encountering polyps, masses, lesions, or colon strictures.[45] However, if lesions could be accurately recognized as nonneoplastic or neoplastic at colonoscopy, then biopsies or resections would be unnecessary.[46] On the basis of these results, proper observation of MC vessels by magnifying NBI would produce a more effective procedure in terms of reducing resources, number of biopsies, total procedure time, and complications from unnecessary polypectomies.

This article is clinically valuable for several reasons. First, it has demonstrated that simple visualization of the surface mesh capillary pattern is effective to differentiate colorectal polyps. Second, the study was designed only for <10 mm polyps, which are the most common and difficult for accurate diagnosis. Finally, it constitutes an easy and reproducible study.

The primary limitation of the study is that MC vessel appearance was judged by a single endoscopist well experienced in magnifying NBI colonoscopy. Interobserver and intraobserver consistency in the endoscopic assessment of colon pit patterns has been reported to be good when the examinations are performed by experienced endoscopists. Recently, a high level of interobserver agreement was seen in both Japanese and European endoscopists evaluating a dark vascular pattern by NBI.[47] However, multicenter international research with endoscopists of different abilities and interobserver and intraobserver variability studies are necessary to validate the results of this study and to establish firm recommendations and guidelines for all endoscopists. The secondary limitation of this study is that patients with polyps larger than 10 mm, with lesions previously evaluated by histologic examination or colonoscopy, and those with invasive carcinoma were excluded from the study. Recently we have reported that the capillary patterns observed by NBI with magnification provide high accuracy for distinction between low- and high-grade dysplasia/invasive cancer and thus can be used to predict the histopathologic features of colorectal neoplasia.[11] Further prospective studies are required whether magnification NBI observation is useful for selection of therapeutic strategies of colorectal tumors and whether nonmagnification NBI truly highlights colorectal tumors efficiently.

In conclusion, we have shown that observation of the MC vessels by NBI with magnification is effective for distinguishing between nonneoplastic and neoplastic lesions without the application of any dye solution. These results suggest that NBI colonoscopy as a form of "optical-equipped–based image-enhanced endoscopy"[48] facilitates simpler and more efficient screening colonoscopy.

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Meshed capillary vessels by use of narrow-band imaging for differential diagnosis of small colorectal polyps (CME)

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Background: Although microvascular vessels on the surface of colorectal polyps are observed by narrow-band imaging (NBI) with magnification, its clinical usefulness is still uncertain.

Objective: Our purpose was to evaluate the usefulness of meshed capillary (MC) vessels observed by NBI magnification for differentiating between nonneoplastic and neoplastic colorectal lesions.

Design: Prospective polyp study.

Setting: National Cancer Center Hospital East, Chiba, Japan.

Patients: A total of 702 consecutive patients who underwent total colonoscopy between September and December 2004 were prospectively evaluated. Patients with polyps >10 mm and those with polyps previously evaluated by histologic examination or colonoscopy were excluded.

Intervention: Lesions were classified into 2 groups: polyps with invisible or faintly visible MC vessels as nonneoplastic and polyps with clearly visible MC vessels as neoplastic. Lesions judged as nonneoplastic were subjected to biopsy and those as neoplastic were removed endoscopically. Histologic analysis was performed in all lesions.

Main Outcome Measurement: Visible or invisible surface MC vessels, prediction of histologic diagnosis.

Results: Of 92 eligible patients enrolled in this study, 150 lesions, including 39 (26%) hyperplastic polyps and 111 (74%) adenomatous polyps, were detected. Observation of MC vessels detected 107 of 111 neoplastic polyps and 36 of 39 nonneoplastic polyps. The overall diagnostic accuracy, sensitivity, and specificity were 95.3%, 96.4%, and 92.3%, respectively.

Limitations: MC vessel judgment performed by a single colonoscopist with extensive experience in magnifying NBI.

Conclusion: Observation of surface MC vessels by magnifying NBI is a useful and simple method for differentiating colorectal nonneoplastic and neoplastic polyps. (Gastrointest Endosc 2009;69:278-83.)

Abbreviations: FAP, familial adenomatous polyposis; HNPCC, hereditary nonpolyposis colorectal cancer; IV, intravenously; MC, meshed capillary; NBI, narrow-band imaging.

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See CME section; p. 303.

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Hyperplastic polyps and other nonneoplastic colorectal lesions do not require endoscopic treatment because they are benign and do not have malignant potential.[1,2] In contrast, the adenoma-carcinoma sequence suggests that colorectal cancers develop from adenomatous polyps and, therefore, their removal could prevent colorectal cancers.[3,4] Thus, in vivo distinction of nonneoplastic and neoplastic lesions would greatly increase the efficiency of colonoscopic procedures.[5]

In a hyperproliferative state, angiogenesis is critical to the transition of premalignant lesions to the malignant phenotype.[6,7] Narrow-band imaging (NBI) is an innovative optical technology that provides a unique image that

emphasizes the morphologic and structural character of lesions as well as the surface capillary pattern.

Previously, we described how the presence of "meshed capillary (MC) vessels" by magnifying NBI are arranged in a honeycomb pattern around the mucosal glands constitutes a useful method for differential diagnosis of colorectal lesions without the need for any dye application.[8] Recently, we have proposed the capillary pattern classification (I-III) for distinction of colorectal lesions.[9-11]

The aim of the current study was to prospectively evaluate the usefulness of observing the surface MC vessels to differentiate between nonneoplastic and neoplastic polyps.

Capsule Summary

What is already known on this topic

- Narrow band imaging (NBI) emphasizes the morphologic and structural character of lesions, as well as the surface capillary pattern.

What this study adds to our knowledge

- NBI detected meshed capillary vessels in 107 of 111 neoplastic and 36 of 39 nonneoplastic polyps, for overall diagnostic accuracy, sensitivity, and specificity of: 95.3%, 96.4%, and 92.3%, respectively.

METHODS

Patients

A total of 702 consecutive patients who underwent screening colonoscopy at National Cancer Center East Hospital, Chiba, Japan, between September and December 2004 were analyzed. The study protocol was approved by the institutional review board, and informed consent was obtained from all patients before the examination. Patients with polyps larger than 10 mm, with lesions previously evaluated by histologic examination or colonoscopy, and those with invasive carcinoma were excluded from the study. Patients with inflammatory bowel disease, hereditary nonpolyposis colorectal cancer (HNPCC), and familial adenomatous polyposis (FAP) were also excluded.

Principle of NBI

NBI is based on modification of the spectral features with an optical color separation filter narrowing the bandwidth of spectral transmittance. In this system, the center wavelengths of the dedicated trichromatic optical filters are 540 and 415 nm, with bandwidths of 30 nm.[12,13] By use of this narrow spectrum, the contrast of the capillary pattern in the superficial layer is markedly improved, and thus clear visualization of vascular structures is achieved during endoscopy. The electronic button on the control section of the colonoscope allowed switching between the conventional and the NBI views instantly.[14]

Colonoscopy procedure

Bowel preparation consisted of 2 to 3 L of polyethylene glycol solution in the morning before the procedure, as previously reported.[15] Hyoscine methobromide (10-20 mg given intravenously [IV]) was administered if there were no contraindications, and light sedation with diazepam (3-5 mg IV) was used in selected subjects. The location of lesions was categorized into 2 groups, according to which side of the splenic flexure they were encountered: proximal colon (including the cecum, ascending colon, and transverse colon) and distal colon (including descending colon, sigmoid colon, and rectum). Lesions were classified macroscopically on the basis of the criteria of the Paris classification of superficial GI lesions.[16]

Evaluation of MC vessels

Colonoscopies were carried out by using a magnifying video colonoscope (CF-H260ZI; Olympus, Optical, Tokyo, Japan) with a standard video processor system (EVIS 260, Lucera Spectrum Olympus Optical). Endoscope withdrawal was performed under conventional white light. All lesions detected by conventional colonoscopy were rinsed with water to remove any overlying mucus on the surface and then were examined by magnifying NBI without the use of any dye solution. Once the NBI system was activated through an easy-to-handle, 1-touch electronic bottom, MC vessels were seen as green-brown in color, and the surrounding normal colon mucosa was seen as a yellowish color. The hue of nonneoplastic lesions is very similar to that of normal epithelial layer, whereas the majority of neoplastic lesions appeared brownish. Lesions with invisible or faintly visible MC vessels were categorized as nonneoplastic, and lesions with clearly visible MC vessels were categorized as neoplastic (Fig. 1).[9-11,14] Size was estimated by using the open width of standard, fully opened biopsy forceps as a reference[5] or after removal (hot biopsy or snare polypectomy). Procedures and endoscopic evaluation were performed by an expert colonoscopist with extensive experience in magnification and NBI (Y. S,). Lesions diagnosed as nonneoplastic were subjected to biopsy, and those diagnosed as neoplastic were removed endoscopically without exception.

Endoscopic treatment

Lesions diagnosed as nonneoplastic and advanced carcinomas underwent biopsy. In lesions identified as adenomatous polyps or intramucosal carcinomas (visible MC vessels), hot biopsy, polypectomy, or EMR was performed. Lesions ≤ 5 mm were resected by coagulation biopsy (hot biopsy), and flat lesions or those >5 mm were treated with loop snare polypectomy or EMR.[17,18]

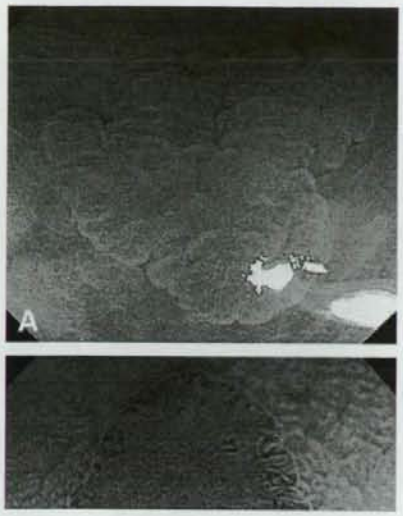

TABLE 1. Patient flow chart

Patient pool (702 patients considered for the study)
Excluded: 453 patients with no polyps found on colonoscopy
Excluded: 68 patient with colorectal lesions with previous evaluation, including histologic examination or colonoscopy
Excluded: 39 patients with invasive carcinoma
Excluded: 41 patients with polyps larger than 10 mm
Excluded: 2 patients with ulcerative colitis (1 with FAP, 1 with HNPCC)
Excluded: 5 patients with polyps that were unretrievable

ineligible on the basis of the exclusion criteria, and in 5 (1%) patients, retrieving the resected specimen was not possible (Table 1). The remaining 92 (13%) patients were enrolled for prospective evaluation. The mean age

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ORIGINAL ARTICLE

Local recurrence after endoscopic resection of colorectal tumors

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Abstract
Background and aims Local recurrence frequently occurs after endoscopic resection of large colorectal tumors. However, appropriate intervals for surveillance colonoscopy to assess local recurrence after endoscopic resection have not been clarified. The aim of the present study was to determine local recurrence rates following en-bloc and piecemeal endoscopic resection and establish appropriate surveillance colonoscopy intervals based on retrospective analysis of local recurrences.
Materials and methods A total of 461 patients with 572≥ 10-mm lesions underwent endoscopic resection and follow-up. We retrospectively compared local recurrence rates on lesion size, macroscopic type, and histological type after en-bloc resection (440 lesions) and piecemeal resection (132 lesions). Cumulative local recurrence rates were analyzed using the Kaplan–Meier method.
Results Local recurrence occurred for 34 lesions (5.9%). Local recurrence rates for the en-bloc and piecemeal groups was 0.7% (3/440) and 23.5% (31/132), respectively ($P<$ 0.001). The difference between the two groups was distinct in terms of lesion size, macroscopic type, and histological type. Of the 34 local recurrences, 32 were treated endoscopically and two cases required additional surgery. The 6-, 12-, and 24-month cumulative local recurrence rate of the en-bloc group was 0.24%, 0.49%, and 0.81%. Then the 6-, 12-, and 24-month cumulative local recurrence rate for the piecemeal group was 18.4%, 23.1%, and 30.7%.
Conclusion Local recurrence occurred more frequently after piecemeal resection than en-bloc resection. However, almost all cases of local recurrences could be cured by additional endoscopic resection, so piecemeal resection can be acceptable treatment.

Keywords Colorectal tumors · Colonoscopy · Neoplasm recurrence · Follow-up studies

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Introduction

Endoscopic resection is used to treat early colorectal tumors around the world. However, the high frequency of local recurrence after piecemeal resection for large colorectal tumors is a serious problem [1–6]. Based on national polyp study [7], the appropriate interval for surveillance colonoscopy after endoscopic resection of adenomatous polyps is 3 years. However, the appropriate intervals after incomplete endoscopic resection has not yet been clarified. In the present study, we retrospectively analyzed the local recurrence frequency after en-bloc and piecemeal endoscopic resection for colorectal neoplasms ≥10 mm in size in large number of follow-up cases. We also analyzed clinicopathologic features and treatment of local recurrences. Our goal was to establish appropriate surveillance colonoscopy programs after endoscopic resection for colorectal tumors based on our retrospective analysis of local recurrence.

Table 1 The clinicopathologic characteristics

	En-bloc (n=440)	Piecemeal (n=132)
Follow-up (months)	22 (1–57)	18 (1–54)
Size (mean, mm)	13.9 (10–40)	23.3 (10–45)
Location		
(Rb/Ra/Rs/S/D/T/A/C)	23/23/32/140/39/73/81/29	12/4/8/20/6/25/29/28
Macroscopic type		
Protruding	324	26
Flat elevated	114	100
Depressed	2	6
Pathological type		
Adenoma	181	35
M-ca	253	88
SM-ca	5	8
Unevaluated	1	1

Rb lower rectum, *Ra* upper rectum, *Rs*: rect-sigmoid colon, *S* sigmoid colon, *D* descending colon, *T* transverse colon, *A* ascending colon, *C* cecum, *M-ca* intramucosal carcinoma, *SM-ca* submucosal invasive carcinoma

Materials and methods

A total of 461 patients (311 men, 150 women), with 572≥10-mm lesions underwent endoscopic resection and were followed up endoscopically between January 1998 and March 2002 at the National Cancer Center Hospital (Tokyo, Japan). Patients that required additional surgical treatment immediately after endoscopic resection and in whom follow-up colonoscopy could not be performed were excluded from the study. Clinical and pathological records were retrospectively analyzed. The mean patient age was 63.8 years (range 19–89). Of 572 lesions, 440 (76.9%) were removed en-bloc and 132 (23.1%) were removed by piecemeal. The clinicopathologic characteristics of the en-bloc and piecemeal groups are shown in Table 1. There was no difference in the follow-up period for the groups. For the piecemeal group, the mean size of the lesion was 23.3 mm. For the en-bloc group, the mean size of the lesion was 13.9 mm. The rates of rectal lesions were about 20% in both groups. In the piecemeal group, the dominant macroscopic type was flat-elevated. In the en-bloc group, the dominant macroscopic was protruded. We compared the local recurrence rates in the two groups by lesion size, macroscopic type, and histological type. Furthermore, we analyzed the clinicopathologic features and treatments of cases with local recurrence. All patients provided informed consent prior to endoscopic resection.

Endoscopic technique

Good bowel preparation is essential for detection and detailed observation of lesions. We used 2 L of polyethylene glycol electrocyte solution on the day of examination. We used conventional or magnifying video colonoscopies (CF200I, CF-Q240I, CF-200Z, CF-Q240ZI, PCF-230, PCF-Q240ZI; Olympus Optical, Tokyo, Japan). Scopolamine butyl bromide was administered intravenously unless contraindicated. The initial dose was 10 mg and was increased as required. If necessary, the conscious sedation was maintained with intravenous boluses of midazolam or pethidine. We routinely used chromoendoscopy with 0.2% indigo carmine dye to accentuate the lesion contours [8]. This procedure was useful for determining the area of endoscopic resection and detecting local recurrence at the site of resection. Furthermore, we used a magnifying endoscope with 0.2% indigo carmine or 0.05% crystal violet to estimate the depth of invasion in the target lesion [8] and to detect the residual tumor immediately after

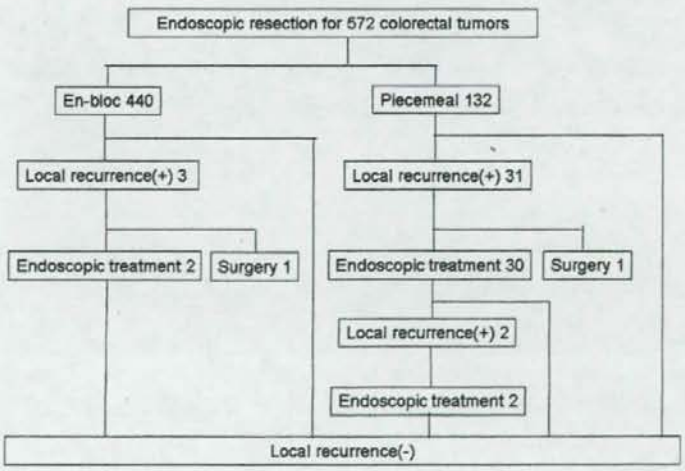

Fig. 1 A chart of 572 colorectal tumors followed up after endoscopic resection

endoscopic resection. Macroscopically, at the margins, lesions can be classified into three major groups: protruding type including sessile (Is), semi-pedunclated (Isp), pedunclated (Ip); flat-elevated type including IIa, IIa+IIc, and Is+IIa; and depressed type including IIc. The indication for endoscopic resection is lesion invasion depth limited to the mucosa and shallow submucosa. After the visible lesion was completely removed, 0.2% indigo carmine was sprayed over the area and the area was magnified. Residual tumor was removed with hot biopsy forceps. We performed all endoscopic treatments in a single session.

Histological examination

All tissue was retrieved for histological evaluation. Removed specimens were fixed in 10% formalin for 24 h and embedded in paraffin wax. Serial sections (3 μm) were stained with hematoxylin and eosin. Two or more pathologists specializing in gastroenterology made histological diagnoses including histological type, invasion depth, vessel invasion, and surgical margin. In the present study, histological type was classified into three groups: adenomas, mucosal carcinomas (M-ca), and submucosal carcinomas (SM-ca).

A principle of additional surgical treatment

Patients that were (1) diagnosed with deep SM-ca >1,000 μm, (2) positive for vessel invasions, (3) positive for poorly differentiated adenocarcinoma at the sites of invasion, and (4) positive for vertical margins were judged to require additional surgical treatment with resection of regional lymph nodes. Cases that were judged to have positive or indistinct for lateral margins were followed up endoscopically.

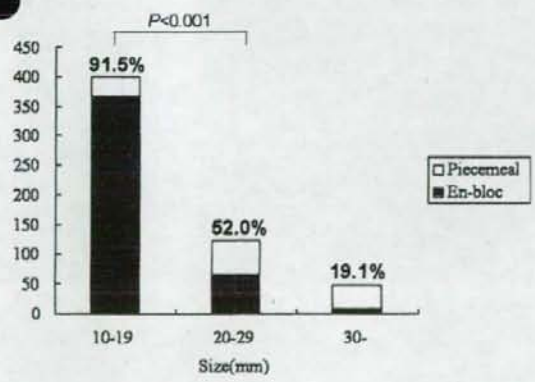

Fig. 2 En-bloc resection rates by lesion size

Table 2 Local recurrence rates by the lesion size

Size (mm)	10–19	20–29	30+	Total
En-bloc	0.8%* (3/366)	0%* (0/65)	0% (0/9)	0.7% (3/440)
Piecemeal	14.7% (5/34)	21.7% (13/60)	34.2% (13/38)	23.5% (31/132)
Total	2.0% (8/400)	10.4% (13/125)	27.7% (13/47)	5.9% (34/572)

*$P<0.001$

Statistical analysis

Local recurrence rates were compared with a chi-square test. Cumulative local recurrence rates were analyzed with the Kaplan–Meier method. Comparison of local recurrence rates were analyzed with log rank test. All statistical analysis was performed with Stat Mate Ver.3 for Windows (ATMS Tokyo, Japan). Calculated P values <0.05 were considered statistically significant.

Results

Local recurrence occurred in 34 lesions (5.9%) of 572 lesions. The local recurrence rates in en-bloc and piecemeal groups was 0.7% (3/440) and 23.5% (31/132, chi-square, $P<0.001$; Fig. 1). The en-bloc resection rates of lesions (Fig. 2) decreased in proportion to increase in size (chi-square; $P<0.001$). The local recurrence rates by lesion size are shown in Table 2. Based on lesion size, local recurrence rates of the en-bloc group were significantly lower than those of the piecemeal group (10–19 and 20–29 mm, chi-square, $P<0.001$). Based on macroscopic type, local recurrence rates of the en-bloc group were significantly lower than those in the piecemeal for protruding and flat-elevated types (chi-square, $P<0.001$; Table 3). Based on histological type, local recurrence rates of the en-bloc group were significantly lower than those of the piecemeal group for adenoma and M-ca (chi-square, $P<0.001$; Table 4).

Table 3 Local recurrence rates by macroscopic type

Type	Protruding	Flat elevated	Depressed	Total
En-bloc	0%* (0/324)	2.6%* (3/114)	0% (0/2)	0.7% (3/440)
Piecemeal	19.2% (5/26)	24.0% (24/100)	33.3% (2/6)	23.5% (31/132)
Total	1.4% (5/350)	12.6% (27/214)	25.0% (2/8)	5.9% (34/572)

*$P<0.001$

Table 4 Local recurrence rates by histological type

Type	Adenoma	M-ca	SM-ca	Unevaluated	Total
En-bloc	1.1%* (2/181)	0.4%* (1/253)	0% (0/5)	0% (0/1)	0.7% (3/440)
Piecemeal	17.1% (6/35)	26.1% (23/88)	25% (2/8)	0% (0/1)	23.5% (31/132)
Total	3.7% (8/216)	7.0% (24/341)	15.4% (2/13)	0% (0/2)	5.9% (34/572)

M-ca intramucosal carcinoma, *SM-ca* submucosal invasive carcinoma
*$P<0.001$

Twenty-eight of the 34 lesions with local recurrence were detected by the first follow-up colonoscopy that occurred at a median of 114 days (range 74–471) after resection. Local recurrence was detected in the remaining six lesions at the second or subsequent colonoscopy that occurred at a median of 726 days (range 337–910). For four of the six local recurrences that were missed by the first colonoscopy, the colonoscopy was performed within 3 months of resection.

The cumulative rate of local recurrence using the Kaplan–Meier method is shown in Fig. 3. The 6-, 12-, and 24-month cumulative local recurrence rate of the en-bloc group was 0.24%, 0.49%, and 0.81%. The 6-, 12-, and 24-month cumulative local recurrence rate for the piecemeal group was 18.4%, 23.1%, and 30.7%. Local recurrences were significantly frequent in the piecemeal group (log rank test, $P<0.001$). Therefore, we considered the proper first follow-up interval for the piecemeal group to be 6 months. The treatment for local recurrence endoscopic resection was performed in 32 cases (94.1%), and almost all of them were performed in a single session (mean 1.1, range 1–2; Fig. 1). Neither bleeding nor perforation occurred during endoscopic treatment. Two patients required additional surgery (Fig. 1), and the finding was intramucosal carcinoma without lymph node metastasis. The rate of additional surgery after endoscopic en-bloc and piecemeal resection was 0.23% (1/440) and 0.75% (1/132).

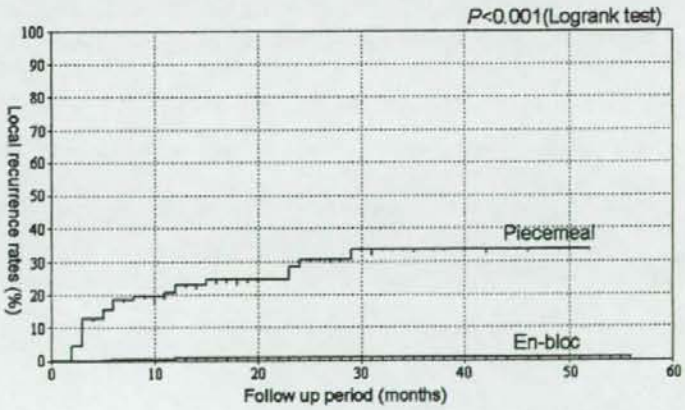

Fig. 3 Cumulative local recurrence rates after endoscopic resection (Kaplan–Meier method)

Discussion

Endoscopic resection for an early colorectal tumor has been used throughout the world since the 1970s [9, 10]. An endoscopic mucosal resection (EMR) with submucosal saline injection technique [1, 11–14] allowed us to remove a large colorectal tumor that appeared to be not only sessile but also flat and depressed. However, local recurrences frequently occurred after endoscopic piecemeal resection for large sessile tumors, which is a serious problem. Previous studies have reported the rate of local recurrence following piecemeal resection to be 25–50% [1, 2, 6]. Consequently, a combination of snare polypectomy and argon plasma coagulator (APC) [4, 5] or YAG laser [3, 15] was attempted to reduce local recurrence. One randomized controlled study demonstrated that there were fewer local recurrences with APC than without APC (1/10 vs. 7/11) [5]. However, the randomized group consisted of the patients in whom initial polypectomy was apparently complete, and local recurrence frequently occurred despite APC in patients with incomplete polypectomies (6/13). On the other hand, Palma et al. [15] reported that YAG laser reduced remnant tumor in ≥40-mm adenomas. However, the number of treatments with the YAG laser were frequently as many as three, which is a disadvantage of the method. The effort to reduce the local recurrence of piecemeal resection has stalled.

In pathologic staging, it is often difficult to evaluate the surgical margins and invasion depth after piecemeal removal of lesions because specimens may be difficult to reconstruct [16]. On the other hand, surgical margins and invasion depth are easily assessed after en-bloc resection

[16]. Moreover, one can easily evaluate the lateral margin after an en-bloc procedure by immediate observation of the retrieved specimen.

Could the en-bloc method reduce local recurrence after endoscopic resection? In the present study of 572 colorectal tumors that were endoscopically resected, local recurrence occurred for 34 lesions (5.9%). Furthermore, the local recurrence rate for the en-bloc group was significantly lower (0.7%) than that for the piecemeal group (23.5%; $P<0.001$). The difference was maintained in subgroups with different lesion sizes (i.e., 10–19 vs. 20–29 mm). We could rationalize that the 10- to 19-mm lesions in which local recurrence occurred were difficult to locate, and therefore, we could not perform en-bloc resection.

Localization of the lesion in the large bowel is an important factor for the detection of remnant tumor immediately after endoscopic resection. Moreover, neither the macroscopic nor the histological type affected the local recurrence rate. Therefore, en-bloc resection appears to be an important factor for reducing local recurrences. Iishi et al. [17]. reported that of 56 large sessile colorectal polyps, the local recurrence after an en-bloc resection was less than that after piecemeal resection (0% vs. 50%). We confirmed this result in a large number of cases in the present study, and we added a detailed analysis for each factor. Although we routinely use magnifying observation of artificial ulcer's edges after endoscopic resection, local recurrence rate of the piecemeal group was significantly higher than the en-bloc group. We speculate this reason that there were micro-residual lesions made by intra-plural snaring method in the center of artificial ulcers, which were difficult to diagnose by observation of ulcer edges. Moreover, higher local recurrence rate might be caused by detailed detection during follow-up colonoscopy using magnified observation.

For the part of large rectal lesions, transanal endoscopic microsurgery (TEM) was considered for an alternative therapy for endoscopic resection. Local recurrence rates (0–10%) of TEM were reported [18], and these were better than our data of endoscopic piecemeal resection. However, TEM required experienced techniques and special instruments, and some complications such as incontinence and urinary retention which never arose in endoscopic resection occur [18].

Recently, several Japanese endoscopists [19, 20] developed novel techniques for large en-bloc resection, endoscopic submucosal dissection (ESD). Gotoda et al. [19] reported EMR on two rectal tumors using an insulation-tipped knife with which they cut the normal mucosa surrounding the target lesions before snaring. Yamamoto et al. [20] successfully removed a 40-mm rectal laterally spreading tumor with submucosal injection of a large amount of sodium hyaluronate. They also cut normal mucosa surrounding the target lesions with a needle knife before snaring. There are several problems with these novel techniques, including technical difficulty, the inability to determine the rate of perforation, and long procedure time. For those reasons, ESD is not widely used.

Based on our result, local recurrence is rare following en-bloc resection. Therefore, the 3- to 5-year interval for surveillance colonoscopy suggested by the national polyp study [7] and the guidelines of the American Gastroenterological Association (AGA) [21] should be appropriate after en-bloc resection. Definite surveillance intervals after incomplete resection have not been proposed by the AGA [21]. In our piecemeal resection group, local recurrence increased gradually from 18.4% at 6 months to 30.8% at 24 months. Based on those findings, an earlier surveillance colonoscopy (e.g., 3 months) would have missed local recurrence. Therefore, a 6-month interval for surveillance colonoscopy after piecemeal resection seems appropriate. That interval will provide accurate diagnosis of local recurrences >50% of the time.

The limitations of our study include using retrospective analysis and being non-randomized. Prospective randomized controlled studies are necessary for determining the appropriate interval for surveillance colonoscopy after piecemeal resection.

In our study, only two instances of local recurrence required additional surgery; the remainder were treated with additional endoscopic resection. We consider piecemeal resection an acceptable treatment until the efficacy and safety of large en-bloc resection are established.

In the future, an effective injection fluid or snare should be developed for safer and larger en-bloc resection based on conventional EMR procedures. We recently injected 10% glycerin solution into the submucosa during EMR, which resulted in a better en-bloc resection rate compared to normal saline [22]. Furthermore, we should make an effort to establish an ESD technique while paying a great deal of attention to safety.

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Nonpolypoid neoplastic lesions of the colorectal mucosa

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Japan, China, USA, Brazil, France, Belgium, Sweden, Germany, UK

INTRODUCTION

The progress in our understanding of early events in the development of colonic neoplasia is the result of 2 advances: (1) improved characterization of lesions detected at endoscopy and (2) new knowledge about the molecular biology of nonpolypoid lesions. Improved characterization of neoplastic lesions has been achieved through the addition of chromoscopy[1-5] and high-resolution endoscopy with magnification and image processing.[6-9] New molecular knowledge about both sessile serrated lesions and flat adenomas has altered our understanding of the histogenesis of nonpolypoid lesions and their endoscopic management. A multidisciplinary workshop held in February 2008 in Kyoto, Japan, explored new aspects of our knowledge. This text summarizes the debate and ultimately the consensus among experts in endoscopy, pathology, and molecular biology of the colon.

In 1975, Muto et al[10] described the histologic transition from a precursor adenomatous polyp to a confirmed colorectal cancer. Previous opinion, that colorectal cancer develops through a single pathway, has now been challenged, and it is clear that colorectal cancer can develop through multiple pathways, as reviewed by Jass[11] and Jass et al.[12] The morphology of premalignant colonic lesions depends on the direction of proliferating cell growth. Essentially, 3 types of lesions are now recognized: polypoid, nonpolypoid, and depressed. Polypoid lesions grow above the surface of the mucosa, rather than below, and the volume of the polypoid component appears to correlate with the histologic stage, as shown in the large series issued from endoscopy and pathology units in Japan and listed in the Paris classification.[13,14] Nonpolypoid lesions may grow flat or slightly elevated and, eventually, may grow and progress to polypoid lesions or to laterally spreading tumors. Depressed lesions deserve special attention because of the difficulty in their detection, the need for special techniques (mucosectomy) to remove them by endoscopy, and a recognized increased risk of rapid progression to cancer, independent of size, as shown in endoscopy and pathology units in Japan.[13,14] Nonpolypoid, depressed lesions progress in depth rather than above the surface of the mucosa, and submucosal invasion is frequent, even for small lesions (Figs. 1 and 2).

Sporadic colorectal neoplasia results from the disruption of normal cellular growth and senescence at a molecular level. In 1990, Fearon and Vogelstein[15] demonstrated that a mutation within the adenomatous polyposis coli (APC) tumor-suppressor gene initiated one of the major neoplasia pathways. This mutation was linked to chromosomal instability (CIN) and loss of heterozygosity (LOH). Subtle molecular differences cause alternative growth patterns, such as polypoid or nonpolypoid (including the flat adenoma and flat cancer), and they, subsequently, will be discussed.

In the last decade, the serrated pathway has been described as an alternative pathway to colorectal cancer. Serrated lesions refer both to hyperplastic (HP) (nonneoplastic) lesions, often called HP polyps, and sessile serrated lesions, often called sessile serrated adenomas (SSAs); the latter are considered the precursor for microsatellite instable (MIS) cancers. An early event in the growth of sessile-serrated lesions is an inactivating mutation within the BRAF gene encoding the B-RAF protein kinase. Progression from nondysplastic sessile-serrated lesions to neoplasia requires epigenetic silencing of hMLH1, one of the mismatch repair (MMR) genes. Inactivating methylation of hMLH1 disrupts the MMR cascade, which results in the accumulation of mutations in a variety of genes, some of which lead to neoplasia and MIS cancers.

Abbreviations: ACF, aberrant crypt foci; APC, adenomatous polyposis coli; CIMP, CpG-Island methylation phenotype; CIN, chromosomal instability; FAP, familial adenomatous polyposis; HGIN, high-grade intraepithelial neoplasia; HNPCC, hereditary nonpolyposis colon cancer; HP, hyperplastic; LOH, loss of heterozygosity; LST, laterally spreading type; m, mucosa; MIS, microsatellite instable; MMR, mismatch repair; MSS, microsatellite stable; NBI, narrow-band imaging; sm, submucosa; SSA, sessile serrated adenoma; TSA, traditional serrated adenoma.

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ENDOSCOPIC CLASSIFICATION OF POLYPOID AND NONPOLYPOID SUPERFICIAL LESIONS

The morphology of superficial neoplastic or nonneoplastic lesions in the colorectal mucosa is protruding (polypoid) or flat (nonpolypoid). Premalignant and malignant

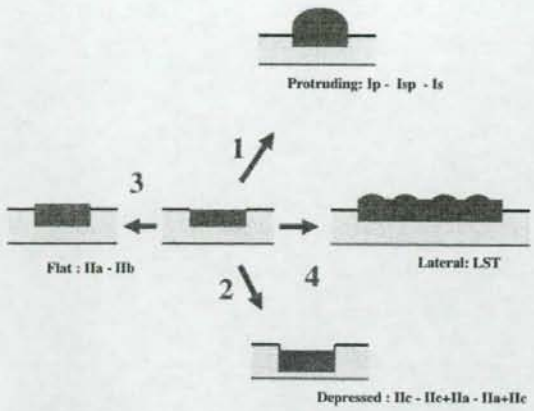

Figure 1. Models of tumor growth during the development of colorectal neoplasia: Progression occurs in 4 distinct models: (1) as a polypoid protruding lesion in an upward direction, (2) as a nonpolypoid depressed lesion, which progresses in a downward direction in depth, (3) as a nonpolypoid lesion, which remains either flat or slightly elevated, and (4) As a LST lesion.

TABLE 1. Morphologic classification of type 0 lesions with superficial appearance at colonoscopy (Paris-Japanese classification)

Polypoid type*	Pedunculated (0-Ip)
	Sessile (0-Is)
	Mixed (0-Isp)
Nonpolypoid type	Slightly elevated (0-IIa)
	Completely flat (0-IIb)
	Slightly depressed (0-IIc)
Mixed types	Elevated and depressed (0-IIa + IIc)
	Depressed and elevated (0-IIc + IIa)
	Sessile and depressed (0-Is + IIc)

*Polypoid lesions are elevated more than 2.5 mm above the surrounding mucosa. Nonpolypoid lesions are flat, elevated less than 2.5 mm, or are depressed less than 2.5 mm. Slightly elevated lesions should not be mistaken for sessile or flat lesions.

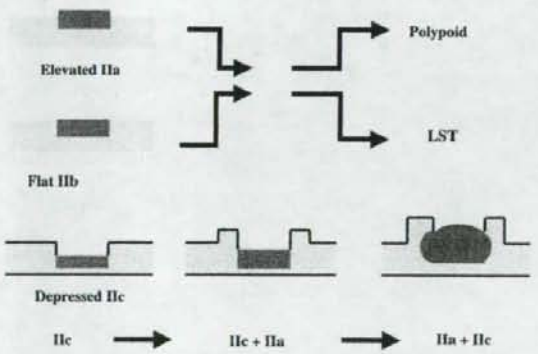

Figure 2. Subtypes of nonpolypoid neoplastic lesions. The nondepressed types, elevated or completely flat (0-IIa, 0-IIb), are stable or progress to polypoid or LST lesions. The depressed type (0-IIc) may progress to a mixed morphology, 0-IIc + 0-IIa and then 0-IIa + 0-IIc. When the tumor increases in depth, the surface of the depression may be elevated, even in small lesions.

neoplastic lesions of the digestive mucosa are called superficial when their appearance at endoscopy suggests that their depth is limited to the mucosa (m) or submucosa (sm). Nonpolypoid (flat) small neoplastic lesions are frequent in human beings, and some of them show a fast progression to cancer, in spite of maintaining a small size. In the absence of adenomatous remnants, these lesions appear to be "de novo" cancer. The nonpolypoid model of neoplastic growth is confirmed in animal studies, because it can occur spontaneously in baboons[16] or after administration of the carcinogen dimethyl hydrazine in rats.[17,18] Nonprotruding carcinomas may be found throughout the colon, whereas protruding carcinomas are more prevalent in the distal portion of the colon.

The endoscopic morphology of superficial neoplastic lesions was described by Japanese endoscopists and was classified into various subtypes: category 0 refers to superficial invasion, whereas categories I to V correspond to advanced cancer with invasion deeper than the submucosa. The Paris classification[13,14] is similar to the Japanese classification, as illustrated in Table 1. Polypoid lesions may be pedunculated (0-Ip), sessile (0-Is), or with a mixed pattern (0-Isp). Nonpolypoid lesions are either slightly elevated, termed 0-IIa (elevation <2.5 mm above the level of the mucosa), completely flat (0-IIb), or slightly depressed (0-IIc). Completely flat and depressed lesions are rare in the colonic mucosa, whereas slightly elevated lesions are more prevalent. Excavated (0-III) superficial lesions are extremely rare in the colon. Slightly depressed (0-IIc) lesions are especially important to recognize, because they often harbor invasive cancer, despite their small diameter. The morphology of superficial neoplastic lesions is shown in the Image Atlas.

In the colon and the rectum, the distinction between polypoid and nonpolypoid lesions and the specific character of depressed lesions was extensively explored in Akita and in Yokohama by Kudo.[19-25] An accurate analysis is hampered by multiple factors that can be controlled if the endoscopist and the pathologist describe the gross morphology of endoscopic or surgically resected specimens in the same subtypes of the Paris classification.[13,14]

First, nonpolypoid lesions are less conspicuous than polypoid lesions, so they are often missed, especially by those endoscopists who are not trained in techniques used in the East. Recent series with high-definition video endoscopes may provide more reliable estimations. Second, nonpolypoid, slightly elevated (0-IIa) lesions are

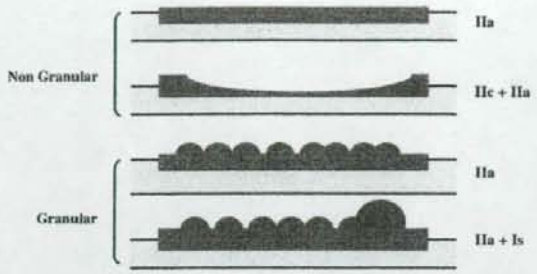

Figure 3. LST lesions. Models of granular and nongranular LST of neoplastic lesions, with the corresponding classification according to the categories of the Paris classification.

often misclassified as sessile (0-Is). For example, 1505 superficial neoplastic lesions found in the National Polyp Study[26] and previously classified as polypoid were reviewed in light of the new terminology. After revision, there were 802 polypoid pedunculated lesions, 229 polypoid sessile lesions, and 474 nonpolypoid lesions (31.4%) called flat. The proportion of severe neoplasia in this group is very low (1.3%), but no distinction was made among elevated, completely flat, or depressed subtypes. Third, all subtypes of nonpolypoid lesions are often called "flat lesions," without distinguishing the important, but rare, depressed lesions, which frequently are invasive cancers. Fourth, nonpolypoid neoplastic lesions may show a mixed pattern of both a polypoid sessile and a nonpolypoid morphology in distinct sectors. Laterally spreading type (LST) lesions, which were described by Kudo[24] in relation to their transversal mode of growth, should be further distinguished based on their granular or nongranular, homogenous or nonhomogenous appearance. Their relationship to the categories of the Paris classification is often a source of confusion. Some LST lesions can be classified as nonpolypoid, in the subtypes 0-IIa or 0-IIa + IIc. Other LST lesions associate with a polypoid (0-Is) or a nonpolypoid pattern. Some nongranular subtypes of LST are called pseudodepressed, to underline the distinction from simple depressed 0-IIc lesions (Fig. 3, Table 2).

TABLE 2. Subtypes of LST lesions: morphologic classification of LST lesions and their correspondence in the Paris-Japanese classification*

Subtypes of LST	Classification in type 0
LST granular	
Homogenous type	0-IIa
Nodular mixed type	0-IIa, 0-Is + IIa, 0-IIa +Is
LST nongranular	
Elevated type	0-IIa
Pseudodepressed type	0-IIa + IIc, 0-IIc + IIa

*The term "laterally spreading type (LST)" refers to the lateral growth of lesions at least 10 mm in diameter; this is in opposition to traditional polypoid (upward growth) or flat and depressed lesions (downward growth).

HISTOLOGIC CLASSIFICATION OF ADENOMAS AND CARCINOMAS

Adenoma

An adenoma is a premalignant lesion that shows intraepithelial neoplasia without invasion of the mucosal stroma and is always associated with cytologic neoplasia. The identification of an adenoma is based on 2 types of alterations: structural and cytologic. The structural or architectural features include simple-to-complex crowding of glands, lateral expansion, and irregularity. According to their architecture, adenomas are classified as tubular, tubulovillous, or villous types: at least 20% of the estimated volume of the lesion should be villous to classify an adenoma as tubulovillous and 80% villous to be defined as a villous adenoma; all other adenomas are classified as tubular. In the Vienna classification, an adenoma with marked structural alterations is classified as high-grade intraepithelial neoplasia (HGIN)[27,28] (Table 3). Cytologic features of cell atypia consist of 2 to 5 rows of palisading or enlarged nuclei, with a dispersed chromatin pattern and prominent nucleoli. High-grade cytologic abnormalities, with a loss of polarity, stratification, and atypical mitotic figures, usually coexist with architectural alterations and may be difficult to distinguish from intramucosal carcinoma.

The clinical relevance of the terminology "advanced adenoma," often used in endoscopic series, is linked to a significant risk of progression to cancer and demands a prompt treatment decision. Advanced adenomas are either large lesions, at least 10 mm in diameter (endoscopic criteria), or adenomas, with a villous architecture, or HGIN (histologic criteria).

Adenocarcinoma

An intramucosal adenocarcinoma is characterized by the invasion of neoplastic cells in the stroma of the tunica (lamina) propria. Extension to the submucosa across the muscularis mucosae characterizes submucosal adenocarcinoma. The term "early" colorectal cancer includes both intramucosal and submucosal adenocarcinomas. Extension beyond the submucosa defines "advanced" cancer. If a carcinoma is contained completely within the mucosa, the risk of lymph-node and vascular invasion is nil; as a rule, endoscopic resection is a legitimate treatment for those lesions. If there is submucosal invasion, then extension to endothelium-lined vascular spaces is regarded as a significant risk for lymph-node invasion or distant metastases. Risk increases in proportion to the depth and width of invasion in the submucosa. When invasion is slight, endoscopic treatment may be legitimate; when invasion is extensive, surgery is required. The boundary between endoscopic or

TABLE 3. Histopathologic classification of superficial neoplastic lesions of the colorectal mucosa

Pragmatic classification*		Correspondence to Vienna classification	Clinical relevance
Normal mucosa or inflammation hyperplasia (metaplasia)	No neoplasia	Negative for neoplasia	Endoscopic treatment
		Indefinite for neoplasia	
Low-grade neoplasia	Noninvasive (low-grade and high-grade adenoma)	Noninvasive low-grade IEN	
		Noninvasive high-grade IEN	
		Indefinite for invasive	Endoscopic or surgical treatment
	Invasive† (low-grade carcinoma; no risk factors)	Mucosal carcinoma or submucosal carcinoma	Surgical treatment
High-grade neoplasia	Invasive (high-grade carcinoma with risk factors)	Mucosal carcinoma or submucosal carcinoma	

IEN, Intraepithelial neoplasia.

*This pragmatic classification applies to the adenoma-adenocarcinoma sequence and to neoplasia in serrated lesions. Risk factors for the progression of cancer include one of the following: vessel permeation, incomplete polypectomy and/or resection, poor differentiation, marked budding of tumor cells, or infiltration equal or deeper than the lower third of the submucosal layer. Risk factors are absent in low-grade invasive cancer and present in high-grade invasive cancer. Low-grade intramucosal neoplasia is treated with legitimacy by endoscopy. High-grade intramucosal neoplasia, identified on cytologic characters, may require a more radical treatment.

†(1) Invasive: in stroma of mucosa or submucosa; (2) intraepithelial neoplasia (IEN); (3) signet-ring-cell carcinoma is equivalent to high grade neoplasia.

surgical treatment can be estimated before treatment, but confirmation of its legitimacy is retrospective when the pathologist examines the complete operative specimen.

Pathologists have proposed various methods of estimation of the degree of invasion in the submucosa in superficial cancer. Pedunculated lesions were graded by Haggitt et al,[29] and sessile lesions were graded by Kudo[21] and Kudo et al[22] and Kikuchi et al[30]; the latter system can also be adapted for nonpolypoid lesions. For example, the risk of lymph-node metastases is 2%, 8%, and 23% for Kikuchi levels sm1, sm2, and sm3 (the upper, middle, and lower level of the submucosa), respectively. The ability to estimate the depth of submucosal invasion in resected nonpolypoid lesions has become more precise with the development of cap mucosectomy and submucosal dissection.

For most endoscopic resection specimens, dividing the submucosa into 3 parts is not applicable, because the limit of the muscularis is not included. A precise assessment of the depth of invasion requires a micrometric measurement from the lower part of the muscularis mucosae to the limit of invasion. This method has been adopted in Japan, where 1000 μ is the lower limit for which adequate endoscopic treatment can be assumed. In daily practice, the pathologist can estimate the depth of invasion in the submucosa as sm1 if less than half of the segment of submucosa is included within the specimen; as sm2, if the invasion is beyond this limit; and as sm3, if the cancer is positive at the cut margin. One can also estimate invasion in depth in 3 levels (sm1, sm2, sm3) and in transversal extension just below the muscularis mucosae in 3 levels (sm1a, sm1b, sm1c). This double measurement is adopted in the analysis of the neoplastic lesions that are resected at the Yokohama endoscopy unit in Japan. A slight invasion of the submucosa corresponds to sm1a or sm1b. An extensive invasion corresponds to transverse extension sm1c or to levels sm2 and sm3 in depth.

Flat adenocarcinoma and de novo cancer

For more than 2 decades, Japanese endoscopists have been giving special attention to nonpolypoid flat or depressed adenomas[31,32] and to flat minute adenocarcinomas[33-35] similar to minute gastric cancers.[36] Particular attention was given by Kudo et al[19-21] and Kudo and Muto[25] to the specific differences between flat and depressed lesions in the colorectal mucosa. A cancer is called de novo when it is assumed to develop without an adenomatous precursor.[37] In spite of being small, and even inconspicuous, such lesions are evolutive and often should be treated by surgery.

The quest for adenomatous remnants in colorectal cancer

Various studies, based on analysis of operative specimens, suggest that a substantial proportion of colorectal adenocarcinomas develop de novo[38-48]: the figures range from 20% to 90%, averaging around 40%. In Japan, the proportion of adenoma remnants was analyzed in relation to morphology. In specimens of early cancer, Shimoda et al[37] showed that the polypoid morphology was frequent (82%) and included adenomatous remnants in 91% of cases (133 of 146); nonpolypoid morphology was less frequent and never included adenoma remnants (0 of 32). The average diameter of nonpolypoid early cancer was smaller, and invasion in the submucosa was more frequent. In contrast,

TABLE 4. Grade of superficial colorectal cancer in Japan*

	Carcinoma with low or high malignancy	
	Low grade	**High grade**
Cytologic parameters		
Cellular atypia	Low proportion	High proportion
K67 labeling cells	Low index	High index
Depth of invasion		
Intramucosal	Most cases	Few cases
Submucosal	Few cases	Most cases
Morphology		
Polypoid	Most cases	Few cases
Depressed	Few cases	Most cases

*Well-differentiated intramucosal or submucosal cancer is classified on cytologic criteria as low-grade or high-grade malignancy. The majority of submucosal cancer is "high grade." The majority (80%-85%) of intramucosal cancer is "low grade." Low-grade intramucosal cancer is also called high-grade adenoma. The term "cancer" is maintained for high-grade intramucosal neoplasia and for submucosal lesions.

the same investigators showed a high (78.2%) proportion of nonpolypoid cancer in 853 operative specimens of advanced cancer, and they estimated that around 80% of colorectal cancers arise as de novo. Kuramoto and Oohara,[43] in 1995, observed the absence of adenoma remnants in 89.7% of flat early cancers (87 of 97) and in only 16.6% of polypoid early cancers (23 of 138). Submucosal invasion occurred in 53.6% of flat early cancers and in 13.8% of polypoid early cancers. Kaneko et al[47] analyzed the morphology of 107 specimens and confirmed that tumors with a nonpolypoid morphology were smaller (33 vs 55 mm in diameter), with a higher proportion of vascular invasion (95% vs 74%). In Europe, Eide[44] found adenoma remnants in 53% of polypoid cancers and in only 12% of nonpolypoid cancers. Bedenne et al[38] estimated that 40% of cancer arose de novo from the analysis of 1630 operative specimens; adenoma remnants were present in 25.8% of protruding tumors and in only 0.5% of ulceroinfiltrative tumors (0.5%). George et al[45] estimated the proportion of de novo cancers at 48% from an analysis of 186 advanced cancers; adenoma remnants were found in 52% of polypoid and in only 2% of nonpolypoid cancers.

Other histopathologic studies based on endoscopic features of the flat, de novo, early colorectal cancers led to a similar conclusions. Goto[46] classified 83 cases of early cancers in 2 types: polypoid (84% of cases) and flat, de novo cancers, without adenoma remnants (22.9% of cases). Kuramoto and Oohara[42] analyzed the morphology of 37 flat early cancers and found frequent invasion in the submucosa, in spite of the small size of the lesions.

Legitimacy of the terminology de novo cancer

In the colorectal mucosa, a de novo cancer is assumed to develop without an adenomatous precursor.[37] This assumption relies primarily on the absence of adenomatous tissue in small and flat malignant lesions, but, it is also possible that malignant transformation has obliterated any remnant of a flat or depressed small adenoma. The hypothesis of the direct malignant growth is supported by the very low occurrence of adenoma remnants in flat early cancer and by the shift in the proportions of the polypoid and nonpolypoid morphology in early versus advanced cancers.

Regardless, a de novo cancer is characterized by a nonpolypoid growth pattern, a smaller size, and a more frequent invasion into the submucosa.[40] Flat adenocarcinomas are characterized by specific molecular events that begin in their early stage. The de novo colorectal cancers represent a small fraction of early cancers but will account for a higher proportion of advanced cancers, with most estimates being in the range of 40%. By using a cohort of patients distributed in 3 groups, that is, negative colonoscopy, polyps, and cancer, Chen et al[39] estimated the dwelling time to cancer in the classical adenoma-carcinoma sequence and in the de novo sequence by a Markov analysis. Their analysis suggests that at least 30% of colorectal cancers arise from the de novo sequence.

Low-grade and high-grade adenocarcinoma

The distinction between low-grade and high-grade adenocarcinoma currently used in Japan applies only to well-differentiated tumors, and the grade is established on cytologic rather than on structural criteria (Table 4), as shown by Ajioka et al[33] and Maeo et al.[48] Low-grade and well-differentiated adenocarcinomas show hyperchromatic and elongated nuclei, in basal arrangement, limited to two thirds of the epithelium and are less evolutive and less invasive than high-grade tumors. High-grade and well-differentiated adenocarcinomas show an increased crowding of round, large, and irregular nuclei, migrating up to the apical pole of epithelial cells and an increased mitotic index, and tend to be more invasive, with possible lymph-node invasion, even when intramucosal. With immunochemistry, high-grade tumors show a high index of Ki-67–labeled cells or, alternatively, an increased expression of proliferating cell nuclear antigen,[48] a diffuse expression of beta-catenin, an adhesion protein that binds cadherin, and a higher expression of dysadherin, a cell-membrane glycoprotein. A positive immune-labeling of CD-10 may indicate a higher risk for liver metastasis.[49]

Immunostaining with dysadherin and beta-catenin was explored by Shimoda (unpublished data, 2008) at the National Cancer Center, Tokyo, in 128 superficial neoplastic colorectal lesions (adenoma or carcinoma), classified into the high-grade or low-grade types. Dysadherin expression was lower in adenoma (32%) than in cancer, in which the rates were 58% and 83% for low-grade and

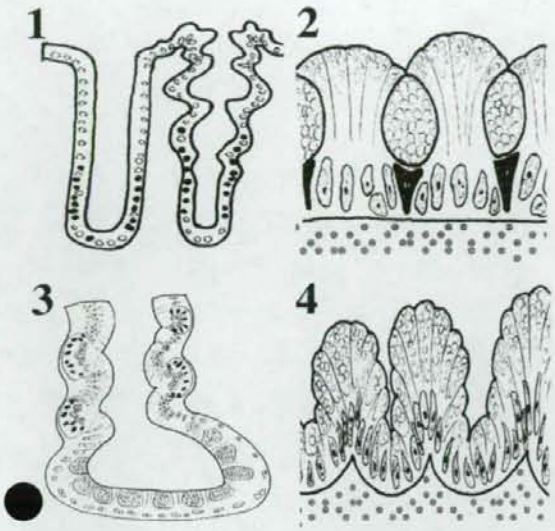

Figure 4. Representation of serrated lesions: (1) HP lesion (notched crypt lumen, cell multiplication, and growth in the "bottom-up" direction), (2) another HP lesion (goblet-rich type with normal cell nuclei), (3) Sessile serrated lesion (a crypt with a notched lumen, discontinuous proliferation zones, horizontal spread of basal crypt with mature goblet cells), often called a sessile serrated adenoma, and (4) Another sessile serrated lesion: increased mucus, elongated nuclei (by J. R. Jass).

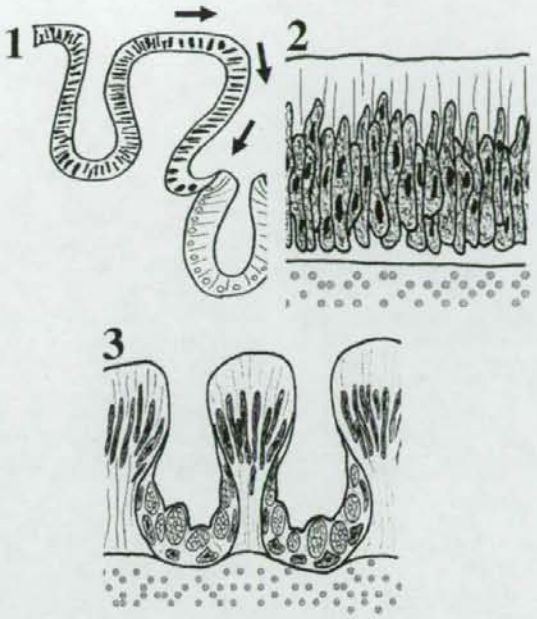

Figure 5. Representation of serrated and adenomatous lesions: (1) adenoma (cell multiplication and growth in the direction of lateral and top-down growth [arrows]), (2) traditional adenoma (elongated and packed nuclei with cellular atypia), and (3) TSA (elongated nuclei, cellular atypia, vertical direction of basal crypts with intraepithelial microacinar insets) (by J. R. Jass).

high-grade intramucosal cancer, respectively, and were 50% and 74% for submucosal cancer, respectively. In addition, the diffuse expression of beta-catenin was absent in adenomas and was frequent in cancer, in which the proportions were 27% and 72% for low-grade and high-grade intramucosal cancer, respectively, and 50% and 79% for low-grade and high-grade submucosal cancer, respectively. The majority of intramucosal cancers are "low grade," whereas most submucosal cancers are "high grade." The distinction between low-grade and high-grade differentiated adenocarcinoma is relevant to the legitimacy of a local excision. Low-grade intramucosal or submucosal cancer is safely treated by endoscopic resection. High-grade cancer (even intramucosal) deserves special management, and surgery may offer a legitimate alternative to endoscopic treatment.

Vienna classification

Some discrepancies between Western and Eastern pathologists deserve emphasis: (1) low-grade or high-grade structural alterations of the epithelium, without invasion of the stroma, have been called dysplasia; the tendency is now to substitute this term with that of "noninvasive intraepithelial neoplasia"; (2) The World Health Organization definition of colonic adenocarcinoma (in contrast to the Japanese experience) requires a confirmation of invasion into the submucosa; intramucosal carcinoma is then classified as HGIN and will not be included in cancer registries. The Vienna classification, and its revised edition,[27,28] achieves a relative consensus between Western and Eastern experts and classifies the severity of epithelial alterations in the mucosa, as well as the extension to the submucosa, as shown in Table 3: (1) negative for neoplasia, (2) intramucosal neoplasia with noninvasive low-grade intraepithelial neoplasia and HGIN and with invasive HGIN, and (3) submucosal adenocarcinoma.

The pragmatic classification adopted in this article is relevant to the treatment decision planned (no intervention, or endoscopic or surgical resection) and includes 2 modifications of the Vienna classification: (1) the categories "indefinite" for noninvasive or invasive neoplasia were withdrawn and (2) the distinction between low-grade or high-grade carcinoma was included. In this situation, low-grade intramucosal neoplasia includes noninvasive (low grade and high grade) intraepithelial neoplasia and low-grade carcinoma. High-grade intramucosal neoplasia corresponds to a high-grade intramucosal carcinoma.

HISTOLOGIC CLASSIFICATION OF SERRATED LESIONS

The term "serrated" refers to the histologic appearance of a variety of polyps, the edge of which has a wavy or

TABLE 5. Classification of serrated colorectal lesions*

Serrated lesions: upper crypts (serration), basal crypts (normal proliferation), small basal nuclei	Microvesicular type; predominance of microvesicular cells	Nonneoplastic†
	Goblet-cell–rich type; predominance of goblet cells	
	Mucin-poor type; reduction in mucin in cells	
Serrated lesions: upper crypts (serration), basal crypts (abnormal proliferation), increased mucus	Sessile serrated lesion (often called adenoma); basal crypts; horizontal growth; architectural distortion; elongated nuclei; more mucus; atypia (structural, not cytologic)	
	TSA; basal crypts; vertical growth; neoplasia (structural and cytologic)	Neoplastic
Mixed polyp: mixed parts of HP lesion, classical adenoma	HP and classical adenoma	
	HP and serrated adenoma	

*The term serrated refers to the notched irregular diameter of the crypt lumen. These lesions are nonneoplastic (HP lesions) or neoplastic (serrated adenomas) or a composite with juxtaposition of HP and adenomatous sectors. Sessile serrated lesions are not classified as neoplastic, because there is no cellular atypia in the serrated zone with abnormal architecture.
†Nonneoplastic lesions can theoretically harbor foci of neoplasia; they are considered as neoplasia developed on a nonneoplastic lesion or they belong to the group of mixed polyps.

serrated contour. The specific architectural feature deserving the term "serrated" is the irregular and enlarged upper part of the crypts, which are notched like a saw with teeth pointing toward the center of the lumen; the serration index describes the severity of the architectural defect. There is some confusion in the classification of serrated lesions as neoplastic or nonneoplastic, based on whether there is a normal or abnormal proliferation within the crypts. So-called HP polyps have a normal proliferative compartment and very rarely progress to neoplasia. In contrast, traditional serrated adenomas (TSAs) are neoplastic. Sessile serrated lesions appear to be a precursor to cancer with MIS, when they show abnormal proliferation within the crypts. Serrated lesions display a morphology that is similar to that of neoplasia arising from the adenoma-adenocarcinoma sequence[50-74]; however, the surface pattern explored with magnification shows specific characters with enlarged and stellar crypt openings. There is some confusion in their morphologic classification (Figs. 4 and 5, Table 5) as polypoid or nonpolypoid. The terminology HP polyp, which suggests polypoid morphology, is legitimate for unequivocally protruding lesions, which belong to categories 0-Ip or 0-Isp. However, most of the frequently small and < 10-mm HP lesions are nonpolypoid and should be classified in the category 0-IIa. Large, sessile serrated lesions located in the right side of the colon adopt a transverse mode of growth, which results in mixed polypoid and nonpolypoid patterns: 0-IIa + IIc or 0-Is + IIa or 0-IIa + IIc, which are often misclassified as LST lesions.

HP polyps

HP polyps are metaplastic, not neoplastic, lesions. They are composed of elongated crypts, with a serrated architecture in the upper half of the crypts, that results in irregular dilatation of the notched lumen.[50,52,54] There is some regular cell proliferation in the basal, nonserrated part of the crypts. Nuclei are small, regular, and basally orientated; there is no stratification in the upper half of the crypts, and both architectural and cytologic features of neoplasia are absent. Three distinct types of cytoplasmic differentiation were described in HP lesions: (1) a microvesicular type, (2) a goblet-cell–rich type, and (3) a mucin-poor type. Practically, it might be very difficult to distinguish these subtypes. The microvesicular type HP lesion may be the precursor of the sessile serrated lesion, whereas the goblet-cell–rich type HP lesion may be the precursor of the TSA. The morphology of HP lesions was described in Japan in a large series (n = 3060), in which the majority of lesions were small and located in the distal portion of the colon.[48] As a rule, the risk of progression to neoplasia is negligible for most small lesions located in the distal portion of the colon and rectum, and they may be left without treatment. However, HP lesions larger than 10 mm and those located in the proximal portion of the colon should be resected.

With HP polyposis, the larger and sessile lesions show a high serration index with laterally branching crypts and abnormal cell maturation (mitoses, nuclear changes). In this condition, more than 30 small, or more than 5 large lesions, larger than 1 cm are present in the colon. The large or giant lesions have a sessile morphology and are located in the proximal portion of the colon. HP polyposis is associated with an increased risk of colorectal cancer, evaluated in a series at 54%.[56] Patients with HP polyposis are at high risk for colorectal cancer developed in the proximal portion of the colon.

TSAs

TSAs show neoplastic crypts with a serrated architecture.[57-70] They differ from HP lesions by the complex serrated architecture of the basal part of the crypts, with

TABLE 6. Categories of the pit pattern at the surface of the colonic mucosa*

Histology	Pit pattern†		Treatment selection
Nonneoplastic	Normal mucosa (normal round crypts, regular)	I	No treatment
	HP lesion (enlarged stellar crypts, regular)	II	
Neoplastic, adenomatous	Neoplastic lesion (elongated, sinuous crests)	IIIL	Endoscopic resection
	Neoplastic lesion (narrowed round pits, irregular)	IIIS	
	Neoplastic lesion (branched or gyrus-like crests)	IV	
Neoplastic, cancer	Malignant lesion (irregular surface)‡	VI	Endoscopic resection
	Malignant lesion (amorphous surface)‡	VN	Surgery

*Exploration conducted in magnification with chromoscopy or NBI.
†The 7 categories observed are classified in reference to prediction of histology and treatment decision.
‡Pit pattern V is divided in 2 categories: VI with an irregular surface and VN, or nonstructural, with an amorphous surface.

ngated nuclei and some stratification in 2 to 3 rows. A BRAF mutation is present in 75% of serrated adenomas.[69] These lesions should be treated in the same way as nonserrated adenomas.

Sessile serrated lesions

Sessile serrated lesions, often called SSAs, differ from traditional adenomas by their flat morphology.[71-73] There is a double ambiguity in their classification under this name. These lesions show no adenomatous changes and should be called "sessile serrated lesions." The term sessile is also confusing, because these lesions often show a nonpolypoid, slightly elevated (0-IIa) morphology rather than a sessile polypoid (0-Is) one.

The frequency of sessile serrated lesions is estimated at about 2% of all colon polyps. However, in a recent study of patients undergoing colonoscopy,[72] the prevalence of sessile serrated lesions was higher (9%). These lesions are associated with the following characteristics: proximal location, female sex, and multiplicity. Architectural features of sessile serrated lesions include the following: (1) an increased serration index in the basal half of crypts, which are dilated, with crypt branching with horizontal growth, and form T-shaped and L-shaped glands just above the muscularis mucosae, (2) an asymmetrical expansion of the proliferation zone into the middle third of crypts, (3) an epithelium-to-stroma ratio often above 50%, (4) an abundant mucus production, with pools of mucin in the lumen of the crypts and on the surface of the mucosa, (5) the presence of slightly enlarged vesicular nuclei with nucleoli. The structural abnormalities that show a complex architecture are compatible with neoplasia, but the cytologic criteria of neoplasia are missing.

The distinction between sessile serrated lesions and serrated adenomas, therefore, mainly depends on cytologic criteria; in addition, Torlakovic et al[73] proposed another difference: the eosinophilic cytoplasm of sessile serrated lesions. Although most sessile serrated lesions will never progress to neoplasia, some, particularly the large sessile serrated lesions in the proximal portion of the colon, progress rapidly to carcinoma[72]; as a rule, those located in the proximal portion of the colon should be resected.

Mixed polyps

Mixed polyps contain distinct sectors that show the architecture of an HP lesion and/or that of a neoplastic serrated lesion.[74] The following mixed patterns have been acknowledged: HP and sessile serrated lesions, HP and TSA, TSA and classical adenoma, sessile serrated lesion and classical adenoma, and TSA and sessile serrated lesion. Mixed polyps should be treated in the same way as TSAs and nonserrated neoplastic lesions.

CLASSIFICATION OF THE SURFACE PATTERN OF NONPOLYPOID LESIONS ON MAGNIFYING ENDOSCOPY

Magnification of the endoscopic image at a power ×80 or more combines optical and electronic technologies and displays the microarchitecture (pits and crests) of the mucosa, which allows classification with clinical relevance for the "pit pattern." Magnification can be coupled with image processing. In the narrow-band imaging (NBI) technique (Olympus Medical Systems Corp, Tokyo, Japan), a special set of filters is interposed on the optical path, and the incident photons are emitted in 2 narrow bands of wavelengths (blue and red). The selective reflection of the NBI light by the superficial layers of the mucosa improves the definition of the surface, and the vessels are highly contrasted in dark brown. Analysis of the disorganized "vascular pattern" in the neoplastic mucosa is now a major application of the NBI technique.

TABLE 7. Categories of the pit pattern of superficial neoplastic lesions: exploration conducted in magnification with chromoscopy or NBI

	Total no. lesions	Pit pattern*				
		IIIL	IIIs	IV	Vi‡	VN‡
Polypoid (0-Ip, Ips, Is)	14,084 (61.1%)	10,208	17	3236	511	112
Nonpolypoid (not depressed, 0-IIa, IIb)	8405 (36.4%)	7453	78	551	245	78
Nonpolypoid (depressed, 0-IIc)†	559 (2.4%)	70	257	1	53	178
Total	23,048	17,731	352	3788	809	368

*Categories of pit patterns in relation to the morphology of 23,048 lesions in the series at the Akita and Yokohama Northern Hospitals during the period April 1985 through July 2007.
†Lesions with a depressed pattern account for 2.4% of all superficial neoplastic lesions (n = 23,048) and for 31.9% of pit pattern types IIIs + Vi + VN.
‡Pit pattern V is divided in 2 categories: Vi, with an irregular surface, and VN, or nonstructural, with an amorphous surface.

TABLE 8. Categories of the vascular pattern at the surface of the colonic mucosa: exploration conducted in magnification with NBI

Histology	Vascular pattern*		Selection of treatment
Nonneoplastic	Normal	Well-delineated capillaries surrounding pits opening	No treatment
	Faint	Poor visibility of capillaries around enlarged pits	No treatment
Neoplastic (tubular, villous adenoma)	Network	Vessels organized in a large and regular mesh	Endoscopic resection
	Dense	Enlarged vessels of regular size at top of elongated epithelial crests	Endoscopic resection
Cancer	Irregular	Enlarged vessels of irregular diameter and diverging directions	Endoscopic resection
	Sparse	Poor distribution of irregular vessels with diverging directions	Surgery

*The 6 categories are classified in reference to prediction of histology and treatment decision.

Classification of the pit pattern

The pit pattern, ie, the microarchitecture of pits, epithelial crests, or ridges, at the surface of the normal or altered colonic mucosa is observed in magnifying endoscopy,[75-77] with the help of chromoscopy by using a 0.2% Indigo carmine solution or other dyes. Alternatively, the contrast of the surface is explored without chromoscopy when NBI is coupled with magnification. The progressive alterations of the pit pattern in neoplastic lesions have been confirmed by many investigators since the initial Kudo's classification of the abnormal patterns: (1) in the normal mucosa, the luminal opening of the crypts are round, regular, and narrow, (2) in the nonneoplastic HP lesions, the crypt lumen is large and stellar shaped, (3) in neoplastic lesions, epithelial crests and ridges substitute for this regular honeycomb distribution, and (4) carcinoma is suggested when the surface is irregular, without epithelial crests, or completely amorphous and nonstructural. A grading of the progression of neoplasia in relation to the pit pattern, classified in categories I to VN, has been proposed in Japan (Table 6), and compared with histology in a very large (>23,000) series of superficial neoplastic lesions of the colorectal mucosa (Table 7). The study confirms that depressed nonpolypoid lesions are more advanced than the other lesions, and the pit pattern type V occurs in 41% of them. The proportion of pit pattern V in nondepressed (nonpolypoid or polypoid) lesions is less than 5%. The clinical relevance of the pit pattern for the grading of neoplasia is still debated when 7 categories are used but is well accepted when a simpler classification in 3 categories is used: (1) nonneoplastic (I and II), (2) neoplastic low grade (III), or (3) neoplastic high grade (IV and V).

Classification of the vascular pattern

The vascular pattern at the surface of the digestive mucosa is observed in magnifying endoscopy and in transparency without chromoscopy; the contrast of the vessels is improved when NBI is coupled with magnification. There are still few descriptions of the vascular pattern in the colonic mucosa. For example, in the normal mucosa, well-delineated capillaries surround the opening of the crypts. The endoscopy unit of the Northern Yokohama Hospital analyzed the abnormal aspects according to the following criteria of the capillaries: degree of visibility, enlarged or