mm); the dotted arrow passes under the top of the lesion. *m*, mucosa, *mm*, muscularis mucosae; *sm*, submucosa.

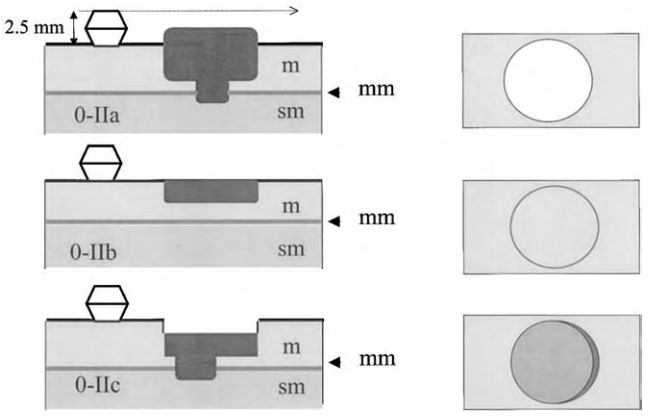


Diagram 3. Neoplasia in the columnar epithelium (Barrett's esophagus, stomach, colon, and rectum): *types 0-II* elevated *(IIa)*, completely flat *(IIb)*, or depressed *(IIc)*. In the transverse section, the lesion is compared with closed cups of a biopsy forceps (2.5 mm); the *dotted arrow* passes above the top of the *IIa* lesion. In the frontal view, the elevated, flat, or depressed zones of the mucosa are presented in distinct shading.

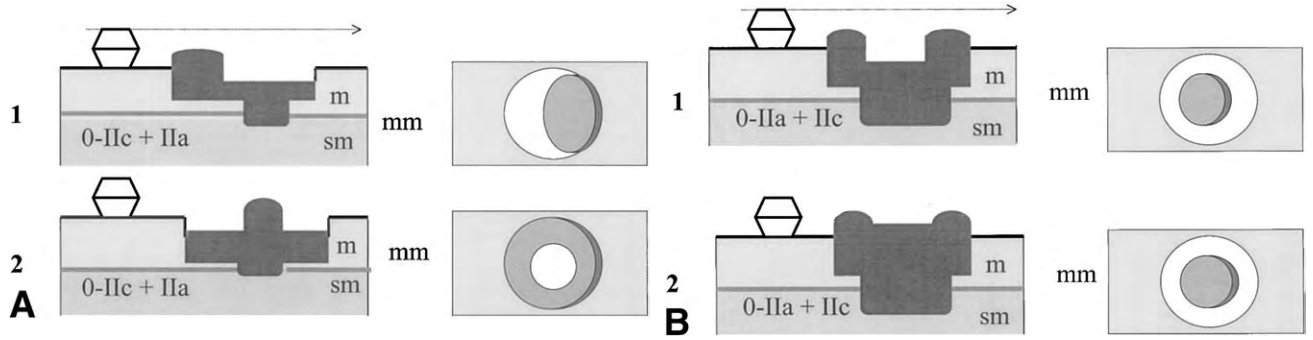


Diagram 4. Neoplasia in the columnar epithelium (Barrett's esophagus, stomach, colon, and rectum): combined *types 0-IIa and 0-IIc*. In the transverse section, the lesion is compared with the closed cups of a biopsy forceps (2.5 mm). In the frontal view, the elevated and depressed zones are presented in distinct shading. **A**, Types *IIc + IIa*: elevated area in a depressed lesion. **B**, Types *IIa + IIc:* depressed area in an elevated lesion. Two variants are shown in transverse section and frontal view. In variant 2, the depressed area at the top does not reach the level of the surrounding mucosa; this is a relatively depressed lesion.

intestinal type epithelium, often called "specialized intestinal metaplasia." In the stomach, intestinal metaplasia is associated with chronic gastritis and *Helicobacter pylori* infection. In both sites there also can be pancreatic metaplasia.

Adenoma and dysplasia

In Western countries, a noninvasive neoplastic and benign lesion of the columnar epithelium is called an "adenoma" when protruding (polypoid) and a "dysplasia" when flat or depressed (non-polypoid),[18-20] although the terms "flat adenoma" and "depressed adenoma" are accepted and commonly used for discrete lesions. Low-grade or high-grade intraepithelial neoplasia, without invasion into the lamina propria also is called adenomatous or dysplastic epithelium. In Asian countries, both types of lesions are called adenoma in the stomach[21-25] or in the large bowel,[26-30] with a distinction between polypoid, flat, and depressed adenomas. In the Vienna consensus classification for intramucosal neoplasia, the terms adenoma and dysplasia are both replaced by "intraepithelial neoplasia."

The morphology of an area of intraepithelial neoplasia has an impact on the prognosis; a higher

risk of progression to cancer is associated with depressed lesions.

The name "de novo" cancer applies to small (often less than 5 mm), flat or depressed cancerous lesions, when there are no adenomatous glands in the operative specimen, suggesting that the carcinoma did not develop from an adenomatous or dysplastic precursor.

The histopathologic classification of neoplasia

A consensus classification of the progression of neoplasia in the digestive mucosa was proposed after the Vienna Workshop[5] and revised recently,[13] as shown in Table 1. The classification applies to stratified squamous epithelium and to columnar epithelium (Barrett's esophagus, stomach, large bowel). In the absence of invasion into the lamina propria of the mucosa, noninvasive neoplastic lesions are classified by the degree of intraepithelial neoplasia into two groups: low grade and high grade.

The interobserver variation in the distinction between low-grade dysplasia and indefinite for dysplasia/intraepithelial neoplasia and also between "negative" or "indefinite" for dysplasia/intraepithelial neoplasia is large; but variation is much less with the diagnosis of high-grade dysplasia compared with other grades. High-grade intraepithelial neoplasia, with severe nuclear changes and architectural complexity, equivalent to carcinoma, has also been called "carcinoma in situ."

Site variations in the terminology. In the stratified squamous epithelium of the esophagus, high-grade intraepithelial neoplasia, intraepithelial carcinoma, and in situ carcinoma, are equivalent names. When there is invasion of the lamina propria of the mucosa, the lesion is called micro-invasive or intramucosal carcinoma.

In the columnar epithelium of Barrett's esophagus, stomach, and large bowel, lesions with high-grade intraepithelial neoplasia and no invasion of the lamina propria have been called intramucosal carcinoma in Japan and high-grade dysplasia in Western countries. Most of the divergence disappears when the Vienna consensus classification is used. In the revised version of the classification, the lesions called intramucosal carcinoma in the East and high-grade dysplasia in the West become subdivisions of the same group (Group 4; see Table 1).

The consensus terminology makes a distinction between high-grade intramucosal neoplasia with no invasion of the lamina propria and high-grade intramucosal neoplasia with invasion of the lamina propria. The latter is called intramucosal carcinoma in the esophagus or stomach. In the large bowel, the risk of nodal invasion is nil in this situation, and there is a tendency in the West to avoid the terminology "carcinoma" for lesions without submucosal invasion, because they are completely cured with local excision. Beyond this stage, all neoplastic lesions with invasion of the submucosa are called invasive carcinoma.

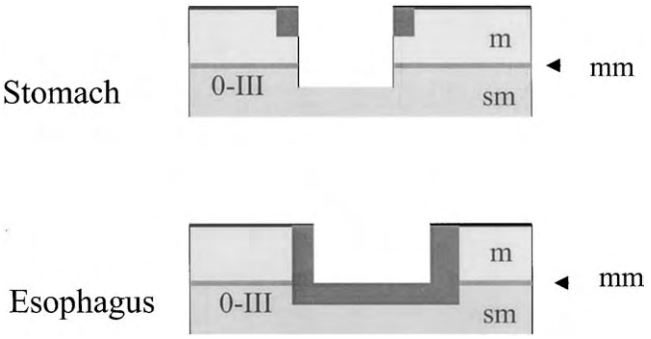


Diagram 5. Neoplasia in the columnar epithelium (Barrett's esophagus and stomach): type *0-III* excavated. In the stomach, the bottom of the lesion is non-neoplastic. In Barrett's esophagus, the neoplastic area covers the entire surface of the lesion.

The TNM classification. Before treatment, with the help of diagnostic tests and procedures, the tumor is staged according to the TNM classification; the depth of tumor invasion in the bowel wall corresponds to the T of the classification. In the esophagus, the stomach, and the large bowel, the endoscopist classifies the morphology of "superficial" neoplastic lesions (intraepithelial neoplasia and carcinoma) in the variants of *type 0*. The pathologist classifies the histology of the tumor in the groups of the Vienna classification of neoplasia.

When an operative specimen is available, the depth of invasion is classified by the pathologist according to the T of the p-TNM classification ("p" is postoperative). In the esophagus and the stomach, intraepithelial tumors with no invasion of the lamina propria (p-Tis), are called carcinoma in situ and are not included in tumor registries. In the esophagus and in the stomach, intramucosal carcinoma with invasion of the lamina propria is called p-T1m; carcinoma with invasion of the submucosa is called p-T1sm. In the large bowel, the terms p-Tm and p-Tis usually are avoided in the West because they have no clinical relevance regarding survival, and they are classified as high-grade intraepithelial neoplasia. When there is invasion of the submucosa, the tumor is p-T1sm. This double histologic and TNM classification is presented in the recent edition of the WHO classification.[12] In summary, a superficial carcinoma in the digestive mucosa will be classified as p-Tis, p-Tm (esophagus, stomach) or p-Tsm (esophagus, stomach, colon).

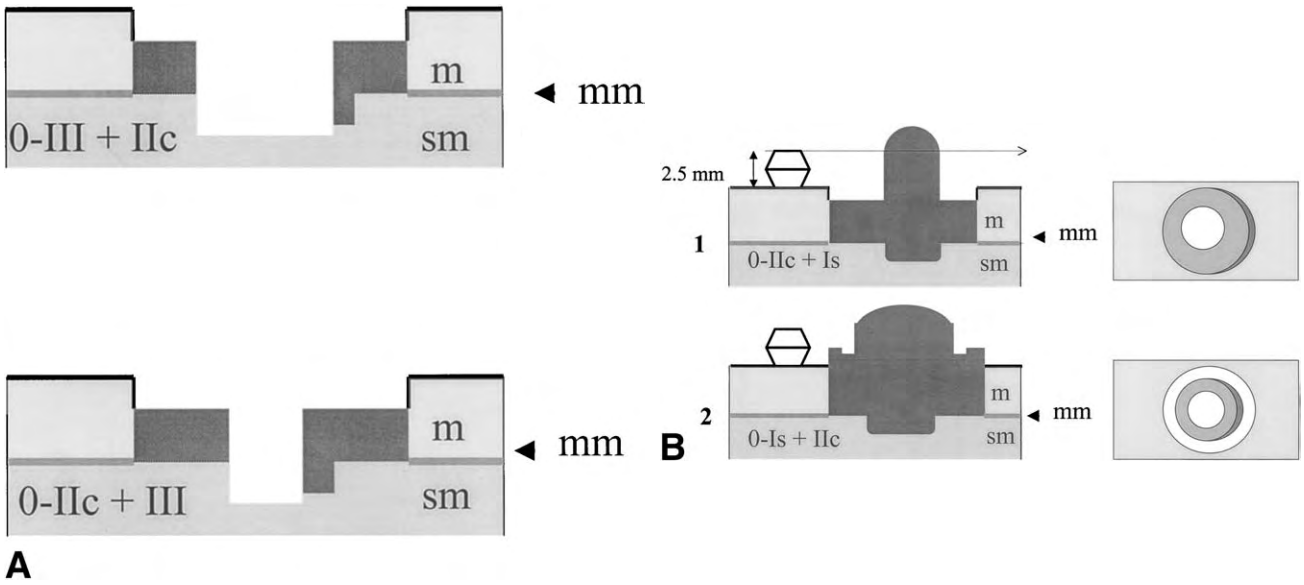


Diagram 6. Neoplasia in the columnar epithelium (Barrett's esophagus, stomach, colon, and rectum): in the transverse view, the lesion is compared with the height of the closed cups of a biopsy forceps (2.5 mm). In the frontal view, the elevated, depressed, or relatively depressed zones of the mucosa are presented in distinct shading. **A**, Combined *types 0-III and 0-IIc. Type III + IIc*: a large excavated lesion in a depressed zone. Type *IIc + III*: a small excavated zone in a depressed lesion. **B**, Combined types *0-Is and 0-IIc. Type IIc + Is*: the *dotted arrow* passes under the elevated zone. *Type Is + IIc*: the depressed zone is more elevated than the adjacent mucosa; this is a relatively depressed lesion.

METHODOLOGY FOR CLASSIFICATION

Endoscopic detection and chromoendoscopy

Recent models of videoendoscopes meet the requirements for the acquisition of a high-quality digital image in terms of resolution, color reproduction, contrast, and structure enhancement. The primary step in diagnosis is to identify the presence of an area of the mucosa slightly discolored (more pale or more red), an irregular microvascular network, or a slight elevation or depression.

The second step in diagnosis is based on chromoendoscopy, to help in the meticulous description of the lesion. Chromoendoscopy should be readily available and should be performed when a target lesion has been detected. The routine use of endoscopic dyes to improve the imaging of a focal lesion does not mean that a systematic application covering the entire mucosal surface must be performed in every case. Diffuse staining to increase the yield of detection has, however, been proposed in those at high risk of neoplasia (e.g., familial colorectal cancer or ulcerative colitis).

A variety of agents have been proposed for chromoendoscopy. Iodine solution (1.5%-2%), a vital stain, is the basic agent used for the stratified squamous epithelium of the esophagus.[31,32] Neoplastic areas remain unstained (negative stain), in contrast to the dark brown positive stain of the normal epithelium. The dye most commonly used on abnormal areas of the stomach and the colon is indigo carmine solution (0.5%-1%), a contrast stain. Chromoendoscopy with indigo carmine helps in the distinction between non-neoplastic (hyperplastic) or neoplastic lesions in the large bowel. Indigo carmine dye spraying, which is practiced routinely in Japan,[33,34] has been used in the West,[35-39] but is still uncommon.[40] Methylene blue chromoendoscopy has been used for the detection of intestinal metaplasia[41-46] in the esophagus and the stomach and has been used in the large bowel by spraying a 0.1% solution in successive segments. In a recent randomized study, this procedure was applied to the surveillance of patients with ulcerative colitis. An increased yield of non-polypoid neoplastic lesions was obtained in the group of patients evaluated with chromoendoscopy with magnification endoscopy.[47] Magnification optics were believed to be a major factor of improved efficacy.[48] The endoscopic application of dilute acetic acid has been proposed as a useful agent in studying the architecture of the metaplastic mucosa in Barrett's esophagus.[49,50]

Video and still-picture recording of lesions detected at endoscopy has been simplified with the digital equipment available in the modern endoscopy unit. Such recordings have proven helpful during follow-up. The selection of the most representative image for each lesion, a routine practice in Japan, also has been a stimulant for the precise description

of the lesion. Routine image recording for all procedures recently has been included in the guidelines of the European Society of Gastrointestinal Endoscopy[51] and is practiced at many institutions worldwide.

Endoscopic classification in *type 0*

During endoscopy, the assessment of the morphology of a superficial neoplastic lesion in the digestive mucosa is based on quantitative and qualitative criteria. At first, the size of the lesion and its diameter are quantified as precisely as possible, preferably by using a graduated gauge. Then the morphology is classified into one of the 5 types of the Japanese-Borrmann classification for advanced cancer or in *type 0* if the appearance of the lesion is compatible with a superficial lesion (mucosa or submucosa). At this stage, the macroscopic classification is decided only from the gross appearance. The classification should not be influenced by any previous information and should not be modified by the findings of the pathologist. This means that the superficial pattern at endoscopy may be invalidated by the results of the pathology. A lesion with a *type 0* endoscopic appearance may turn out to be an advanced cancer on pathology in the p-TNM classification, or the reverse. In the Japanese studies, most superficial endoscopic lesions are classified according to subtypes of *type 0*; this applies to squamous cell carcinoma in the esophagus,[52-55] and to adenocarcinoma in the gastric cardia,[56] in the distal stomach,[57-67] and in the colon and the rectum.[68-73] The Japanese classification has sometimes been used by Western investigators for neoplastic lesions in Barrett's esophagus[74] and also in the large bowel (with the cooperation of Japanese experts).[16,17,75-77]

Type 0 lesions are classified in 3 distinct groups:
type 0-I, polypoid
type 0-II, non-polypoid and nonexcavated
type 0-III, non-polypoid with a frank ulcer

The subgroups I and II are again segmented.

Type 0-I includes two variants:
pedunculated (*0-Ip*)
sessile (*0-Is*)

Type 0-II includes 3 variants:
slightly elevated (*0-IIa*)
completely flat (*0-IIb*)
slightly depressed without ulcer (*0-IIc*)

The distinction between a depressed (*0-IIc*) and an excavated or ulcerated lesion (*0-III*) is readily made in the operative specimen. In the excavated lesion, there is a sharp discontinuity in the epithelial layer, and the muscularis mucosae is interrupted. A consensus macroscopic description of superficial neoplastic lesions has been published recently (Table 2).[15]

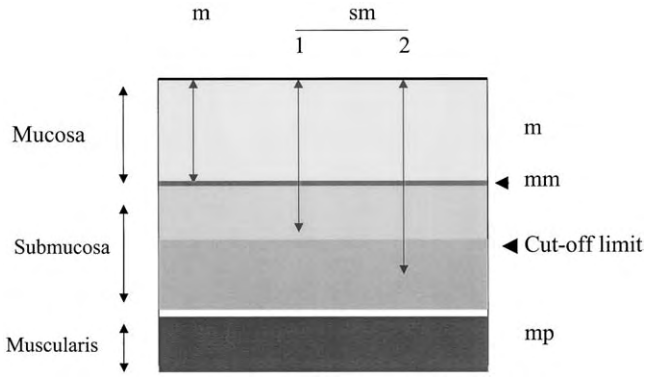


Diagram 7. Depth of invasion of the submucosa in the columnar epithelium (Barrett's esophagus, stomach, colon, and rectum) assessed in the specimen obtained after surgery. Depth of submucosal invasion is divided into two groups: superficial (sm1) and deep (sm2) with respect to a cutoff limit determined on a micrometric scale (500 μ in the stomach, 1000 μ in the colon).

Mixed types associate two distinct types of morphology. The pattern consisting of an elevation (*IIa*) and a depression (*IIc*) is easily diagnosed at endoscopy. However, the exact placement of this mixed type in the Japanese classification requires a precise evaluation of the morphology, and there is room for interobserver disagreement because the relative surface of each type is not the only factor relevant to prognosis. A depressed lesion with elevated borders or a central elevation is classified as *type 0-IIc + IIa*. An elevated lesion with a central depression at its top is classified as *type 0-IIa + IIc*. This mixed type includes relatively depressed lesions in which depressed areas do not reach below the level of the normal mucosa. As a rule, *type IIa + IIc* lesions have a poorer prognosis, with a risk of large invasion in the submucosa than all other types of lesions, including the *IIa* pattern. Other mixed types and site variations of the classification are described; this results in excessive complexity (Tables 3-13, pages S15-S17).

Hints for application of the classification

- In a pragmatic and simple approach, it is mandatory to classify superficial lesions routinely in at least one of the 5 major types: *0-I, 0-IIa, 0-IIb, 0-IIc, 0-III*, shown in Table 2 and Diagram 1. The relative proportions of each type differ in the esophagus, the stomach, and the large bowel.

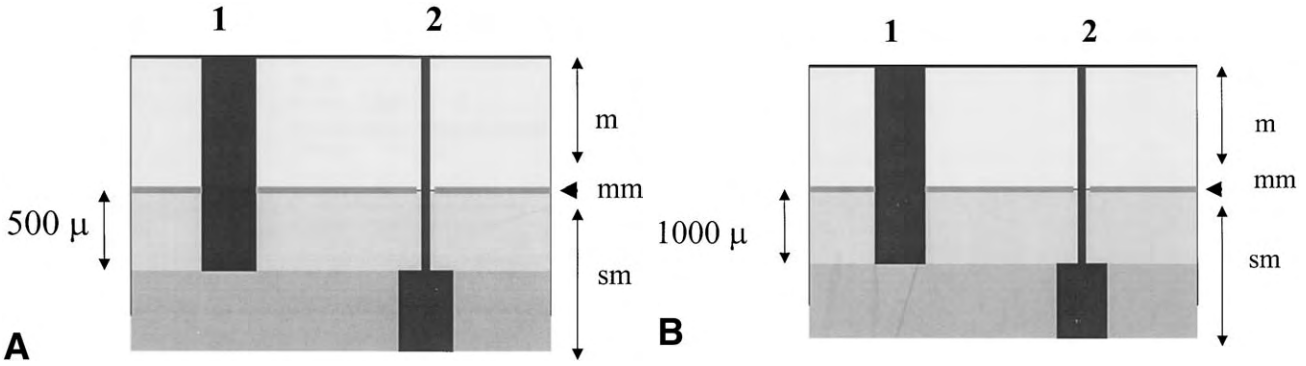


Diagram 8. Depth of invasion of the submucosa in the columnar epithelium, assessed for the clinical relevance of EMR and for the risk of nodal metastases. Group 1 (m and sm1): EMR is possible. Group 2 (sm2): surgical treatment is preferred. **A**, Barrett's esophagus and stomach: the cutoff limit between sm1 and sm2 is 500 μ. **B**, Colon and rectum: the cutoff limit between sm1 and sm2 is 1000 μ.

- Polypoid *0-I* lesions can be divided into *type 0-Ip* and *type 0-Is* (pedunculated and sessile). In the absence of clinical relevance, an intermediate *type 0-Isp* (semipedunculated) is not necessary; such lesions are managed as *type Is* lesions.
- Special attention is attached to depressed *type 0-IIc* lesions. The distinction between a depressed (*0-IIc*) and ulcerated lesion (*0-III*) during endoscopy is based upon the depth of the depression and the analysis of the epithelial surface in the depressed area. Superficial erosions in a depressed lesion involve only the most superficial layers. In the ulcerated lesion, there is loss of the mucosa and often of the submucosa. In the large bowel, *type 0-IIc* lesions, even of small diameter, are often at a more advanced stage of neoplasia, with deeper invasion than the other types.
- With small and elevated neoplastic lesions, the respective classification in the polypoid sessile *type 0-Is* or in the non-polypoid elevated *type 0-IIa* is made easier by placing a biopsy forceps next to the lesion as a calibrating gauge. This standard applies to the height of the lesion and not to its diameter. Lesions protruding above the level of the closed jaws of the biopsy forceps (approximately 2.5 mm) are classified as *0-Is*; lesions protruding below this level are classified as *0-IIa*.
- When there is a depression at the center of a neoplastic lesion, its level is compared with that of the adjacent mucosa. The lesion is classified as absolutely depressed when the level of depression is lower than the surface of the adjacent mucosa and as relatively depressed when the depression is still higher than the surface of the adjacent mucosa; this applies particularly to the large bowel.
- The same qualitative and quantitative scale is used for the classification of neoplasia in the columnar mucosa of Barrett's esophagus, stomach, and large bowel. The scale applies as well for neoplasia in the duodenum or the small intestine. The principal variations in the morphology of *type 0* neoplastic lesions are shown in Diagrams 1-6.
- In the esophagus, neoplasia in the stratified squamous epithelium is classified in identical major subtypes but with a distinct quantitative scale. The standard of comparison is a single cup of the opened biopsy forceps. Lesions protruding above the level of the cup (approximately 1.2 mm) are classified as *0-Is*. The depth of depressed lesions is compared with half the level of a single cup (approximately 0.6 mm). The morphology of *type 0* neoplastic lesions in the stratified epithelium of the esophagus is shown in Diagram 9.

Lesions included in the classification

The classification of *type 0* neoplastic lesions applies to carcinomas, benign intraepithelial neoplasia, whether low grade or high grade, and also to non-neoplastic lesions that are capable of harboring a neoplastic component (e.g., hyperplastic polyps).

A number of morphologic alterations of the mucosal surface associated with inflammation are only listed as risk factors and are not included in the *type 0* classification. This applies to the inflammatory lesions of esophagitis, associated with squamous cell cancer in parts of Asia[78,79] and to chronic gastritis secondary to *H pylori* associated with gastric cancer. The rule also applies to specialized intestinal metaplasia in Barrett's esophagus, a known risk factor for cancer[80-83] and to intestinal metaplasia (in association with inflammation and atrophy) in the stomach.

Although there is a distinct endoscopic appearance of intestinal metaplasia when using chromoendoscopy or magnification endoscopy, this morphologic appearance is not included in the *type 0* classification.

In the stomach, a majority of lesions with low-grade intraepithelial neoplasia never progress to cancer, while high-grade, noninvasive intraepithelial neoplasia progresses to cancer much more readily.[84] Studies with biomarkers confirm that neoplastic lesions in the cardia have a distinct natural history as compared with those in the distal stomach.[85] Specific immunohistochemistry characteristics are attributed to intestinal metaplasia at the esophagogastric junction[86-89] and in the stomach.[90] Adenomas of the stomach are rare and most will not progress to cancer.[91] Isolated non-neoplastic hyperplastic polyps rarely undergo neoplastic transformation, but this does occur in gastric polyposis.[92] Serrated adenomas are rare in the stomach.[93]

In the large bowel, non-neoplastic polyps are frequent. In the material collected for the National Polyp Study in the United States, 8.5% of the patients were excluded for this reason.[94] Most non-neoplastic hyperplastic polyps are not protruding, and their slightly elevated appearance would be classified as a *type 0-IIa*. Aberrant crypt foci are considered to be the earliest precursors of colorectal neoplasia, but progression to macroscopic neoplastic lesions probably is rare.[95-97] In fact, aberrant crypt foci, which can be detected on magnification endoscopy as small protrusions, can be considered to be the most diminutive examples of *type 0* lesions.

In the large bowel, the correlation between the macroscopic appearance and the histology of superficial neoplastic lesions has been reviewed recently.[98] Many Japanese experts are convinced that there are two major pathways for neoplastic lesions, stressing the role of non-polypoid precursors [99-105] and the faster rate of progression of depressed lesions.[106-107] However, this also can be interpreted as differences in terminology, because small but high-grade adenomas in the West may be called "de novo carcinomas" in Japan.

In the Western interpretation, a small adenoma with high-grade dysplasia may evolve rapidly into a small flat invasive carcinoma that loses evidence of its adenomatous origin. This is likely a major route in hereditary non-polyposis colon cancer (HNPCC). There is a recent trend in the Western studies[108-111] to accept a broader spectrum of progression for neoplastic lesions, including the role of non-polypoid lesions and the concept of de novo cancer. Indeed, there are likely numerous pathways at the molecular level. Molecular biology also suggests that non-polypoid lesions have a distinct evolution with

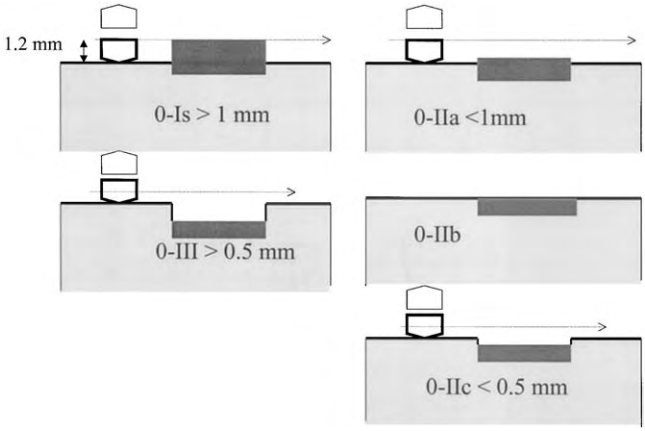


Diagram 9. Squamous cell neoplasia in the esophagus. Adapted scale of thickness in transverse section for the major subtypes: polypoid, non-polypoid, and excavated. The m and sm are represented as a single layer. The protruding lesions are compared with one open cup of a biopsy forceps (1.2 mm); the *dotted arrow* passes above the top of the *Is* and *IIa* lesions. The depressed lesions are compared with half the height of an open cup.

a greater likelihood of early p53 and delayed K-*ras* mutations.[112-120] Serrated adenomas, classified as neoplastic lesions, may show biomarkers similar to non-polypoid neoplastic lesions.[121-126]

Endoscopic staging

The morphology of a *type 0* neoplastic lesion has predictive value for depth of invasion into the digestive tract wall, providing an "endoscopic staging." Thus, endoscopic descriptive morphology can assist in treatment decisions involving endoscopic resection or surgery. The primary role for endoscopic staging is to predict the risk of submucosal invasion and the associated risk of nodal metastases.

For a *type 0-I* lesion, diameter is a reliable predictive criterion. The risk of submucosal invasion increases with the diameter. On the other hand, with *type 0-II* lesions, the morphologic subtypes have greater importance. Invasion of the submucosa is more frequent in depressed lesions (*IIc*).

The less than perfect reliability of endoscopic staging can be improved by EUS, particularly with high frequency probes (20 MHz). Both endoscopic morphologic staging and EUS have their limits. Endoscopy tends to understage superficial lesions, and EUS tends to overstage them. When the two methods agree, the predictive value is high.[58]

The specimen collected after EMR

In the endoscopy unit, the single tissue specimen obtained after en bloc mucosectomy should be gently stretched. The deep margin of the specimen can be

marked with dye or India ink. The specimen should then be pinned on cardboard or a similar soft, porous material with the mucosal surface up and placed in neutral formalin.

For lesions removed with a piecemeal technique, the endoscopist should, if possible, reconstruct the complete surface of the lesion on cardboard from the fragments. The surface of the fixed specimen should be examined and photographed. A more detailed examination, by using crystal violet staining and stereomicroscopy, may prove helpful in correlative studies of the surface between pathology and magnification endoscopy.

The specimen (surgery or EMR) in the pathology laboratory

In the pathology laboratory, the specimen is withdrawn from the fixative and pre-cut in parallel fragments, 2 mm in width for EMR specimens and 5 to 6 mm in width for surgical specimens. The margins in the adjacent normal mucosa are included for analysis in the serial histologic sections. The pathologist evaluates the histology (ideally according to the Vienna classification) and assesses the degree of differentiation of the tumor, the depth of invasion, and the completeness of excision.

The resection is complete if the margins of the specimen are free from tumor tissue on serial sections; this concerns the proximal and the distal margins of surgically resected specimens and all the margins (vertical and lateral) on EMR specimens.

Depth of cancer invasion into the submucosa is a critical factor in predicting the risk of nodal metastases in superficial tumors of the digestive mucosa. This applies to prognosis after a segmental surgical resection and guides treatment after EMR. The risk of nodal metastasis is relatively low when cancer invasion is limited to the superficial submucosa, and significantly higher when invasion reaches the deep submucosa (Tables 15-18, page S18).

In surgically resected specimens from the esophagus, the muscularis propria is present, and the full thickness of the submucosa is available. This allows a reliable, semiquantitative evaluation of the depth of tumor invasion in the submucosa, divided into 3 sectors of equivalent thickness: sm1, sm2, and sm3. However, in EMR specimens, the complete submucosa is not available, and the semiquantitative evaluation of the depth of invasion is not fully reliable. The only precise method is a quantitative micrometric measure in microns (μ) of the depth of invasion, measured from the bottom of the mucosa (i.e., the lower layer of the muscularis-mucosae). The risk of nodal metastasis is assumed to be low when the depth of invasion is less than a determined cutoff.[127]

In surgically resected specimens from the stomach and the colon, the semiquantitative evaluation of the invasion in the submucosa (divided in two or 3 sectors) is less and less used. Currently, the quantitative micrometric measure is the common guideline for the specimens issued from a surgical or an endoscopic resection. The categorization of cancer invasion as superficial or deep in the submucosa is determined by an organ-specific limit fixed at a certain depth. With the quantitative method of measurement, sm1 means "less invasive than the cutoff limit," and sm2 means "deeper than the cutoff limit." In Japan, the pathologists have established distinct empirical cutoff limits for columnar neoplasia in the stomach[128] and columnar neoplasia in the large bowel.[129,130] Application of these categories to surgical specimens is the only way to achieve comparability between EMR and surgical resections.

Invasion of the submucosa in squamous cell neoplasia of the esophagus

In the esophageal mucosa, 3 distinct layers are described; they correspond, respectively, to the epithelium (m1), the lamina propria (m2), and the muscularis mucosae itself (m3). In the operative specimen where the full thickness of the wall (including muscularis propria) is available, the submucosa is arbitrarily divided in 3 successive sectors of equivalent thickness (sm1, sm2, sm3), as shown in Diagram 10. This precise subdivision into 6 layers has been proposed because the risk of nodal metastases increases from nil to high with the depth of invasion in the successive layers of the mucosa and submucosa. The correspondence between depth of invasion in a complete transverse section of the esophageal wall and the most appropriate treatment is shown in Diagram 11a. Cancer invading only the superficial levels (m1 + m2) usually can be treated successfully with EMR. Invasion into deep levels (sm2 + sm3) usually requires surgery for a cure. Middle level invasion (m3 + sm1) requires balancing clinical factors with surgery, preferred when the performance status of the patient is high. However, in a specimen obtained after EMR, the full thickness of the submucosa is not available, and this division is not valid. Therefore, invasion in the submucosa is measured with a micrometric scale, from the bottom of the mucosal layer (i.e., the lower layer of the muscularis mucosae). In Japan, an empirical cutoff value has been adopted. When cancer invasion of the submucosa is less than 200 μ, the risk of nodal metastases is small, and EMR can be considered safe.[127] The cutoff limit is shown in Diagram 11b. In this situation, the quantitative scale should be used instead of describing the layers as sm1 and sm2.

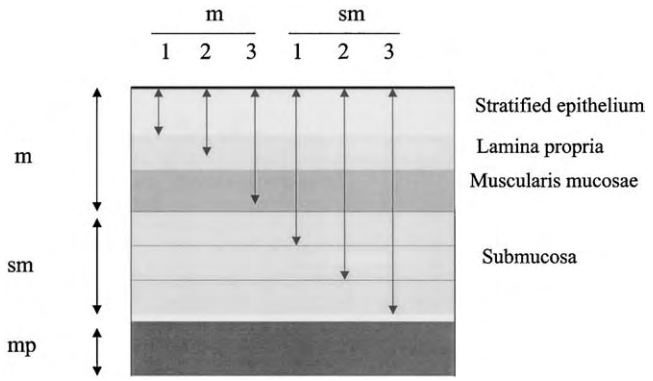


Diagram 10. Depth of invasion of squamous cell neoplasia in the esophagus. Mucosal carcinoma is divided into 3 groups: m1 or intraepithelial, m2 or micro-invasive (invasion through the basement membrane), m3 or intramucosal (invasion to the muscularis mucosae). The depth of invasion in the submucosa is divided into 3 sections of equivalent thickness: superficial (sm1), middle (sm2), and deep (sm3).

Invasion of the submucosa in columnar neoplasia of the stomach and the large bowel

For adenocarcinomas in Barrett's esophagus and the stomach, subdivisions also are proposed to stratify depth of invasion in the submucosa by using the same quantitative method for operative and EMR specimens. In EMR specimens from Barrett's esophagus or the stomach, the cutoff value for invasion into the submucosa is 500 μ (Diagram 8a). The rationale for this value is that when the depth of invasion is less than 500 μ into the submucosa (sm1), the risk of nodal metastases is low[128] and endoscopic treatment can be considered adequate (Table 17). On the contrary, surgery is preferable when invasion is more than 500 μ deep (sm2).

In the colon, the risk of nodal metastases is low when cancer invasion of the submucosa is limited to the most superficial third and extends laterally to less than 50% of the width of the mucosal lesion. Nodal metastases frequently occur, associated with lesions, with massive invasion of the submucosa, either laterally in the superficial third or in deeper invasion reaching the middle or the lower third.

Some investigators use, as in the esophagus, a semiquantitative evaluation of invasion depth in the colonic submucosa in 3 sectors (1, 2, 3) of equivalent thickness and in 3 groups (a, b, c) for lateral extent in the superficial layer. A limited invasion corresponds to sm1a and sm1b, and a massive invasion to sm1c, sm2, and sm3. In EMR specimens from the large bowel, the cutoff value adopted for quantitative micrometric measure is 1000 μ[130] (Diagram 8b). An EMR can be considered safe when invasion of the submucosa is less than 1000 μ.

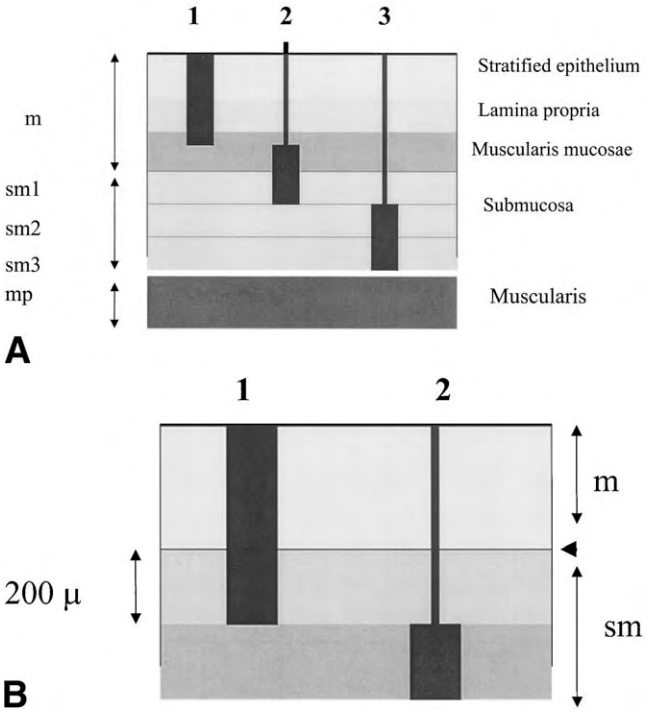


Diagram 11. Depth of invasion of squamous cell neoplasia in the esophagus adapted for relevance to EMR and the risk of nodal metastases. **A**, Full-thickness specimen. Group 1 (m and sm1): EMR is possible. Group 3 (sm2 and 3): surgical treatment. Group 2 (m3 and sm1): uncertain indications. **B**, Specimen obtained after EMR: the cutoff limit between sm1 and sm2 is 200 μ EMR is adequate for sm1.

Contribution of magnifying endoscopy

In videoendoscopy, charge-coupled device (CCD) chips with high pixel density provide high-resolution images. In recent instruments, magnification is available by using either an optical zoom (×30-×80) or a combined optical and electronic magnification. Zoom magnification is used selectively on target lesions, because at maximum magnification focal length is short and depth of field is small. The magnified image can be further improved by electronic modification, which results in structural enhancement of the surface. The electronic enhancement involves a selective amplification of the intensity of some wavelengths of light reflected from the mucosal surface and collected by the CCD. A simplified spectroscopic method, narrow band imaging, also is in development. In this system, the incident light is restricted to narrow bands in the 3 basic colors (red, blue, green) to obtain distinct images (deep, intermediate, and superficial), which are superimposed, resulting in increased relief.

Magnifying endoscopy has two distinct applications: the analysis of the surface architecture of the epithelium (pit pattern) with the help of a contrast

dye (chromoendoscopy by using indigo carmine), and the analysis of the vascular network in transparency across translucent unstained epithelium.[46,49,131-151] Contrast magnification endoscopy has been used for esophageal squamous cell cancer in Japan,[147,148,151] for Barrett's esophagus in Japan and in the West,[46,49,131-134] for the stomach in Japan,[135-138] and for the large bowel in Japan[139-144] and the West.[47,145,146] A recent randomized trial[144] has confirmed the efficacy of this technique for differentiating non-neoplastic lesions that do not require treatment from neoplastic lesions.

Interpretation of the surface pit pattern with magnification is easier in the large bowel than in the stomach because of gastric inflammation associated with the high prevalence of *H pylori* in many populations. In the large bowel mucosa, distinct types of pit patterns have been described for normal mucosa and for non-neoplastic and neoplastic lesions (low-grade or high-grade intraepithelial neoplasia). In carcinoma, the surface pattern is either irregular or amorphous. In addition, magnification may be helpful in the discrimination of hyperplastic polyps and serrated adenomas, the latter showing an alternating pattern or regular pits (non-neoplastic areas) and cerebriform crests (neoplastic areas).[71] Magnification in mucosal transparency explores the microvascular network across the translucent unstained epithelium and requires no contrast dye.[147-151] This technique is based on the evaluation of the changes in caliber (dilatation) and shape of neoplastic vessels. In the esophagus, this evaluation can contribute to the differentiation of squamous cell neoplasia from inflammation and also to the suspicion of carcinoma with invasion into the submucosa.[148,151]

The classification presented in this text is based on the technology of standard endoscopy. However, progress in image processing may offer different perspectives.[152] Magnifying endoscopy has potential to be used routinely in the upper digestive tract in Barrett's esophagus. In the large bowel, magnification may potentially be used routinely for the differentiation between non-neoplastic and neoplastic lesions (optical biopsy), and for the distinction between intramucosal lesions and lesions with invasion of the deep submucosa.

ELEMENTS FOR A CONSENSUS CLASSIFICATION

Endoscopic morphology of subtypes within *type 0*

In the Japanese studies, there are several large series showing the distribution and variations in the morphology of superficial neoplastic lesions *type 0*. Some series include the endoscopic description of the lesion with its corresponding histopathology. In series from endoscopy units, the pathology component is the weak point, while endoscopic description is the weak point in series from a surgical unit or a pathology laboratory. The relative proportions of each type and subtype vary according to the histology of the epithelium (stratified squamous vs. columnar), the organ (esophagus vs. stomach or colon), and the recruitment of the cases (mass screening vs. opportunistic cases). Tables 3-8 show the distribution of the morphologic subtypes; Tables 9-14 show data on the depth of invasion in mucosa or submucosa. Tables 15-18 show data on the frequency of nodal invasion in superficial neoplastic lesions. Endoscopic images of the mucosal surface and of superficial neoplastic lesions *type 0* are presented in Figures 1 to 95, classified by morphologic appearance.

Neoplastic lesions in columnar epithelium

Barrett's esophagus. Available data on the morphology of superficial neoplastic lesions in Barrett's esophagus are scarce; *type 0-II* lesions are the most frequent (70%), but depressed type lesions (*0-IIc*) are uncommon (Table 4). The endoscopic morphology of a target lesion has poor reliability in the prediction of invasive or noninvasive neoplasia because multiple foci are frequent and cancer with invasion of the submucosa may occur near an area with noninvasive epithelial neoplasia.

Esophagogastric junction and cardia. Neoplastic lesions at the esophagogastric junction and the cardia tend to be considered in a single group in Japan, but the cardia is often associated with Barrett's mucosa in Europe and North America. The distribution of morphologic variants in *type 0* is the same as in Barrett's esophagus. The proportion of depressed (*0-IIc*) lesions is less than in the subcardiac stomach.[56]

Sub-cardiac stomach. Most superficial neoplastic lesions in the sub-cardiac stomach are *type 0-II*, and most of them (70%-80%) are depressed (*0-IIc*). *Type 0-I* (polypoid) lesions are rare, as well as *type 0-III* (ulcerated) (Tables 5 and 8). Polypoid adenomas are rare precursors of invasive cancer. Flat or slightly depressed areas of low-grade or high-grade noninvasive intraepithelial neoplasia often are called flat or depressed adenomas in the Japanese studies.[21,25] The global risk of submucosal invasion in *type 0-II* lesions is just under 40% in the large series from 1990 to 1999, reported by the National Cancer Center Hospital in Tokyo (Table 10, page S16) or in the results from the national mass screening campaign in 1997 (Table 14). The figure is still lower (19%) in the series

Distribution of Morphologic Subtypes

Table 3. Squamous epithelium of the esophagus—morphology*

	n	%
0-I		16
Ip + Is	262	
0-IIa,b		34
IIa	303	
IIb	221	
0-IIc		45
IIc	707	
0-III		5
III	69	
Total	1562	

*Distribution (numbers and percentages) of major macroscopic categories within *type 0*. Multicenter analysis conducted in Japan in 143 institutions: 1562 lesions with pathology confirmation in the operative specimen (unclassified in 290 other lesions).[53]

Table 4. Barrett's esophagus—morphology*

	N	%
0-I		21
Ip + Is	14	
0-IIa,b		61
IIa	17	
IIb	23	
0-IIc		13
IIc	3	
IIa + IIc	6	
0-III		5
III	3	
Total	66	

*Distribution (numbers and percentages) of major macroscopic categories within *type 0*. Single endoscopy series (high-grade neoplasia in 3 lesions and intramucosal carcinoma in 63 lesions).[74]

Table 5. Stomach—morphology*

	n	%
0-I		3
0-I	66	
0-IIa,b		17
0-IIa	356	
0-IIb	9	
0-IIc		78
0-IIc	1486	
0-IIc + IIa	21	
0-IIa + IIc	132	
0-III		2
0-IIc + 0-III	15	
0-III	13	
Total	2098	

*Distribution (numbers and percentages) of major macroscopic categories within *type 0*. Surgical series (2098 lesions in the period 1990-1999) with pathology confirmation from National Cancer Center Hospital in Tokyo (unclassified in 3 other lesions.) (From M. Sasako, unpublished data presented at Paris workshop.)

Table 6. Colon—morphology*

	n	%
0-I		57
Ip + Is	5455	
0-IIa,b		39
IIa + IIb	3674	
0-IIc		4
IIc	404	
0-III		0
III	0	
Total	9533	

Note: Lesions described as lateral spreading type were including in type 0-IIa.

*Distribution (numbers and percentages) of major macroscopic categories within *type 0*. Endoscopy series (9533 lesions in the period 1985-1996) from Akita Red Cross Hospital.[68]

Table 7. Colon—morphology*

	n	%
0-I		50
Ip	1303	
Is	504	
0-IIa,b		44
IIa	1604	
IIb	33	
0-IIc		5
IIc, IIc + IIa	60	
IIa + IIc	97	
IIs + IIc	43	
0-III		0
III	0	
Total	3680	

Note: 76% of the polypoid lesions were classified as Ip.

*Distribution (numbers and percentages) of major macroscopic categories within *type 0*. Pathology series (3680 lesions) from Niigata Hospital. (From H. Watanabe, unpublished data from Paris workshop.)

Table 8. Stomach compared to colon—morphology*

	Stomach		Colon	
	n	%	n	%
0-I		6		79
Ip + Is	213		1768	
0-IIa,b		17		13
IIa	488		296	
IIb	42		3	
0-IIc		70		7
IIc	1717		39	
IIc + IIa	118		—	
IIa + IIc	415		127	
0-III		7		<1
IIc + III	198		—	
III + IIc	20		—	
III	12		3	
Total	3223		2236	

Note: 37% of polypoid lesions were classified as Ip.

*Distribution of major macroscopic categories within *type 0*. Results of the National Mass Screening in Japan in 1999. Unclassified types (141 for stomach and 119 for colon) not included in this table.[67]

Depth of Invasion

Table 9. Squamous epithelium of the espophagus—depth of invasion*

	m1 + m2 n (%)	m3 + sm1 n (%)	sm2 + sm3 n (%)
0-I			
Ip + Is	11 (4)	44 (16)	207 (79)
0-IIa,b			
IIa	62 (20)	94 (31)	147 (48)
IIb	152 (69)	36 (16)	33 (15)
0-IIc			
IIc	256 (39)	245 (34)	206 (27)
0-III			
III	2 (3)	9 (13)	58 (84)
Total	483 (31)	428 (27)	651 (41)

Note: The depth of invasion is divided into 3 groups: superficial (2/3 of the mucosa of (m1 + m2); intermediate (last layer of the mucosa + first layer of the submucosa or m3 + sm1); deep (2/3 of the submucosa or sm2 + sm3).

*Depth of invasion into the mucosa (m) or submucosa (sm) with reference to major macroscopic categories within *type 0.* A multicenter analysis conducted in Japan in 143 institutions: 1562 lesions with pathology confirmation in the operative specimen.[53]

Table 10. Stomach—depth of invasion*

	N° total	N° m	N° sm	% sm
0-I				
0-I	66	28	38	57%
0-IIa,b				
0-IIa	356	254	102	29%
0-IIb	10	8	2	20%
0-IIc				
0-IIc	1488	931	557	37%
0-IIc + IIa	19	10	9	47%
0-IIa + IIc	132	46	86	65%
0-III				
0-IIc + III	15	9	6	40%
Total	2086	1286	800	38%

*Depth of invasion into the mucosa (m) or submucosa (sm) in neoplastic lesions, *type 0*, with pathology control, treated by surgery or endoscopic mucosectomy (2086 lesions in the period 1990-1999) in the National Cancer Center Hospital in Tokyo. (From M. Sasako, unpublished data from Paris workshop.)

Table 11. Stomach—depth of invasion*

	2000-2001
N° cancer m	382 (81%)
N° cancer sm	89 (19%)
Total	471

*Depth of invasion, into the mucosa or submucosa, in neoplastic lesions *type 0,* with pathology confirmation, treated only by endoscopic mucosectomy (471 lesions) in the National Cancer Center Hospital in Tokyo. (From M. Sasako, unpublished data from Paris workshop.)

from 2000 to 2001, where all cases were treated by EMR, reported by the National Cancer Center Hospital in Tokyo. The endoscopic morphology of a *type 0-II* lesion has a predictive value for the risk of submucosal invasion. The risk is higher for *type 0-I* and combined *type 0-IIa + IIc*, and lower for *type 0-IIb* lesions. Concerning clinical relevance, non-depressed (*type 0-IIa or 0-IIb*) lesions with a diameter less than 2.0 cm can be treated safely by endoscopy; the safety limit is lowered to 1.0 cm for all types of lesions with a depressed (*0-IIc*) morphology.

Large bowel. Many non-neoplastic lesions of the large bowel mucosa with a superficial and non-depressed morphology are hyperplastic polyps. In the absence of magnification, the endoscopic prediction of their nature is not always easy, justifying a tissue sample for histologic analysis. Some polyps with a surface suggesting a hyperplastic polyp have a neoplastic component (adenoma). These are now classified as serrated adenomas by histology. In Western countries, most superficial neoplastic lesions of the large bowel (80% or more) have a polypoid morphology, while the frequent non-neoplastic hyperplastic polyps have a "flat" morphology. In Japan, the proportion of polypoid neoplastic lesions is lower in the series published by specialized units such as the Akita Red Cross Hospital (Table 6) or the Niigata Hospital (Table 7). In these series, non-polypoid lesions represent up to 50% of all "superficial" neoplastic lesions. Most *type 0-II* lesions are elevated and non-depressed (*type 0-IIa*), and the flat type (*type 0-IIb*) is extremely rare. Depressed lesions (*type 0-IIc*) also are rare (4%-5% of all lesions). Is there a difference between East and West observations of the morphologic distribution of superficial neoplastic lesions in the large bowel? This seems unlikely. Different proportions suggest possible misclassification between *type 0-Is* and *type 0-IIa* lesions in less specialized units.

In Japan, in the national mass screening campaign based on the fecal occult blood test, the proportion of lesions *type 0-Ip or 0-Is* is the same (about 80%) as in the West [67] (Table 8) and is lower than in the series from the Niigata Hospital (50%). Among *type 0-I* lesions, the proportion of those classified as pedunculated (*type 0-Ip*) is much smaller (652/1768 = 37%) in the mass screening series from Japan[67] than in the series from the Niigata Hospital (1303/1843 = 70%) (Table 7), suggesting a biased evaluation of protrusion of sessile lesions in the endoscopic image.

Depth of Invasion, *continued*

Table 12. Colon—depth of invasion*

	5 mm or less	6-10 mm	11-15 mm	16-20 mm	21 mm or more
0-I					
Ip + Is	0/5400 (0%)	49/4045 (1.2%)	80/1002 (8%)	58/330 (17%)	56/187 (30%)
0-IIa,b					
IIa + IIb	2/6214 (<0.1%)	2/1015 (0.2%)	9/493 (1.8%)	17/165 (10%)	53/235 (23%)
0-IIc					
All *IIc*	17/236 (7%)	58/132 (44%)	42/63 (67%)	18/20 (90%)	13/15 (87%)
0-III					
III	0	0	0	0	0
Total	19/11,850 (<0.2%)	109/5,192 (2%)	131/1,558 (8%)	93/1,523 (18%)	122/437 (28%)

*Proportion (numbers and percentages) of invasion into the submucosa, with reference to the major macroscopic categories within *type 0* and to the diameter of the lesion (in 5 groups). Endoscopy series with pathology confirmation (19, 560 lesions in the period April 1985-April 2003) in Red Cross Hospital in Akita and Showa Northern Hospital in Yokohama. (From S. Kudo, unpublished data from Paris workshop.)

Table 13. Colon—depth of invasion*

	n/N	%
0-I		
Ip	69/1303	5
Is	185/540	34
0-IIa,b		
IIa	64/1604	4
IIb	0/33	0
0-IIc		
All *IIc*	123/200	61
0-III		
III	0	
Total	3680	

*Proportion (numbers and percentages) of invasion into the submucosa with reference to major macroscopic categories within *type 0.* Pathology series (3680 lesions), from the Niigata Hospital. (From H. Watanabe, unpublished data from Paris workshop.)

Table 14. Stomach compared with colon—depth of invasion*

	Stomach n (%)	Colon n (%)
m	1905 (60)	1663 (70)
sm	1268 (40)	715 (30)
Total	3173	2378

*Proportion (numbers and percentages) of invasion into the submucosa (sm) within lesions *type 0* in the series of the National Mass Screening in 1999 in Japan.[67]

The bias also occurs in Western countries where there is little attempt to classify most small polyps by using the Japanese system, because it is perceived to have little application in the large bowel, especially with diminutive polyps, most of which are "flat" (*0-IIa*). The archives of the National Polyp Study were recently revised and sessile lesions were reclassified as flat adenomas (*0-IIa*) when they did not fulfill the standard polypoid criteria (*0-I*).[7,94] It was concluded that 27% of all adenomas removed in this large multicenter study could be reclassified as non-polypoid *type 0-IIa* lesions. In conclusion, the morphology of superficial neoplastic lesions in the colon seems likely to be the same in the East and in the West.

The endoscopic morphology of "superficial" neoplastic lesions in the large bowel predicts the risk of invasion into the submucosa. The parameters include the diameter of the lesion and the variant in the *type 0* classification. In the large Japanese series from the endoscopy unit of the Red Cross Hospital in Akita and the Showa Northern Hospital in Yokohama (Table 12), submucosal invasion occurs in less than 1% when the lesion is less than 1.0 cm. The rate of submucosal invasion increases in proportion to the diameter in polypoid lesions (*type 0-Ip or 0-Is*), reaching 30% when the diameter is over 2.0 cm. In addition, the risk of submucosal invasion is higher in *type 0-Is* than in *type 0-Ip* lesions (Table 13). In non-depressed and non-polypoid lesions (*type 0-IIa and 0-IIb*), the proportion of submucosal invasion is less than in *type 0-I* when the diameter is taken into account. In depressed lesions (all types, including the *0-IIc* morphology), the risk of submucosal invasion is high even when the diameter is less than 1.0 cm.

In conclusion, depressed lesions require special attention in spite of their rarity. Invasion of the submucosa occurs even in small lesions. Deep invasion of the submucosa is a strong contraindication to endoscopic resection and can be predicted in the following circumstances:

- when the diameter of the lesion is more than 15 mm

Frequency of Nodal Invasion

Table 15. Squamous epithelium of the esophagus—nodal invasion*

m1 + m2 n/N (%)	m3 + sm1 n/N (%)	sm2 + sm3 n/N (%)
5/352 (<2)	86/449 (19)	393/889 (44)

Note: The depth of invasion is divided into 3 groups: superficial (2/3 of the mucosa of (m1 + m2); intermediate (last layer of the mucosa + first layer of the submucosa or m3 + sm1); deep (2/3 of the submucosa or sm2 + sm3).

*Proportion of nodal metastases with reference to the depth of invasion in the mucosa (m) of submucosa (sm). A multicenter analysis conducted in Japan in 143 institutions: 1690 lesions with pathology confirmation in the operative specimen.[53]

Table 16. Squamous epithelium of the esophagus—nodal invasion*

m1 + m2 n/N (%)	m3 + sm1 n/N (%)	sm2 + sm3 n/N (%)
0/71 (0)	4/47 (8)	37/86 (43)

Note: The depth of invasion is divided into 3 groups: superficial (2/3 of the mucosa of (m1 + m2); intermediate (last layer of the mucosa + first layer of the submucosa or m3 + sm1); deep (2/3 of the submucosa or sm2 + sm3).

*Proportion of nodal metastases with reference to the depth of invasion in the mucosa (m) of submucosa (sm). An endoscopic series with pathology confirmation from Tokyo Medical and Dental University, 1985-1995 (204 lesions *type 0*). (From H. Inoue, unpublished data from the Paris workshop.)

Table 17. Stomach—nodal invasion*

Size in mm	< 500 μ n/N (%)	> 500 μ n/N (%)
< 10	1/31 (3)	5/39 (13)
10-20	4/71 (6)	28/195 (14)
21-30	4/71 (6)	52/273 (19)
> 30	6/92 (7)	86/319 (27)
Total	15/265 (6)	171/826 (21)

Note: The depth of invasion into the submucosa is divided into two groups with respect to the cutoff limit: 500 μ from the lowest layer of the muscularis mucosae.

*Proportion of nodal metastases with reference to the depth of invasion into the submucosa. Results (numbers and percentages) presented in two groups of depth and 4 groups for size of the lesion. Cases with pathology confirmation (1091 lesions *type 0*), treated by surgery or endoscopic mucosectomy in National Cancer Center Hospital in Tokyo.[63]

Table 18. Colon—nodal invasion*

	n/N	%
sm1	1/147	<1
sm2	7/105	6
sm3	10/71	14

Note: The depth of invasion is divided into 3 groups, corresponding to superficial, intermediate, and lower third in the thickness of the submucosa.

*Proportion of nodal metastases with reference to the depth of invasion into the submucosa (sm) presented in 3 groups. Endoscopic series with pathology confirmation in Red Cross Hospital in Akita (323 in lesions *type 0*). (From S. Kudo, unpublished data from the Paris workshop.)

- when the border of an elevated and depressed (*type 0-IIa + IIc*) lesion presents as a smooth circle without indentations
- when the lesion fails to lift after injection of saline solution in the submucosa (the non-lifting sign)

Neoplastic lesions in the stratified squamous epithelium

A distinct and reduced quantitative scale is adopted to assess the height of "superficial" neoplastic lesions in the stratified squamous epithelium of the esophagus. Most of these lesions (80%) have a *type 0-II* morphology (Table 3). The endoscopic morphology has some predictive value for depth of invasion in the esophageal wall. Some investigators in Japan recommend a detailed description of the lesion, including its color and its surface pattern (translucent, granular, or nodular).[57] More protruded or more depressed lesions are associated with deeper invasion in the submucosa. This applies particularly when the lesion has a mixed morphologic pattern. In a multicenter analysis conducted in Japan (Table 9), the total risk of submucosal invasion is high (71%) in *type 0* lesions. The highest risk occurs in *type 0-Ip or 0-Is* and in *type 0-III* lesions, and the lowest risk is in *type 0-IIb* lesions.

Lymphatic nodal metastases in lesions *type 0*

The link between the presence (or the depth) of submucosal invasion and the risk of lymph node metastases is shown in Tables 15-18. The correlation between the morphology of *type 0* neoplastic lesions, the risk of submucosal invasion, and the correlated risk of nodal metastases guides the respective indications or contraindications for endoscopic treatment.

In neoplastic lesions of the stratified squamous epithelium of the esophagus, the risk of lymph node metastases is over 40% when invasion reaches the deep submucosa (sm2 and sm3) (Tables 15 and 16) and is surprisingly high (19%) when it reaches only the deep mucosa (m3) or the superficial submucosa

Table 19. Colon—pit pattern*

	III s	III L	IV	V	Total
0-I					
Ip + Is	8	5926	1872	294	8100
0-IIa,b					
IIa + IIb	58	3944	299	173	4474
0-Iic					
IIc	234	62	1	133	430
0-III					
III					0

Endoscopic series (13,004 lesions in the period April 1985-February 2002) from the Red Cross Hospital in Akita and Showa Northern Hospital in Yokohama. (From S. Kudo, unpublished data from the Paris workshop.)

*Pit pattern of the surface of the lesion (examined with magnification) with reference to the macroscopic categories within *type 0*.

Table 20. Colon—pit pattern*

	n/N	%
0-I		
Ip + Is	294/8100	3.6
0-IIa,b		
IIa + Iib	173/4474	3.8
0-IIc		
IIc	133/430	31
0-III		
III	0	

*Proportion of pit pattern V in the surface of the lesion (under magnification) with reference to the macroscopic categories. Endoscopic series (13,004 lesions *type 0* in the period April 1985-February 2002) from the Red Cross Hospital in Akita and Showa Northern Hospital in Yokohama. (From S. Kudo, unpublished data from the Paris workshop.)

Table 21. Colon—pit pattern*

	III s n/N (%)	III L n/N (%)	IV n/N (%)	V n/N (%)
sm cancer	9/228 (4)	0/8186 (0)	73/1922 (4)	233/577 (41)

*Proportion of invasion into the submucosa (sm) (numbers and %) in reference to the pit pattern of the surface (under magnification). Endoscopic series with pathology confirmation (10,913 lesions *type 0* in the period April 1985-February 2002) from the Red Cross Hospital in Akita and Showa Northern Hospital in Yokohama. (From S. Kudo, unpublished data from the Paris workshop.)

(sm1). Elective indications for endoscopic therapy in esophageal squamous neoplasia should be limited to m1 and m2 lesions, where the risk of lymph node metastasis is nil or nearly nil. This occurs in approximately 30% of *type 0* lesions (Table 9).

In neoplastic lesions of the stomach, the risk of lymph node metastases is high when invasion of the submucosa is more than 500 μ in depth, corresponding to sm2 lesions in surgical specimens.[128] In addition, the risk increases with the diameter of the lesion. On the other hand, the risk is low when invasion of the submucosa is less than 500 μ (sm1) even if the diameter increases. Elective indications for endoscopic therapy should be limited to this group. Data from the National Cancer Hospital in Tokyo are shown in Table 17.

In neoplastic lesions of the large bowel, the risk of lymph node metastases is high when cancer invades the deep submucosa, as shown in the series from the Red Cross Hospital in Akita (Table 18), where invasion of the submucosa was estimated by the semiquantitative method. The submucosa was divided into 3 sectors of equivalent thickness (sm1, sm2, and sm3). The risk of nodal metastases was high when the invasion reached sm3 near the muscularis propria. On EMR specimens, the risk of nodal metastasis is nil or small when invasion into the submucosa is less than 1000 μ.[129,130]

Magnifying endoscopy in *type 0* lesions

In the upper digestive tract, magnification with the help of contrast chromoendoscopy and electronic enhancement is of considerable help for analysis of the distinct types of epithelium (oxyntic, cardia, and intestinal metaplasia) in Barrett's esophagus. The degree of architectural disorganization in the areas of intestinal metaplasia also helps in the detection of early neoplasia. Magnification in transparency shows the microvascular network of neoplastic lesions in the stratified squamous epithelium and in the stomach.

In the large bowel, the organization of the surface epithelium, or pit pattern, has been analyzed with magnification and contrast,[153-158] and grossly classified into 5 patterns or types, which can be grouped into 3 categories: type I and type II (non neoplastic); type IIIS, IIIL, and IV (low-grade and high-grade intramucosal neoplasia); and type V, with distorted epithelial crests or an amorphous surface (carcinoma with suspicion of submucosal invasion). Some characteristic pit patterns in magnification endoscopy are demonstrated in the atlas of endoscopic figures in this report.

The distribution of pit pattern categories III to V, suggesting neoplasia, from the series of the Red Cross Hospital in Akita and the Showa Northern Hospital in Yokohama are shown in Table 19. Pit pattern V, predictive of cancer, is frequent in depressed and non-polypoid lesions *(type 0-IIc)* (Table 20). Such lesions also have a high risk of submucosal invasion (Table 21).

An empirical description of the magnified surface pattern of neoplastic lesions as invasive or noninvasive proved reliable for treatment decisions in a series of colorectal neoplastic lesions with histologic control.[159] The invasive pattern, characterized by irregular and distorted epithelial crests, suggests that submucosal invasion is more than 1000 μ. The noninvasive pattern suggests intramucosal neoplasia or submucosal invasion less than 1000 μ (an appropriate indication for endoscopic treatment). In this series, histology confirmed epithelial neoplasia in 98% of 2951 lesions, with a noninvasive pattern and confirmed deep submucosal invasion in 86% of 156 lesions with an invasive pattern.

CRITICAL POINTS IN THE METHODOLOGY

Minimal standard terminology for the endoscopic classification

The classification of *type 0* lesions is based on the distinction between polypoid (*type 0-I*); non-polypoid, nonexcavated (*type 0-II*); and non-polypoid, excavated (*type 0-III*) lesions. In addition, *type 0-II* lesions are divided with respect to the absence (*type 0-IIa* and *0-IIb*) or the presence of a depression (*type 0-IIc*). This minimal standard terminology (Tables 1 and 2) covers most of the clinical relevance of the morphology and applies to esophagus, stomach, and colon. The site-specific adaptations follow the common guidelines and stress the prognostic value of each subtype.

Role of chromoendoscopy

The routine use of chromoendoscopy is helpful for the identification of the subtypes of neoplastic lesions within *type 0*. This is especially true in the esophagus and stomach where type *0-II* lesions are invariably underdetected if chromoendoscopy is not performed. The contrast endoscopic image is improved when electronic structural enhancement functions are used. Iodine is the only way to unmask flat (*type 0-IIb*) neoplastic areas in esophageal stratified squamous epithelium and to reveal simultaneous additional neoplastic foci. Indigo carmine solution (0.4%-0.5%) is the universal contrast dye for columnar mucosa. Indigo carmine solution determines the actual limits of the lesion, reveals occult neoplasia, and enhances the presence of depressed occult areas where the dye accumulates.

Preparation of the tissue specimen for the pathologist

This applies particularly to neoplastic lesions resected by EMR. The macroscopic endoscopic classification is confirmed by the pathologist, but the specimen is ideally prepared and evaluated as well by the endoscopist in the endoscopy unit. Comparison of the endoscopic description to that observed in the fixed specimen provides quality assurance and continuing education and encourages detailed analysis during endoscopy.

The future of magnification endoscopy

The practice of magnification helps considerably in the analysis of the endoscopic morphology of neoplastic lesions. Magnification endoscopy is not yet available in all units, but it may be more readily available in the near future. The contribution of magnification is important at this time for two indications:

- the detection of specialized epithelium in Barrett's esophagus
- the detection of disorganized epithelial architecture in depressed neoplastic lesions of the large bowel, where an "amorphous" surface pattern suggests invasive cancer.

CRITICAL POINTS OF CLINICAL RELEVANCE

Recent trends in endoscopy

The precise classification of all endoscopic mucosal lesions is greatly facilitated by high-quality endoscopic imaging. Chromoendoscopy further increases the yield of abnormal findings, especially small, non-polypoid lesions. In the large bowel, small non-depressed neoplastic lesions are frequent, their risk of progression to cancer is small, and they must be differentiated from non-neoplastic, hyperplastic lesions, which have virtually no additional risk for cancer. The choice between surveillance and delayed or immediate treatment is based on the endoscopic morphology of the lesion and biopsy results.

The development of curative endoscopic therapy for superficial neoplastic lesions is increasingly the standard of care on a worldwide basis. While the size of a polypoid (*type 0-I*) lesion is a relatively good guide to assess the risk of invasive malignancy, a more sophisticated analysis is required for *type 0-II* lesions. In the latter situation, the detection of a depressed morphology is of utmost importance, even when the lesion is small. Two errors that should be avoided with respect to EMR are:

- resection for non-neoplastic lesions, which is avoided by biopsy before resection
- endoscopic resection of an invasive neoplastic lesion that really requires surgical excision

In conclusion, the classification of *type 0* neoplastic lesions requires more attention to detail from the operator at each step of endoscopy, which then ensures the best outcome for diagnosis and treatment of those lesions.

Non-polypoid neoplastic lesions as precursors of colorectal cancer: pros and cons

Cons. The benefits of using chromoendoscopy and magnification endoscopy routinely to detect *type 0-II* lesions during colonoscopy have been questioned by Western specialists.[6] Their view is based on the following arguments:

- Most *type 0-II* small colorectal lesions are of little biologic importance and are for the most part non-neoplastic or have low-grade intraepithelial neoplasia.
- Most neoplastic *type 0-II* lesions are non-depressed (*0-IIa* or *0-IIb*) and have a low potential for invasion.
- Most lesions are detectable without chromoendoscopy, the latter being used primarily to enhance a lesion that has already been detected (and usually destroyed) by standard endoscopy.
- After a colonoscopy "negative for cancer," the number of cancers detected (and considered as missed cancer) during a 5-year follow-up is small. In a 66-month follow-up study in 154 subjects after a negative colonoscopy in the United States,[160] only one large adenoma (and no cancer) was found. Also from the United States in the National Polyp Study,[161] a cohort of 1418 subjects was followed an average 5.9 years after a colonoscopy, including removal of "nonadvanced adenomas" (polyps with no villous architecture, diameter less than 1.0 cm). Only 5 cancers (0.35% of the group) were detected during this follow-up.
- The benefit of detecting such lesions and demonstrating that these techniques save lives at a cost that is acceptable per year of life saved is unproven.

Pros. The assumption that the miss rate for small "advanced" neoplastic lesions is extremely low after a negative colonoscopy is challenged by other sound arguments:

- The miss rate for small (<1 cm) adenomas during colonoscopy is high in Western countries.[160] Small and advanced neoplastic depressed lesions are missed as well. The routine use of chromoendoscopy may have a major educational role in improving the detection of small lesions during standard endoscopy.
- Subjects with an average risk for cancer can be reassured with over 95% confidence by the statement "negative for cancer" after colonoscopy, even if the miss rate is high. Indeed, the risk of developing an incident cancer during a 5-year follow-up after a "negative colonoscopy" remains low, in conformity with the average risk of the population stratified by age.
- Different results are obtained from a retrospective study of a cohort of patients with a confirmed cancer; the analysis,[162] from 1990 to 1996, involved 557 patients in whom a colorectal cancer was diagnosed. In this group, 29 individuals (5.2%) had one or more negative colonoscopies during the previous 5 years. The missed tumors were advanced (T3) in 13 of the 29. The "false negative" initial procedures are explained either by a missed polyp or cancer (e.g., behind a haustral fold) or by a missed small neoplastic lesion with a rapid growth,[163] such as is known to occur in HNPCC.
- The two European randomized trials on screening for colorectal cancer with a biennial FOBT[164,165] show a high proportion of interval cancers detected in the 2-year interval after a "negative" test. Small and evolving depressed (or non-depressed) neoplastic lesions could explain this result.
- We only "see what we already know." This assertion was recently stressed[166] with respect to endoscopic detection. The relationship between the result of a test (positive or negative) and the presence or absence of a disease (positive or negative) is described in terms of sensitivity and specificity by using a 2×2 table, where the positive predictive value is given by the Bayes formula. However, when the performance of the human tester in identifying the test parameter (e.g., a small depressed neoplastic lesion) is low, the positive predictive value drops dramatically.

The polyp-cancer sequence has been considered the prevalent route for the development of colorectal carcinoma in Western countries. This premise has been challenged by the finding that some adenomas are flat or depressed. The results of a recent pathology series from Sweden suggests that more than 40% of advanced colorectal cancers develop from a non-polypoid precursor.[109] There is ample confirmation in the pathology series from Japan that depressed *(type 0-IIc)* colorectal carcinomas are at a more advanced stage than non-depressed lesions *(type 0-IIa and 0-IIb)* of the same size (Tables 12 and 13). In spite of being rare, the *type 0-IIc* lesions play a significant

role as precursors of advanced cancer in Japan and likely do so in the West as well. This observation should, therefore, change the aim and the technique of the colonoscopic examination.

The "false-negative" rate of gastroscopy for gastric cancer

Polypoid precursors play a minor role in the development of advanced gastric cancer, and depressed non-polypoid lesions *(type 0-IIc)* are the usual precursors. Their detection is prone to an appreciable miss rate, even in Japan, in spite of extreme care during the examination.[167] A study of "false negative" results for gastric cancer after gastroscopy has been conducted in Japan.[168,169] In the Fukui area, all endoscopic examinations of the stomach performed at a large regional hospital were compared with the files of the population-based tumor registry established in the same area. The data were collected in the tumor registry with a delay of 1 to 3 years after performance of the procedure. The results of 37,014 gastroscopies in the Fukui regional hospital (1984-1989) were compared with the files of the Fukui cancer registry (1984-1992). A further study on repeat endoscopy was conducted from 1993 to 1996. Two questions have been posed:

- After a gastroscopy "negative for cancer" can an individual accept the result with a high degree of confidence?
- Is a gastroscopy "negative for cancer" associated with a significant miss rate for gastric cancer?

In 1993, a group of 3672 subjects with a "negative gastroscopy" was selected to repeat the procedure after a delay of 1 to 3 years. A gastric cancer was found in 32 individuals (<1%). Therefore, the sensitivity of the test was over 99%. In the period 1984 to 1992, 814 patients with gastric cancers listed in the tumor registry had prior gastroscopy in the hospital. Cancer was detected in 659 and missed in 155 that were classified as "negative for cancer." The "global false-negative" rate of gastroscopy for gastric cancer was, therefore, as high as 19%. Retrospective review of the 155 missed cases confirmed the absence of macroscopic abnormal findings on the images obtained during the initial endoscopic exploration in 70 cases, and biopsy specimens were negative in 40. While it is always possible that some fast-growing carcinomas really did develop in the interval between gastroscopies, it was suspected that this is further evidence that careful endoscopy with a high index of suspicion for any endoscopic abnormality is necessary to detect early lesions.

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Protruded Neoplastic Lesions (type 0-I)

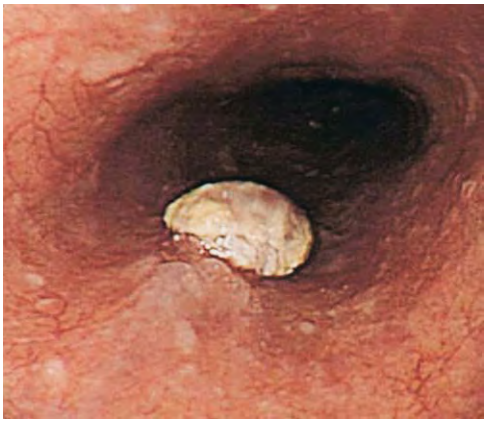

Figure 1. Esophagus (squamous epithelium): *type 0-I*, unstained, submucosal carcinoma (sm2).

Figure 2. Same case as in Figure 1, chromoendoscopy with iodine stain.

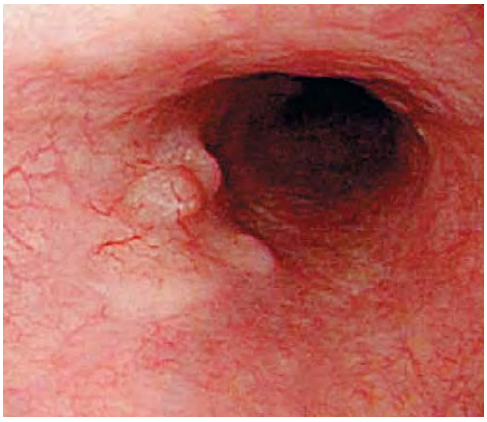

Figure 3. Esophagus (squamous epithelium): *type 0-I*, unstained, submucosal carcinoma (sm2).

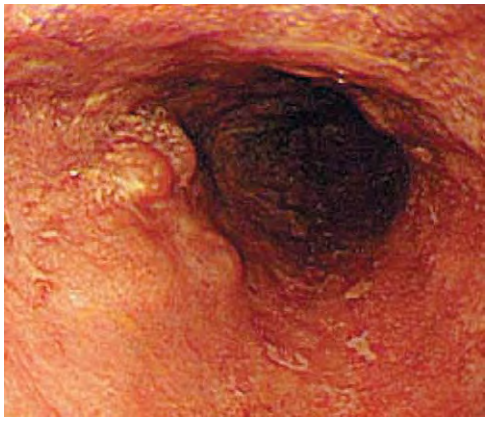

Figure 4. Same case as in Figure 3, chromoendoscopy with iodine stain.

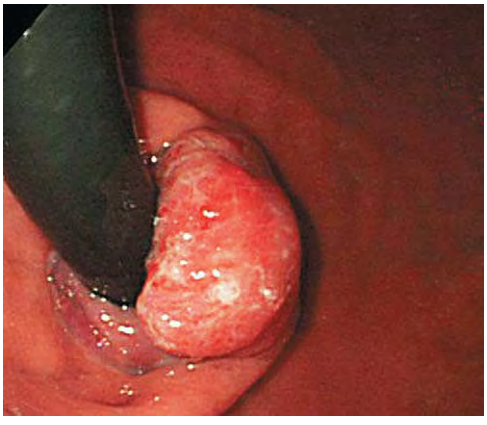

Figure 5. Cardia *type 0-I*, retroflexed view, unstained, submucosal adenocarcinoma (sm2).

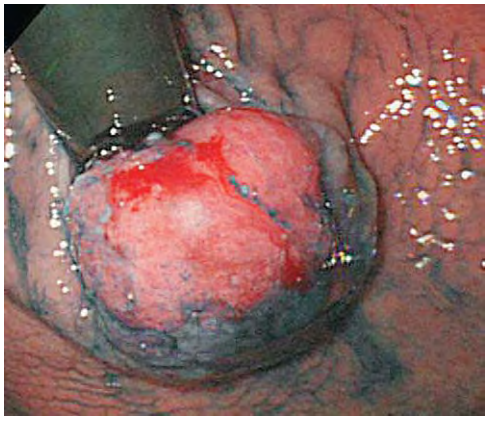

Figure 6. Same case as in Figure 5, retroflexed view, chromoendoscopy with indigo carmine.

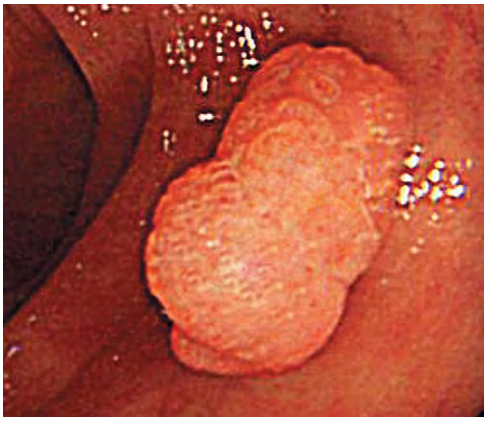

Figure 7. Large bowel type 0-I, unstained, intraepithelial neoplasia.

Figure 8. Same case as in Figure 7, chromoendoscopy with indigo carmine.

Figure 9. Large bowel *type 0-I*, two lesions, unstained, intraepithelial neoplasia.

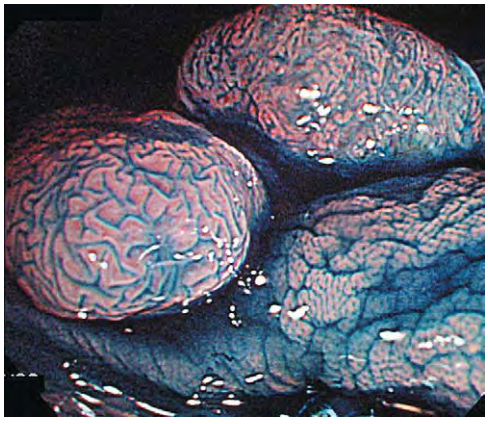

Figure 10. Same case as in Figure 9, chromoendoscopy with indigo carmine.

Slightly Elevated Neoplastic Lesions *(type 0-IIa)*

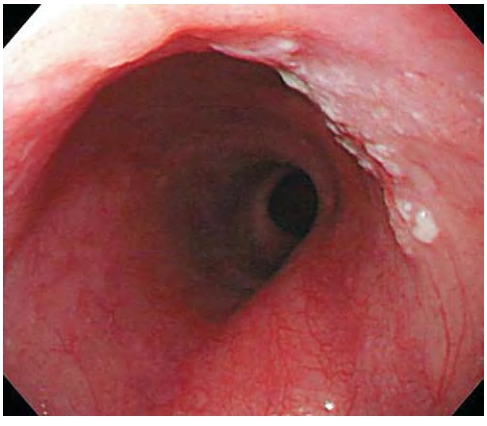

Figure 11. Esophagus (squamous epithelium): *type 0-IIa*, unstained, intramucosal carcinoma.

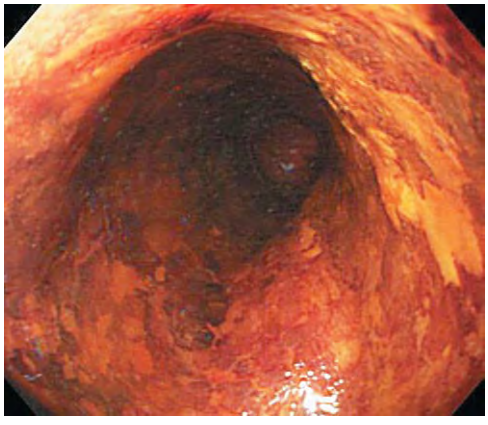

Figure 12. Same case as in Figure 11: chromoendoscopy with iodine stain.

Figure 13. Same case as in Figure 11: operative specimen, unstained.

Figure 14. Same case as in Figure 11: operative specimen with serial sections, stained with iodine.

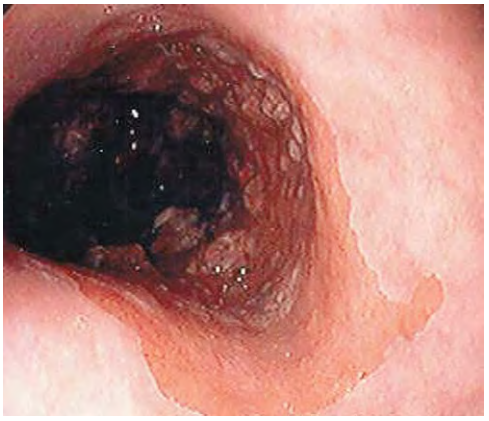

Figure 15. Barrett's esophagus: *type 0-IIa*, multinodular lesions, unstained, intramucosal adenocarcinoma.

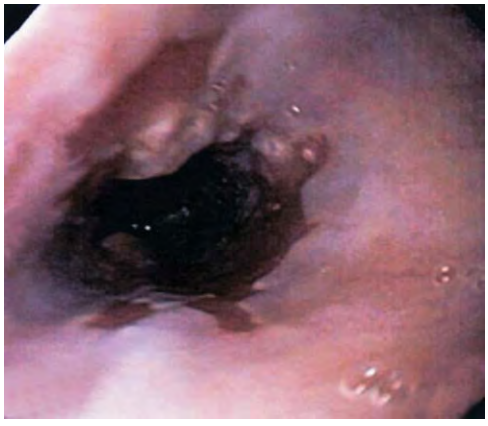

Figure 16. Barrett's esophagus: *type 0-IIa*, a small nodule, unstained, intramucosal adenocarcinoma.

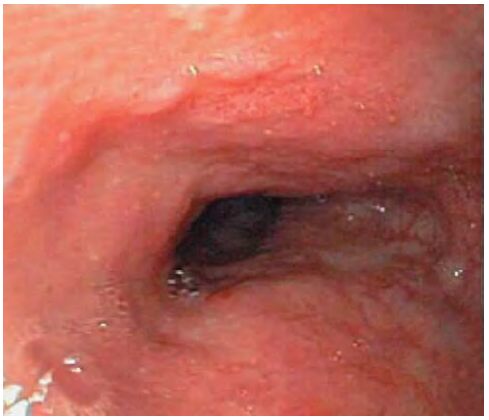

Figure 17. Barrett's esophagus: *type 0-IIa*, multinodular lesions, unstained, intramucosal adenocarcinoma.

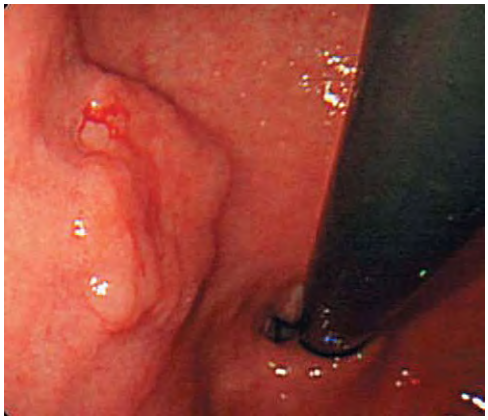

Figure 18. Gastric cardia: *type 0-IIa*, retroflexed view, unstained, intraepithelial neoplasia.

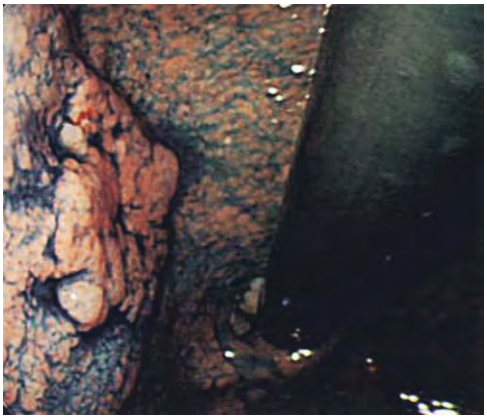

Figure 19. Same case as in Figure 18: retroflexed view, chromoendoscopy with indigo carmine.

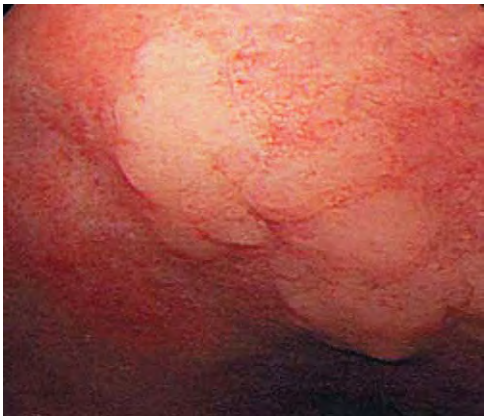

Figure 20. Sub-cardiac stomach: *type 0-IIa*, unstained, intramucosal carcinoma.

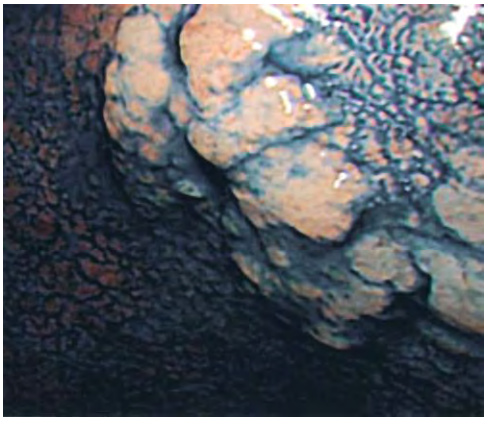

Figure 21. Same case as in Figure 20: chromoendoscopy with indigo carmine.

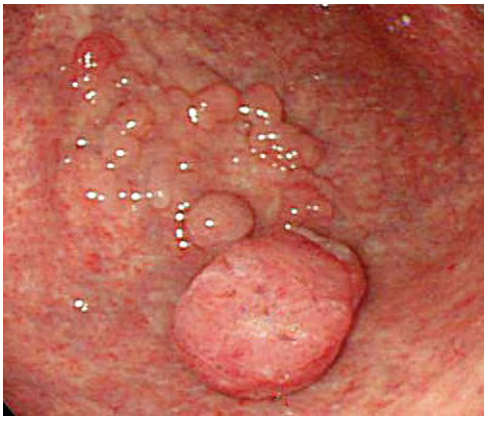

Figure 22. Sub-cardiac stomach: *type 0-IIa + I*, unstained, submucosal carcinoma.

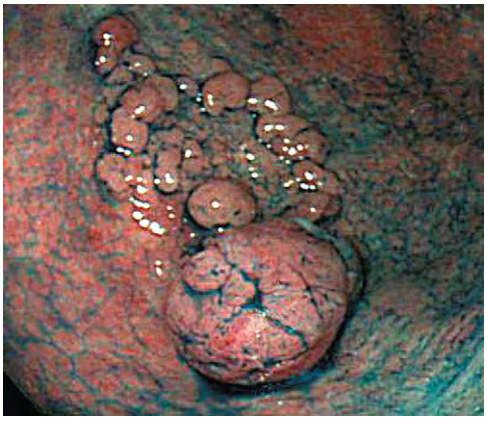

Figure 23. Same case as in Figure 22: chromoendoscopy with indigo carmine.

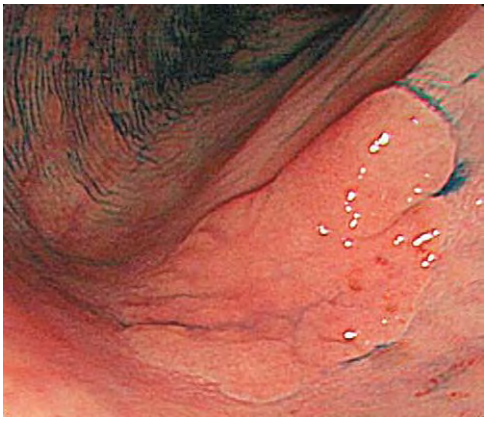

Figure 24. Large bowel: *type 0-IIa*, laterally spreading type, intraepithelial neoplasia.

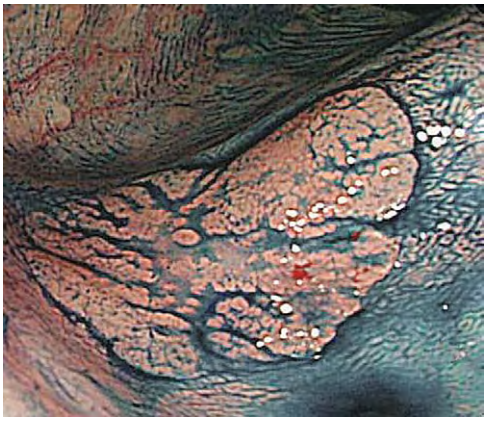

Figure 25. Same case as in Figure 24: chromoendoscopy with indigo carmine.

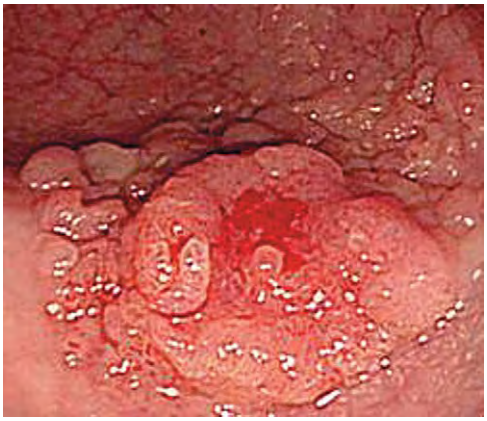

Figure 26. Large bowel: type 0-IIa: unstained, laterally spreading type, intraepithelial neoplasia.

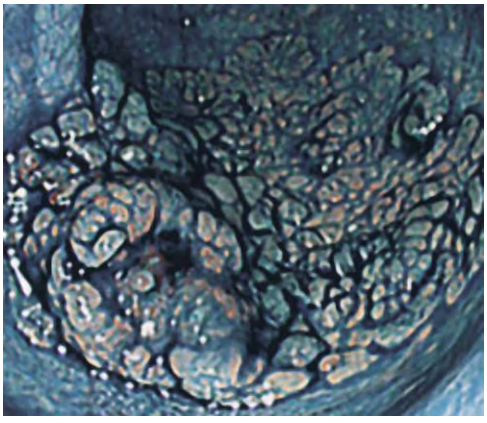

Figure 27. Same case as in Figure 26: chromoendoscopy with indigo carmine.

Flat Neoplastic Lesions *(type 0-IIb)*

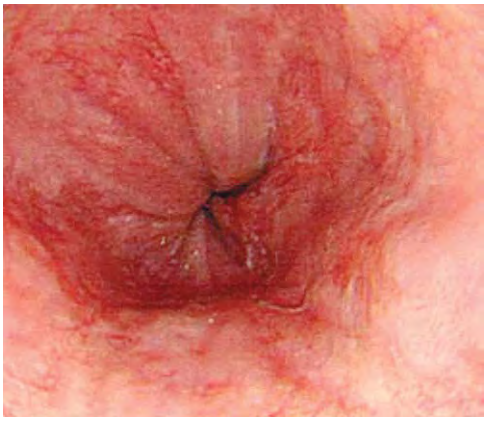

Figure 28. Esophagus (squamous epithelium): *type 0-IIb*, unstained, intraepithelial neoplasia.

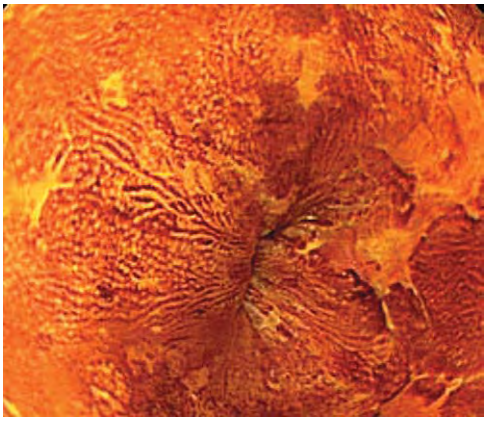

Figure 29. Same case as in Figure 28: chromoendoscopy with iodine stain.

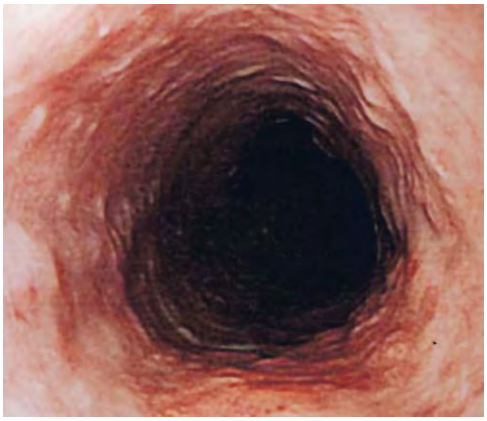

Figure 30. Esophagus (squamous epithelium): *type 0-IIc*, unstained, intramucosal carcinoma (m3).

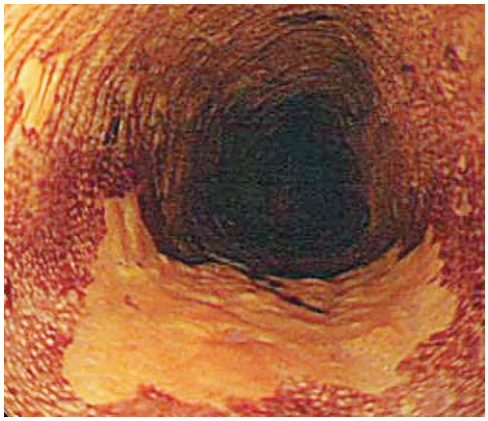

Figure 31. Same case as in Figure 30, chromoendoscopy with iodine stain.

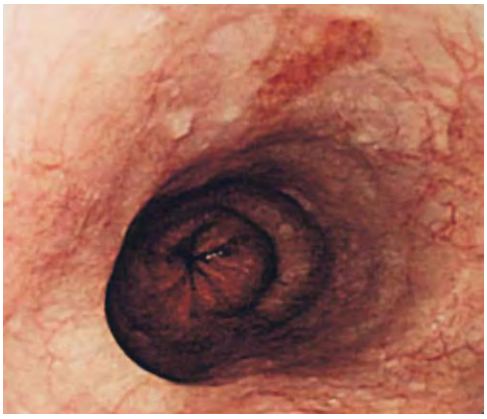

Figure 32. Esophagus (squamous epithelium): *type 0-IIc*, unstained, intramucosal carcinoma (m3).

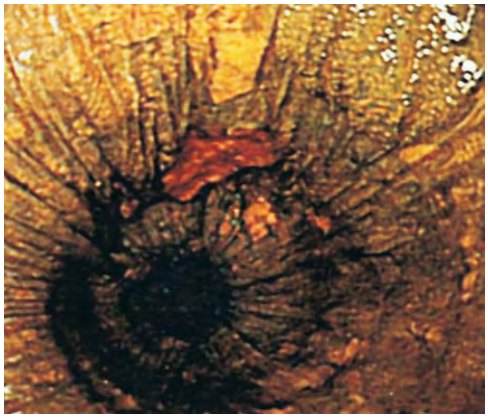

Figure 33. Same case as in Figure 32, chromoendoscopy with iodine stain.

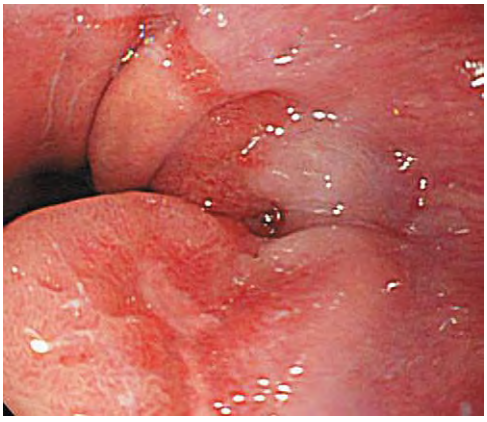

Figure 34. Gastric cardia: *type 0-IIc*, unstained, submucosal adenocarcinoma (sm2).

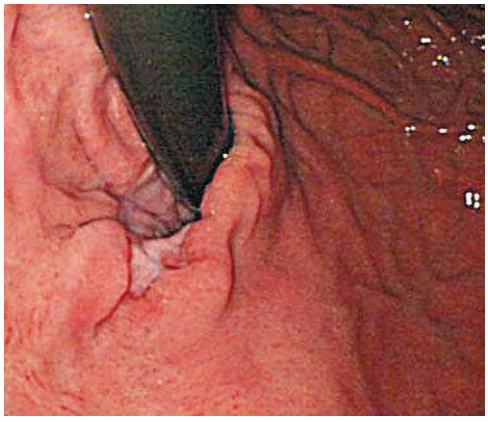

Figure 35. Same case as in Figure 34: retroflexed view, unstained.

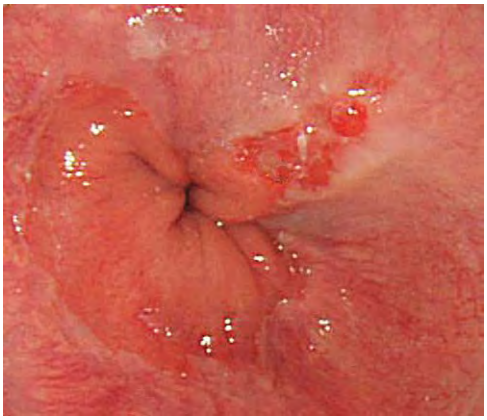

Figure 36. Gastric cardia: *type 0-IIc*, unstained, submucosal adenocarcinoma (sm2).

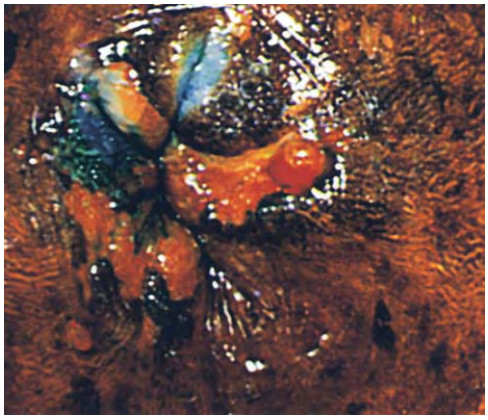

Figure 37. Same case as in Figure 36, chromoendoscopy with iodine stain and indigo carmine.

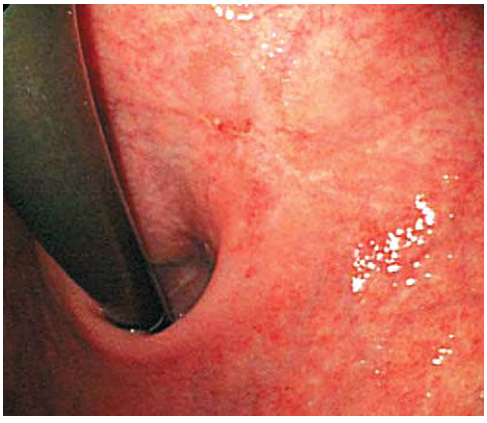

Figure 38. Gastric cardia: *type 0-IIc*, unstained, retroflexed view, submucosal adenocarcinoma (sm2),

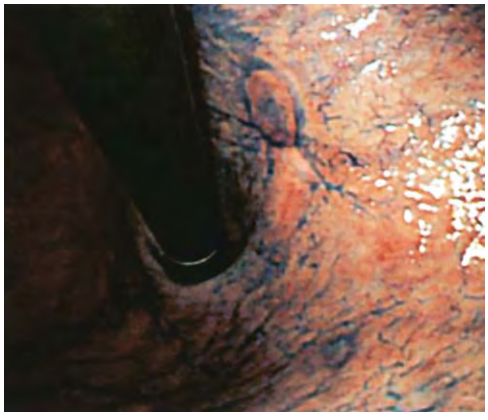

Figure 39. Same case as in Figure 38: retroflexed view, chromoendoscopy with indigo carmine.

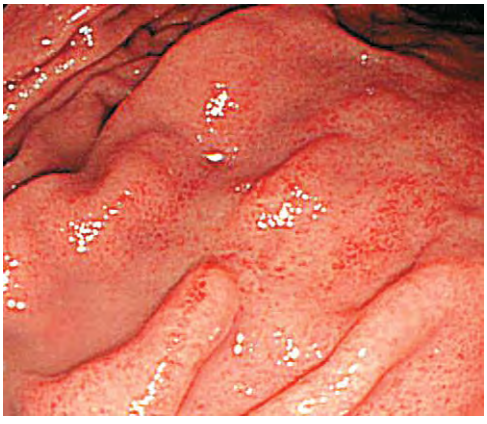

Figure 40. Sub-cardiac stomach: *type 0-IIc*, unstained, submucosal adenocarcinoma.

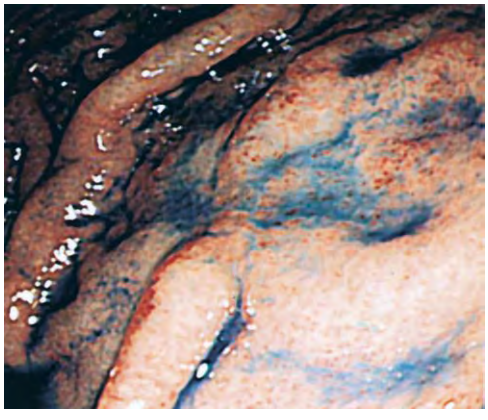

Figure 41. Same case as in Figure 40: chromoendoscopy with indigo carmine.

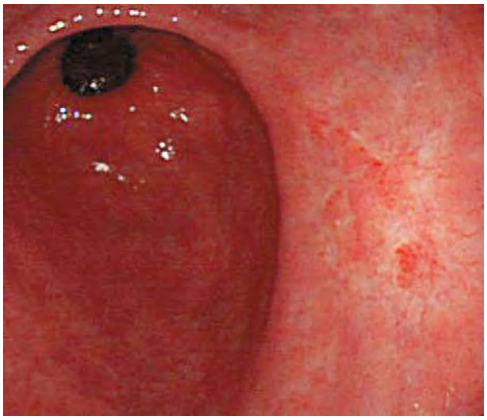

Figure 42. Stomach, posterior: *type 0-IIc*, unstained, submucosal adenocarcinoma (sm2).

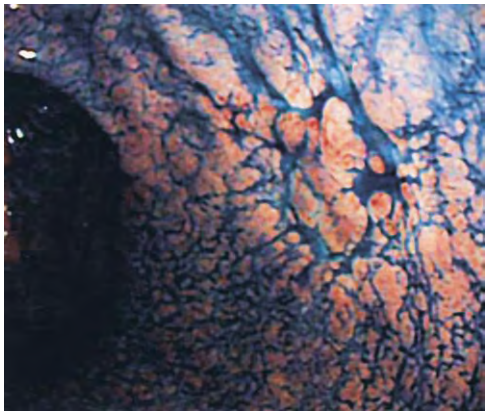

Figure 43. Same case as in Figure 42: chromoendoscopy with indigo carmine.

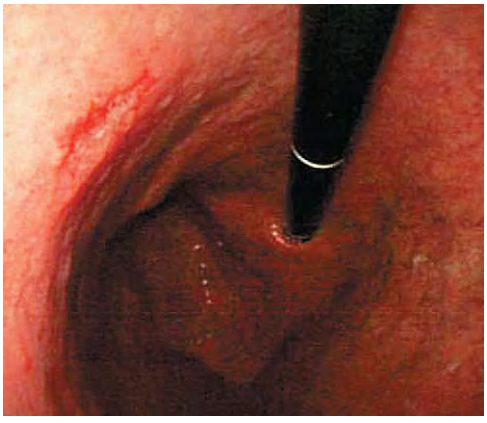

Figure 44. Sub-cardiac stomach: *type 0-IIc*, unstained, submucosal adenocarcinoma.

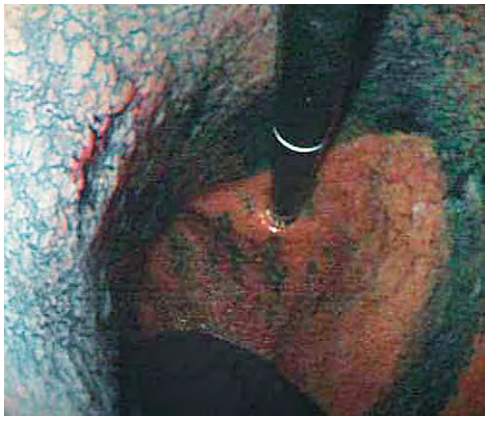

Figure 45. Same case as in Figure 44: chromoendoscopy with indigo carmine.

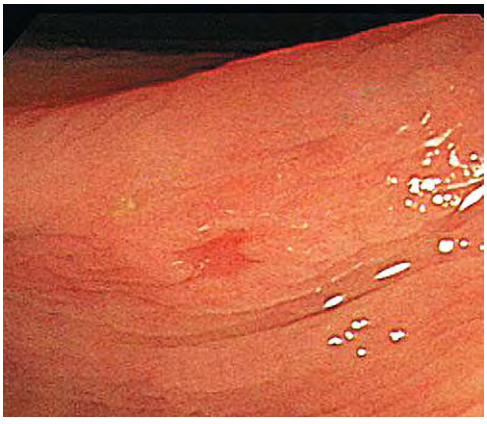

Figure 46. Large bowel: *type 0-IIc*, unstained, intraepithelial neoplasia.

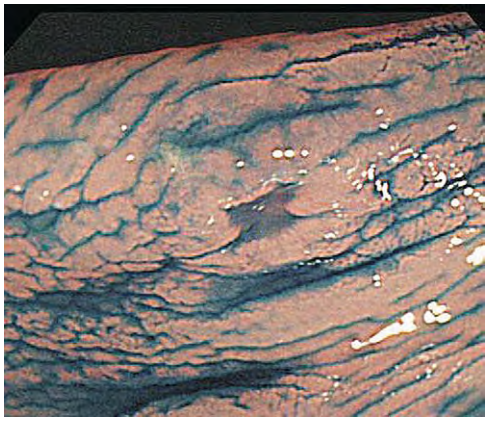

Figure 47. Same case as in Figure 46: chromoendoscopy with indigo carmine.

Slightly Elevated and Depressed (mixed pattern) Neoplastic Lesions *(type 0-IIa + IIc)*

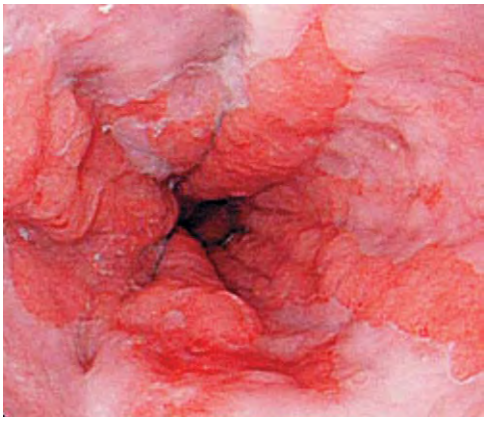

Figure 48. Barrett's esophagus, same case as in Figure 15: *type 0-IIa + IIc*, multinodular lesions and depressions, unstained, intramucosal carcinoma.

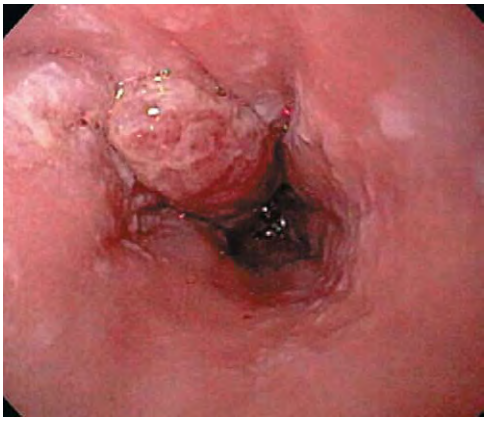

Figure 49. Barrett's esophagus: type *0-IIa + IIc*, depression on the edge of the protrusion, unstained, adenocarcinoma (sm).

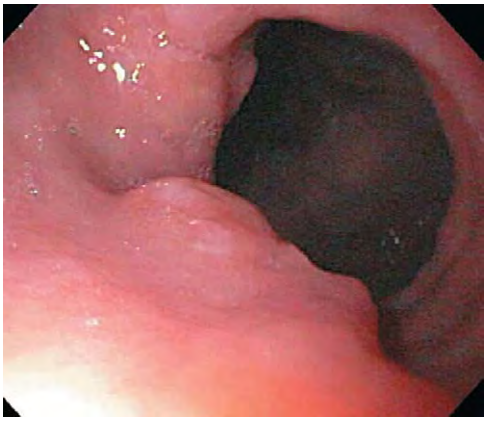

Figure 50. Barrett's esophagus: *type 0-IIa + IIc*, depression centered on the protrusion, unstained, adenocarcinoma (sm).

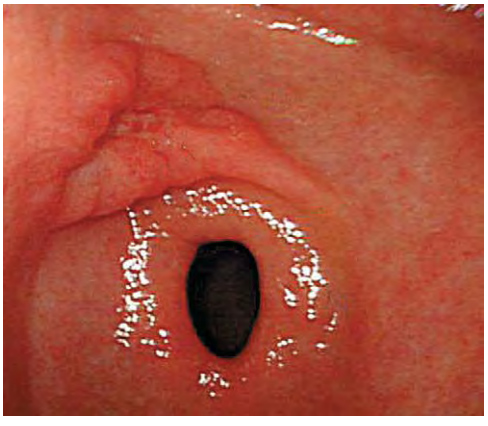

Figure 51. Stomach, prepyloric: *type 0-IIa + IIc*, unstained, carcinoma (sm).

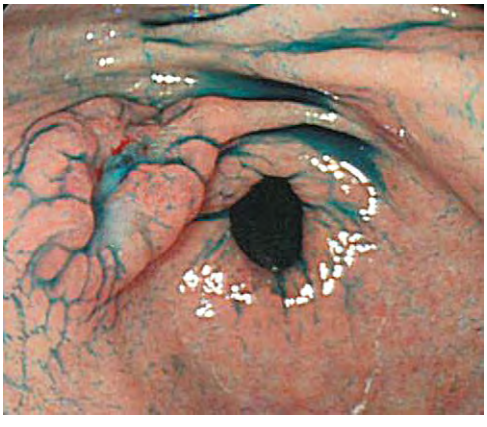

Figure 52. Same case as in Figure 51: chromoendoscopy with indigo carmine.

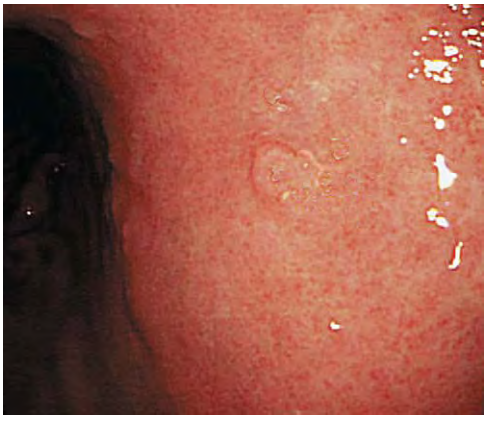

Figure 53. Sub-cardiac stomach: *type 0-IIa + IIc*, unstained, submucosal adenocarcinoma (sm1).

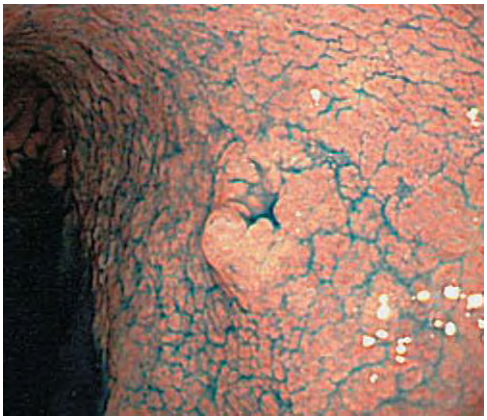

Figure 54. Same case as in Figure 53, chromoendoscopy with indigo carmine.

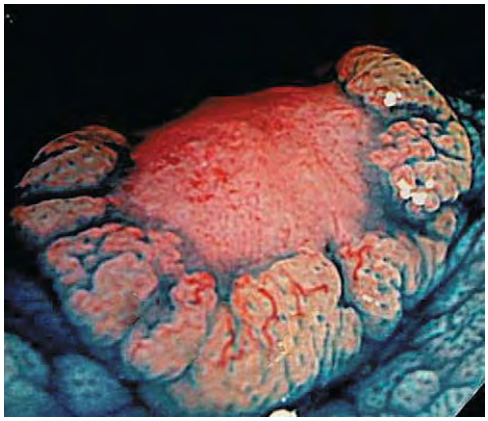

Figure 55. Large bowel: *type 0-IIa + IIc*, elevated lesion with a relative depression, chromoendoscopy with indigo carmine, submucosal adenocarcinoma (sm2),

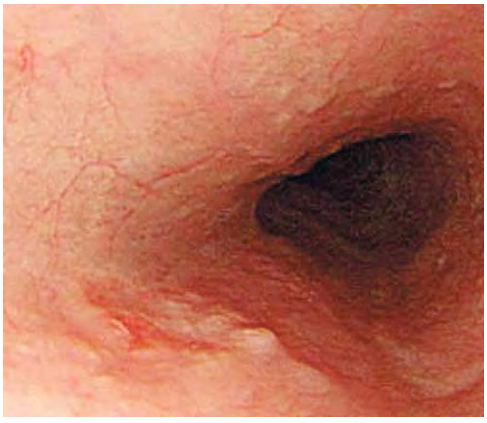

Figure 56. Esophagus (squamous epithelium): *type 0-IIc + IIa*, unstained, submucosal carcinoma (sm2).

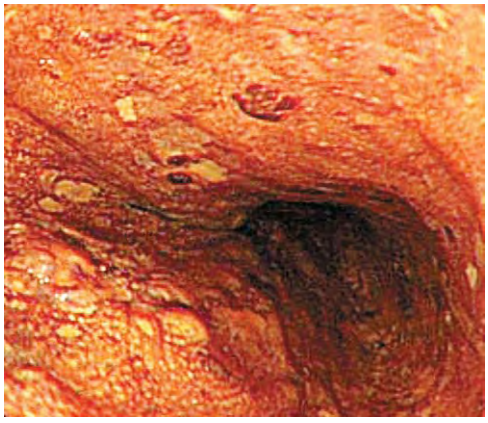

Figure 57. Same case as in Figure 56: chromoendoscopy with iodine stain.

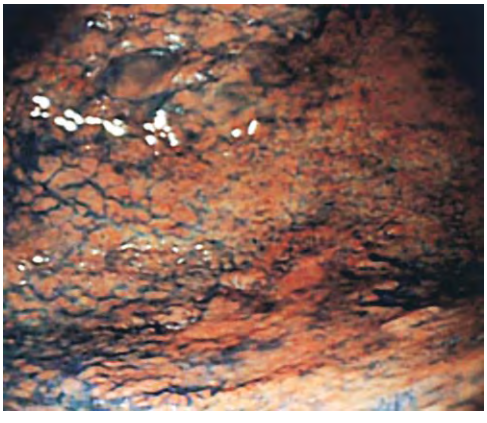

Figure 58. Stomach, posterior: *type 0-IIc + IIa*, chromoendoscopy with indigo carmine, intraepithelial neoplasia.

Figure 59. Large bowel: *type 0-IIc + IIa*, chromoendoscopy with indigo carmine, submucosal adenocarcinoma (sm1).

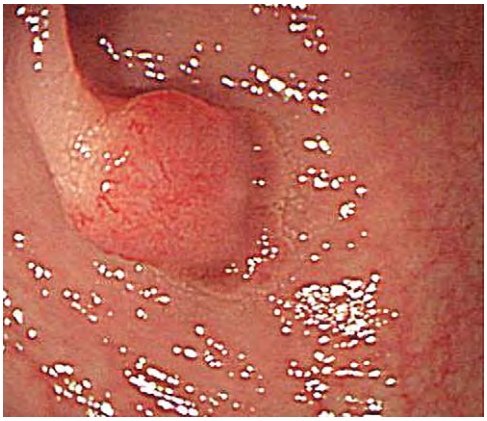

Figure 60. Large bowel: *type 0-IIc + IIa*, unstained, submucosal adenocarcinoma (sm2).

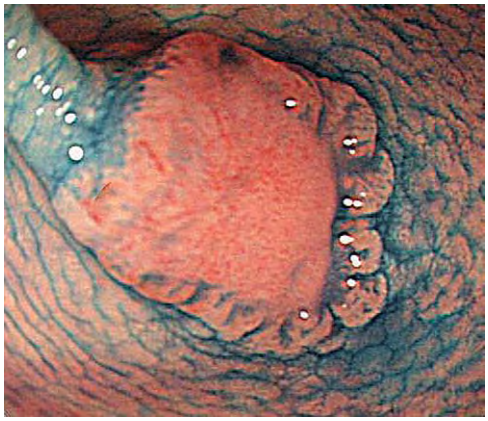

Figure 61. Same case as in Figure 60: chromoendoscopy with indigo carmine.

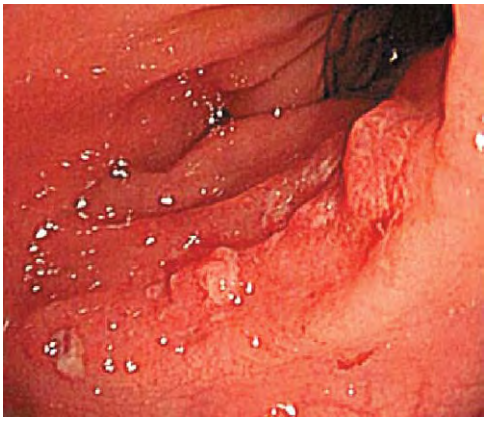

Figure 62. Large bowel: *type 0-IIc + IIa*, unstained, submucosal adenocarcinoma (sm2).

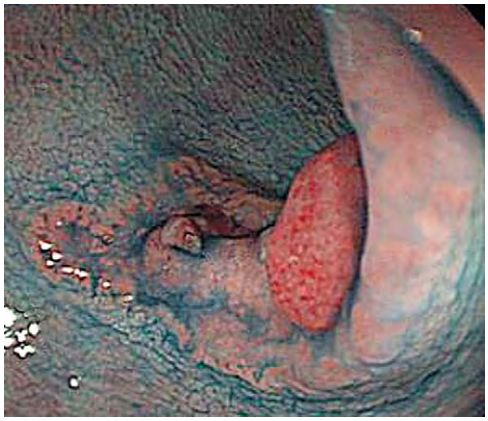

Figure 63. Same case as in Figure 62, chromoendoscopy with indigo carmine.

Excavated Neoplastic Lesions *(type 0-III)*

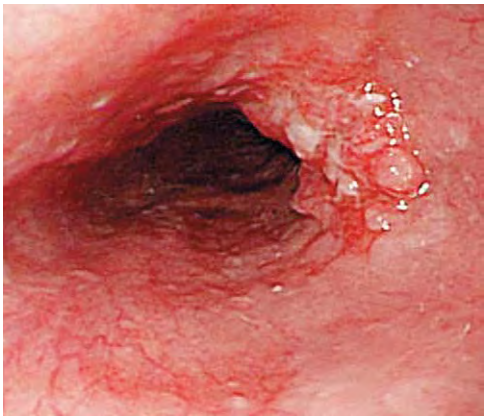

Figure 64. Esophagus (squamous epithelium): *type 0-III*, unstained, submucosal carcinoma (sm3).

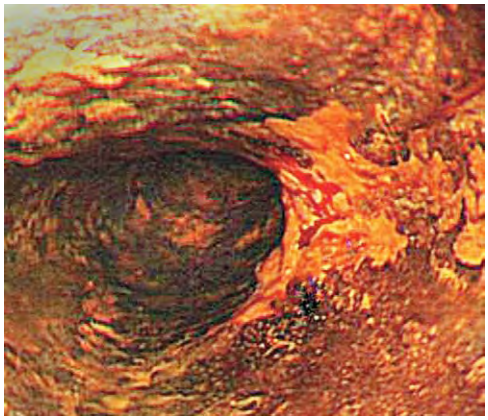

Figure 65. Same case as in Figure 64: chromoendoscopy with iodine stain.

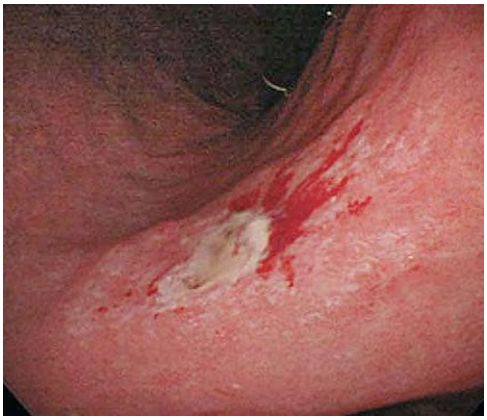

Figure 66. Sub-cardiac stomach: *type 0-IIc + III*, unstained, intramucosal carcinoma.

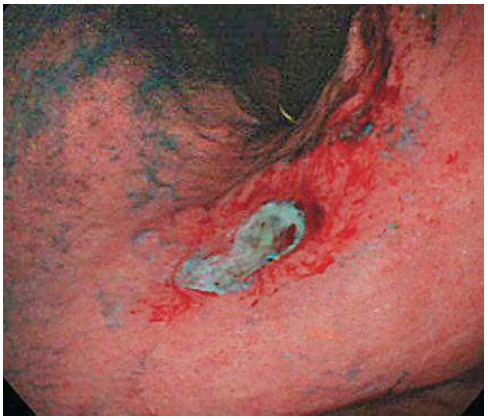

Figure 67. Same case as in Figure 66: chromoendoscopy with indigo carmine.

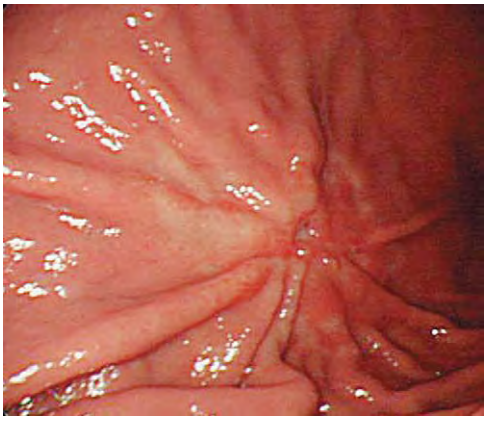

Figure 68. Sub-cardiac stomach: *type 0-IIc + III*, unstained, intramucosal carcinoma.

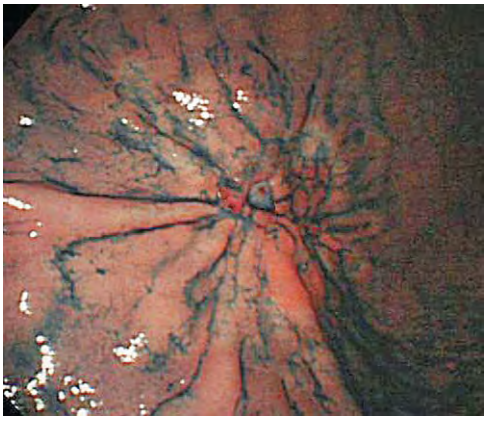

Figure 69. Same case as in Figure 68: chromoendoscopy with indigo carmine.

Neoplastic Lesions with a False Appearance of *Type 0*

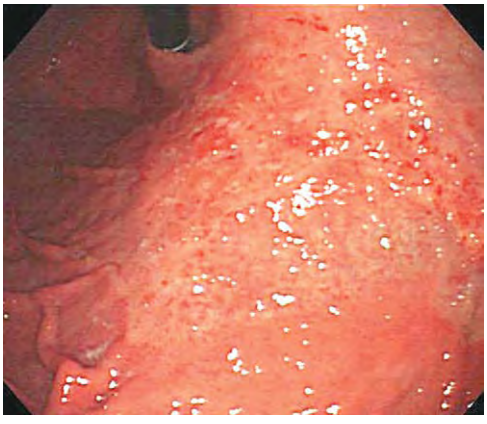

Figure 70. Sub-cardiac stomach: slightly depressed and widespread area, *type 0-IIc*, unstained. Classified as advanced cancer (T3S) in the operative specimen (p-TNM).

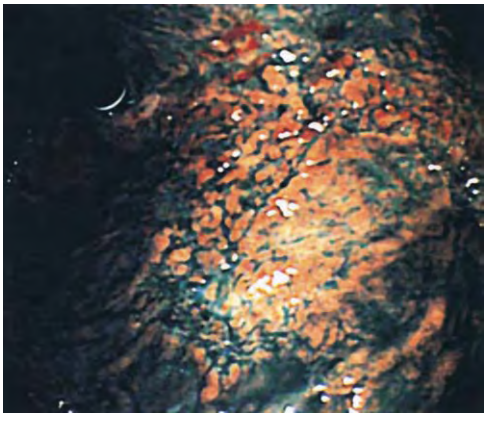

Figure 71. Same case as in Figure 70: chromoendoscopy with indigo carmine.

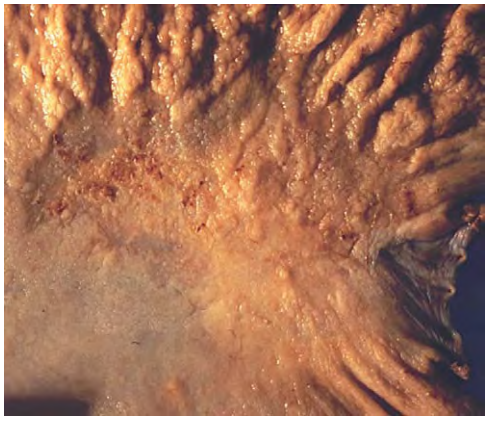

Figure 72. Same case as in Figure 70: operative specimen after immersion in formalin.

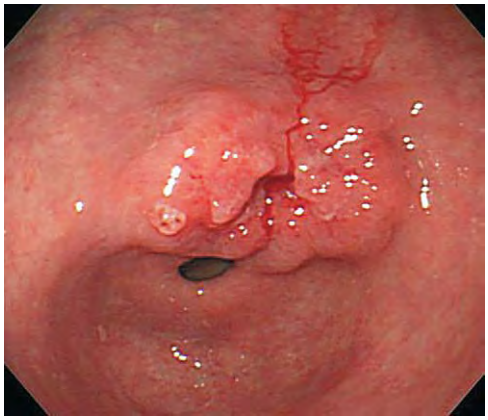

Figure 73. Stomach, prepyloric: an ulcerated carcinoma with raised margins suggesting advanced cancer *type II* in the Borrmann classification at endoscopy. Classified submucosal adenocarcinoma (T1sm2) in the operative specimen (p-TNM).

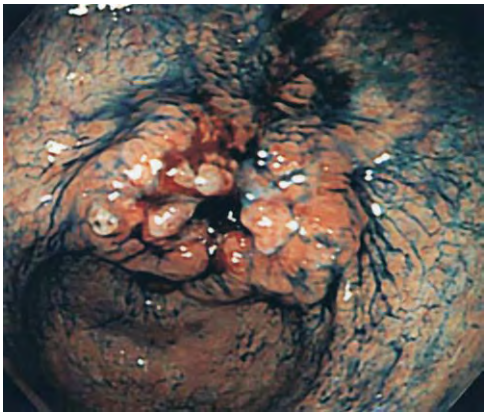

Figure 74. Same case as in Figure 73: chromoendoscopy with indigo carmine.

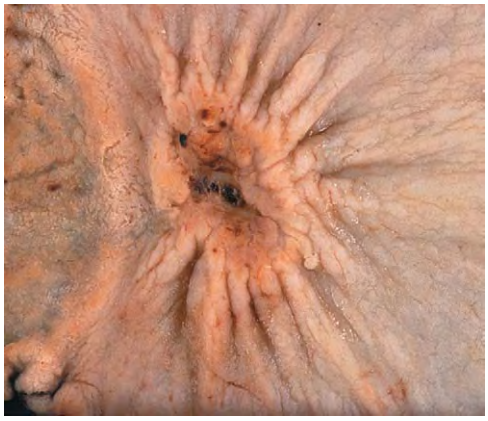

Figure 75. Same case as in Figure 73: operative specimen after immersion in formalin.

Magnification Endoscopy

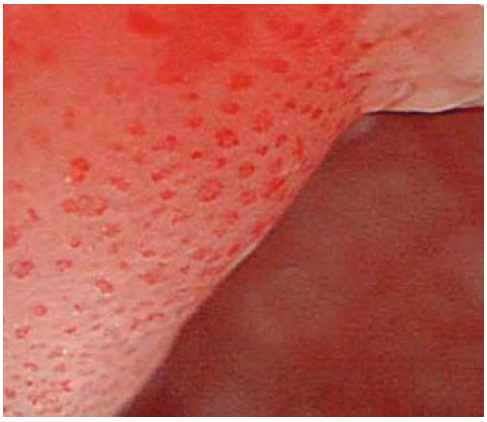

Figure 76. Esophagus (squamous epithelium): magnification in transparency, squamous cell cancer: vessels in punctate pattern.

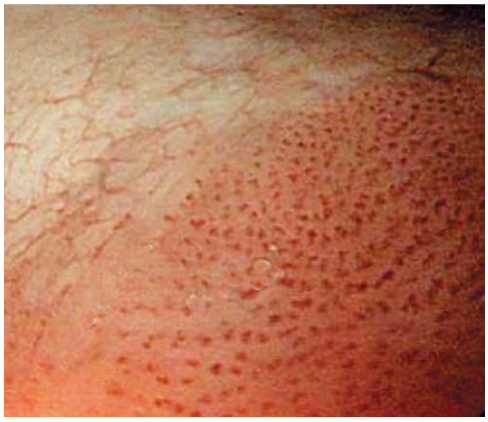

Figure 77. Same lesion as in Figure 20, magnification in transparency and narrow band imaging.

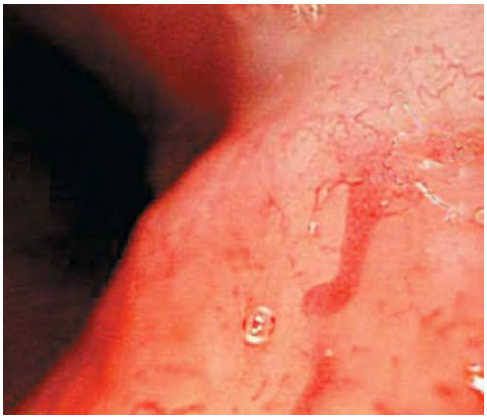

Figure 78. Esophagus (squamous epithelium): magnification in transparency, squamous cell cancer: a large and irregular vessel in the tumor.

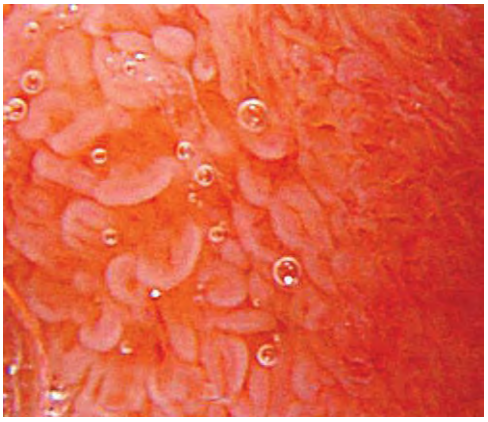

Figure 79. Barrett's esophagus: magnification in an area of intestinal metaplasia, chromoendoscopy with acetic acid.

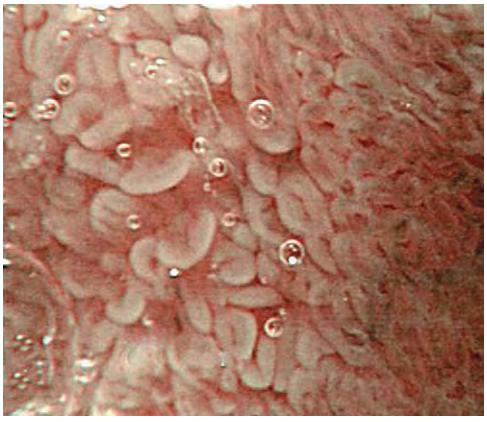

Figure 80. Barret's esophagus, same image as in Figure 79: magnification and narrow band imaging.

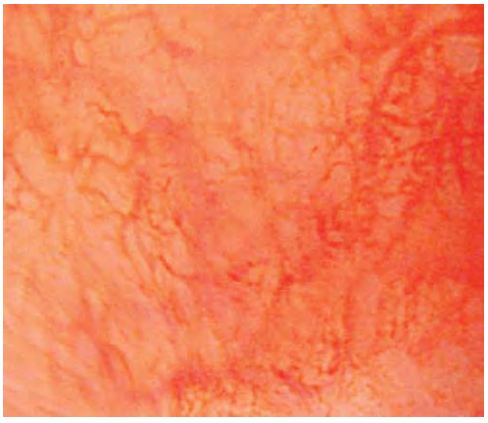

Figure 81. Barrett's esophagus: magnification in an area of intraepithelial neoplasia, chromoendoscopy with acetic acid.

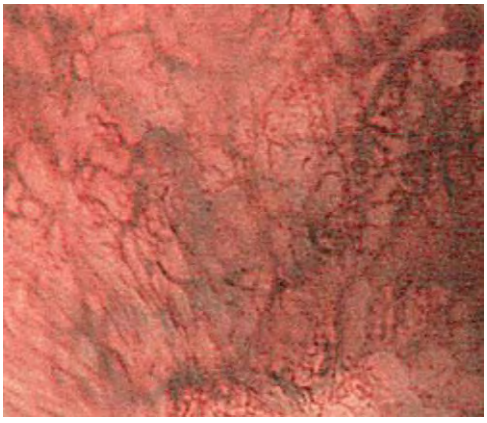

Figure 82. Barrett's esophagus, same image as in Figure 81: magnification and narrow band imaging, the vascular network is enhanced.

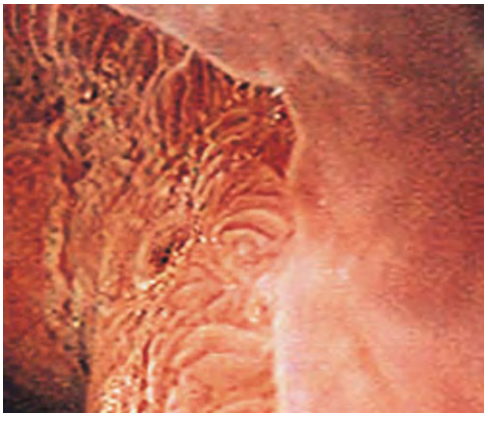

Figure 83. Gastric cardia: magnification at the squamo-columnar epithelial junction, chromoendoscopy with acetic acid.

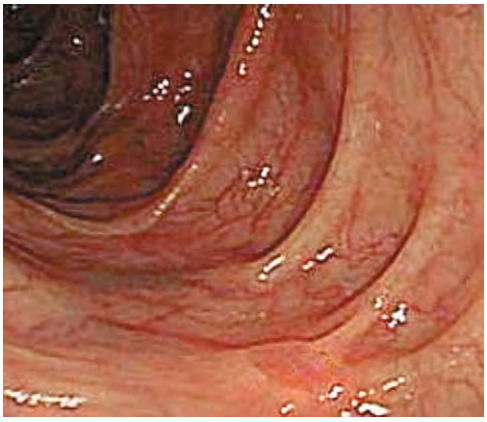

Figure 84. Large bowel: *type 0-IIc*, unstained, submucosal adenocarcinoma (sm1a).

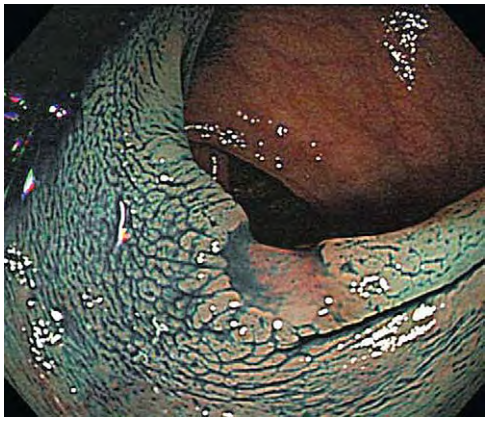

Figure 85. Same case as in Figure 84: chromoendoscopy with indigo carmine.

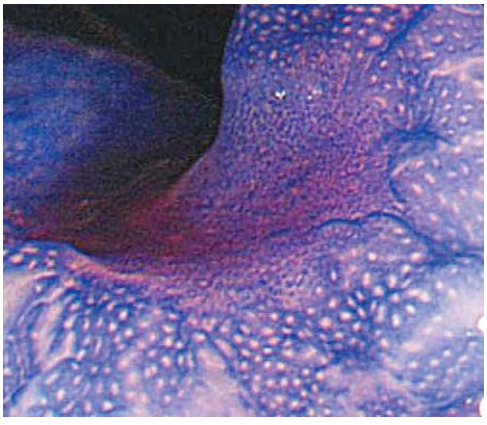

Figure 86. Same case as in Figure 84: magnification and chromoendoscopy with crystal violet. The borders of the pits are colored: narrow pits in the depression (pit pattern IIIs) and round pits over the normal mucosa (pit pattern I).

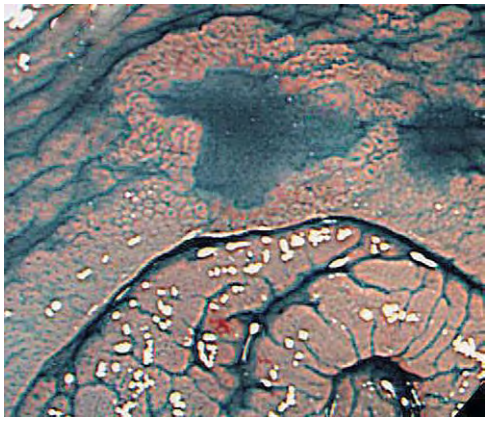

Figure 87. Large bowel: *type 0-IIc*, cecum near appendix, chromoendoscopy with indigo carmine.

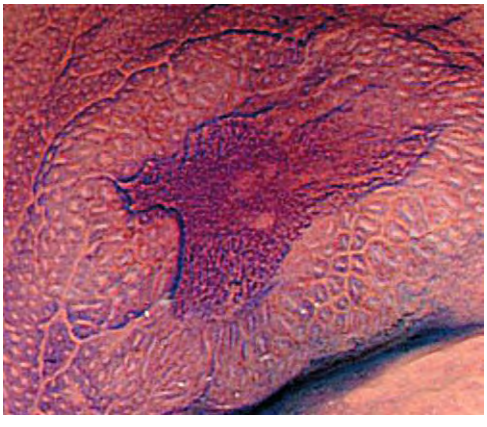

Figure 88. Same case as in Figure 87: magnification and chromoendoscopy with crystal violet.

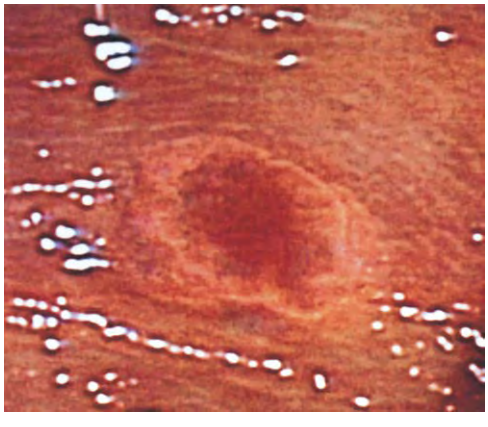

Figure 89. Large bowel: *type 0-IIc*, unstained, intraepithelial neoplasia.

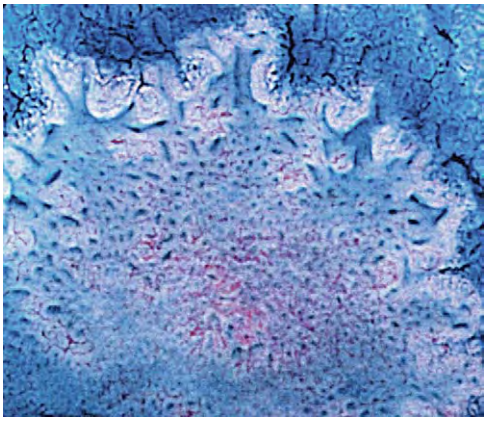

Figure 90. Same case as in Figure 89: magnification and chromoendoscopy with indigo carmine. Narrow pits in the depression (pit pattern IIIs); only the lumen of the pits are colored.

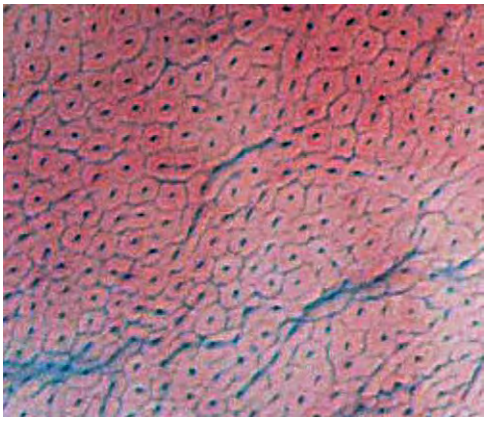

Figure 91. Large bowel: magnification and contrast with indigo carmine, normal colonic mucosa, small and homogeneous pit openings (pit pattern I).

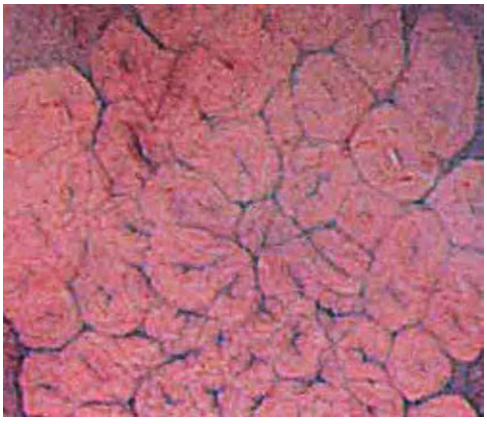

Figure 92. Large bowel: magnification and chromoendoscopy with indigo carmine, non-neoplastic hyperplastic polyp, large and homogeneous star-like pit openings (pit pattern II).

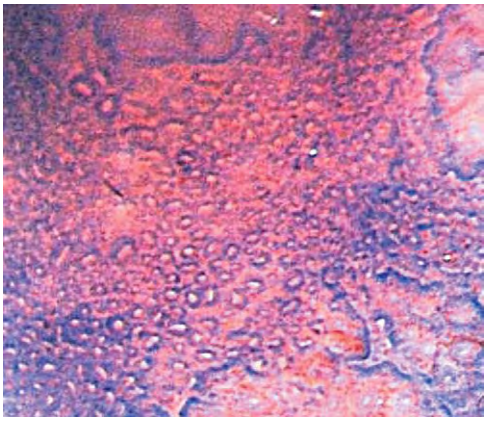

Figure 93. Large bowel: magnification and chromoendoscopy with crystal violet, neoplastic lesion, intraepithelial neoplasia, narrow pits (pit pattern IIIs).

Figure 94. Large bowel: magnification and chromoendoscopy with indigo carmine, neoplastic lesion, intraepithelial neoplasia, long and non-branched epithelial ridges (pit pattern III L).

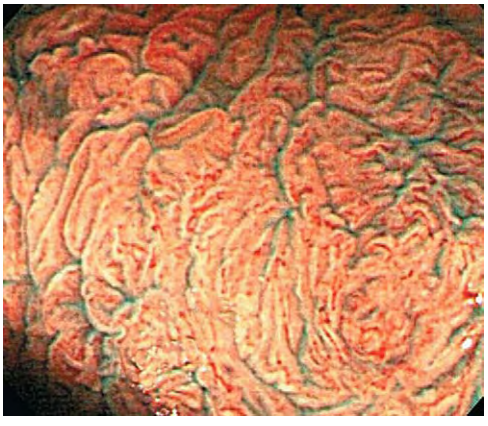

Figure 95. Large bowel: magnification and chromoendoscopy with indigo carmine, neoplastic lesion, intramucosal carcinoma, long, irregular and branched epithelial ridges (pit pattern VI).