# Flat Early Cancers of the Large Intestine

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From January 1976 to December 1987, 37 early colorectal cancers of the flat type were treated. Thirty-four of them (91.9%) were not accompanied by adenoma, and were thought to have arisen *de novo*. There is indeed a *de novo* route of cancer development in the human large intestine, and cancers *de novo* merely show polypoid growth. Flat type cancers arising *de novo* tend to reach deeper layers at an earlier stage than polypoid-type carcinomas in adenoma. Of those with a diameter of less than 10 mm, only 40% stayed in the mucosa. Consequently, advanced cancers cannot be prevented by snare polypectomy alone. More attention should be directed to the discovery of small, flat, nonpolypoid cancers.
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I N RELATION to the histogenesis of colorectal cancer, polyp–cancer sequence[1] and adenoma–carcinoma sequence[2] have been emphasized for many years, and the majority of colorectal cancers have been considered to have evolved from adenomas. Accordingly, it has been the common belief that advanced cancers of the large intestine can be prevented mainly by endoscopic polypectomy.

Can advanced cancers really be prevented only by polypectomy? We have stated that *de novo* development of cancer, in addition to adenomatous development, is a major route, and that *de novo* cancers of the large intestine appear flat at the earliest stage.[3] This recognition and the frequent use of a colonoscope make it possible to detect early flat-type colorectal cancers. The clinicopathologic characteristics of flat early cancers are presented here.

## Materials and Methods

Thirty-two patients were collected from 489 new colorectal cancer patients (293 men and 196 women) without familial adenomatosis coli, who were treated by operation or endoscopical polypectomy at the Third Department of Surgery, University of Tokyo, from January 1, 1976 to December 31, 1987. They were selected on the basis of having one or more flat early cancers of the large intestine. Thirty-seven incidents of flat cancers, remaining pathologically in the mucosal and submucosal layers, were detected in 32 patients (Table 1). These 37 early flat-type cancers were clinicopathologically analyzed.

Flat lesions were composed of slightly elevated-type, flush-type, and depressed-type lesions. The height of these lesions did not exceed 50% of the longer diameter. In a few cases where the endoscopic image was different from the postoperative macroscopic figure, the endoscopic impression was given priority over the macroscopic picture for classification purposes, because the endoscopic image affected the treatment procedure more directly than the macroscopic figure. Early cancers showing peduncular or semipeduncular polypoid growth and flat adenoma were excluded from the inquiry. Three minute cancers, which were detected by step-sectioning study,[3] were also excluded.

The lesions, which were either resected operatively or by snare polypectomy, were fixed in 10% buffered formaldehyde, and longitudinally sectioned in 3-mm widths. All blocks were embedded in paraffin. Standard pathologic examination was carried out using hematoxylin and eosin stains.

## Results

### Clinical Data

There were a total of 17 men and 15 women. The average age was 64.0 ± 7.9 years, respectively (range, 46–78 years). One patient had five and another had two flat early cancers. The location and frequency of the cancers were as follows: the rectum (18), the sigmoid colon (ten), the transverse colon (five), the ascending colon (two), and the cecum (two).

In 23 cases, operations were carried out as the initial treatment procedure. Twelve of them involved minor surgery, that is, wedge resection and segmental resection, and 11 of them involved radical surgery in which bowel segments were resected at least 5 cm from the border on

TABLE 1.   Details of Flat-Type Early Cancers of the Colon and Rectum

| Patient | Age (yr) | Sex | Location | Size (Max in mm) | Depth of invasion | Diff | Ly | V | Remnant of adenoma |
|---|---|---|---|---|---|---|---|---|---|
| Elevated type without depression | | | | | | | | | |
| 1 | 59 | F | R | 30 | SM | Poor | − | + | − |
| 2 | 68 | F | R | 25 | SM | Mod | − | − | − |
| 3 | 53 | F | F | 25 | SM | Well | − | − | − |
| 4 | 62 | M | T | 25 | M | Well | − | − | − |
| 5 | 73 | M | R | 21 | M | Well | − | − | − |
| 6 | 62 | M | A | 16 | M | Well | − | − | − |
| 7 | 78 | M | S | 13 | M | Well | − | − | − |
| 8 | 64 | F | R | 12 | SM | Well | − | − | − |
| 9 | 54 | F | C | 10 | M | Well | − | − | − |
| 10 | 69 | M | S | 10 | M | Well | − | − | − |
| 11 | 78 | M | S | 10 | SM | Well | − | − | − |
| 12 | 67 | F | S | 8 | SM | Well | − | − | − |
| 13 | 72 | M | S | 7 | SM | Well | − | − | − |
| 14 | 60 | M | S | 7 | SM | Mod | − | − | − |
| 15 | 62 | F | S | 6 | M | Well | − | − | − |
| 16 | 65 | M | R | 6 | M | Well | − | − | − |
| Elevated type with depression (Type A) | | | | | | | | | |
| 17 | 60 | F | C | 30 | SM | Mod | + | − | + |
| 18 | 46 | F | R | 25 | M | Well | − | − | − |
| 19 | 78 | F | R | 18 | M | Well | − | − | − |
| 20 | 59 | F | S | 17 | SM | Well | − | − | − |
| 21 | 47 | M | S | 15 | SM | Well | − | − | − |
| 22 | 62 | M | T | 14 | M | Well | − | − | − |
| 23 | 72 | M | R | 12 | SM | Well | − | − | − |
| 24 | 72 | M | S | 10 | SM | Well | − | − | − |
| 25 | 70 | M | R | 8 | SM | Well | − | − | + |
| 26 | 49 | M | R | 8 | M | Well | − | − | + |
| 27 | 63 | M | T | 7 | SM | Well | − | − | − |
| Elevated type with depression (Type B) | | | | | | | | | |
| 28 | 62 | M | R | 33 | SM | Mod | − | + | − |
| 29 | 71 | M | R | 27 | SM | Mod | + | − | − |
| 30 | 67 | F | R | 24 | SM | Mod | + | − | − |
| 31 | 67 | M | R | 10 | SM | Mod | + | − | − |
| 32 | 69 | F | R | 10 | SM | Mod | − | − | − |
| Flush type | | | | | | | | | |
| 33 | 62 | M | T | 20 | M | Well | − | − | − |
| 34 | 60 | F | R | 4 | M | Well | − | − | − |
| Depressed type | | | | | | | | | |
| 35 | 66 | M | R | 45 | SM | Sig | + | − | − |
| 36 | 65 | F | A | 15 | SM | Mod | + | − | − |
| 37 | 62 | M | T | 12 | M | Well | − | − | − |

Diff: differentiation of carcinoma; Ly: invasion to the lymphatic vessels; V: venous invasion; R: rectum; S: sigmoid colon; T: transverse colon; A: ascending colon; C: cecum; SM: invasion to submucosal layer; M: mucosal cancer; well: well-differentiated adenocarcinoma; Mod: moderately differentiated adenocarcinoma; Poor: poorly differentiated adenocarcinoma; Sig: signet-ring cell carcinoma; Max: maximum.

either side of the lesion, including the attached mesentery and the distant lymph nodes. Snare polypectomy was carried out in five patients. Three patients who had initially undergone snare polypectomy (one) and wedge resection (two) later required radical surgery. Four lesions were resected in company with an advanced cancer.

There were 39 concomitant adenomatous polyps in 11 patients. Three of 39 adenomas had focal cancer (7.7%). One or more hyperplastic polyps and nodules were histologically proved in six patients.

## Histopathologic Findings

In 34 cases of all the flat early cancers (91.9%), no residual adenoma was found, and only three of them (8.1%) were accompanied by adenoma (carcinoma in adenoma). Most of the flat early cancers were considered to have arisen *de novo*.

Of the 37 cancers under analysis, 26 were well differentiated, nine were moderately differentiated, and two were poorly differentiated adenocarcinoma or signet-ring

Elevated type without depression
16 ( 8 )

Elevated type with depression
(Type A)        11 ( 7 )

Elevated type with depression
(Type B)        5 ( 5 )

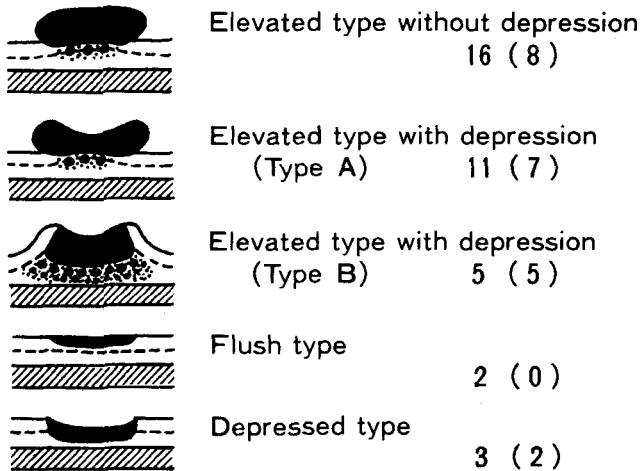Flush type
2 ( 0 )

Depressed type
3 ( 2 )

FIG. 1. Classification of flat-type early colorectal cancers. Numbers indicate the total number of lesions, and numbers in parenthesis show the number of lesions with submucosal invasion (----: muscularis mucosa; ■: carcinoma; ▨: proper muscle).

cell carcinoma. Adenocarcinoma was limited to the mucosa in 15 cases (40.5%), and submucosal invasion was found in 22 cases (59.5%). Among cancers with a longer diameter of less than 10 mm, 60% (nine of 15) had submucosal invasion. Lymphatic and venous invasion were observed in eight tumors. Lymph node involvement was found in only two case with signet-ring cell carcinoma and moderately differentiated adenocarcinoma, which had shown submucosal invasion. Of all the cases in which cancer was observed to have invaded the submucosa, the smallest lesion was 7 mm in longer diameter (Patients 13, 14, and 27). Even of the small, elevated-type cancers not exceeding 10 mm in maximum diameter, 50% of them had submucosal invasion.

## Classification of Flat Colorectal Cancers

Fiberscopic pictures of flat early cancers were classified into four types with two subtypes (Fig. 1), and further inquiry was made.

*Elevated type without depression:* Sixteen lesions were placed in this category (Figs. 2A and 2B). Cancerous glands were higher than the adjoining normal mucosa. The top of the tumors displayed no depression or ulceration. Fifty percent of them were cancers involving submucosal invasion, and the other 50% were cancers remaining within the mucosal layer.

*Elevated type with depression:* Two subtypes were grouped together in a single endoscopic category, termed elevated type with depression, and 16 cases fell into this category (Fig. 1). The first is a type in which carcinoma is present on the "shoulder" of the elevation (the outer slope of the elevated ridge), *i.e.,* Type A, and the second is a type in which carcinoma is absent at the "shoulder" of the elevation, *i.e.,* Type B. In seven of the 11 Type A cases there was evidence of submucosal invasion. Nevertheless, they consisted of well-differentiated, larger cancerous glands, and the extent of the submucosal invasion was smaller. They had no ulceration which was caused by slough of protruding portion of polyp (Figs. 3A and 3B).

All Type B cases were found in the rectum (five of five), and involved submucosal infiltration. The differentiation of the cancerous glands was moderate in all cases, and the glands were composed of smaller-sized cancer glands. The extent of the submucosal invasion with round cell infiltration was greater, and the glands on the outer slope of elevated ridge are noncancerous colonic mucosa (Figs. 4A and 4B). Type B was considered to be an aggressive
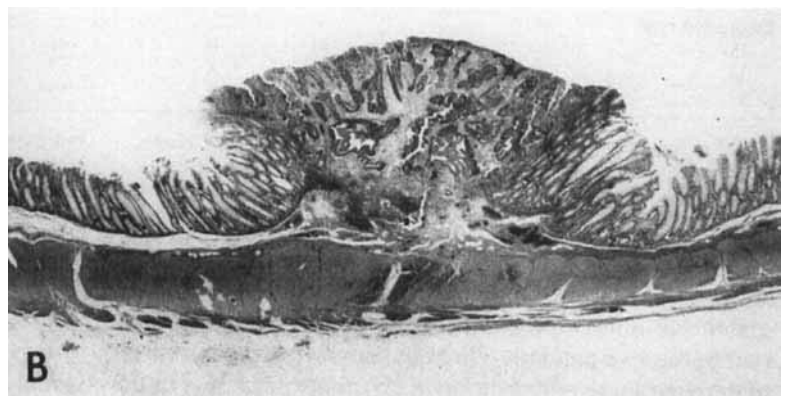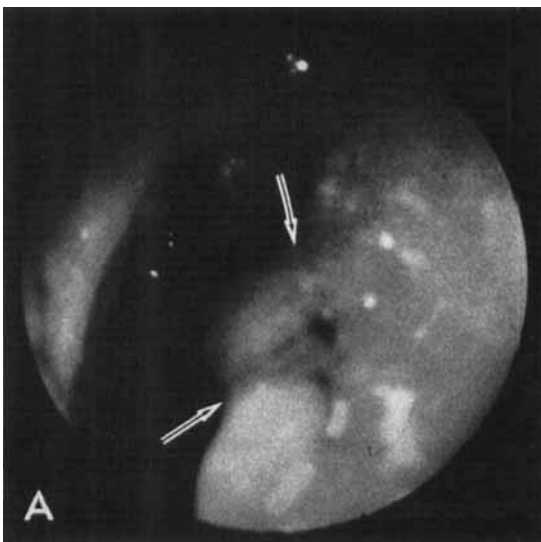
FIGS. 2A AND 2B. (A) Endoscopic image of elevated-type early cancer without depression at the sigmoid colon (arrows). Cancer is invading to a fold. (B) There was submucosal invasion although it was 7 mm in diameter (H & E, ×5).
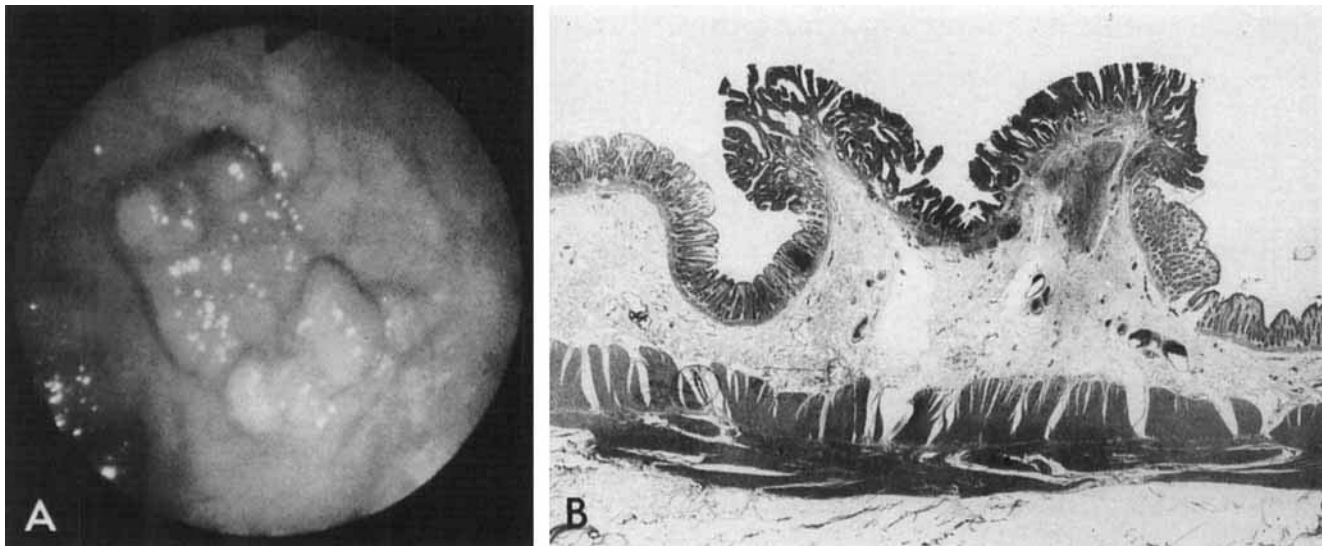
FIGS. 3A AND 3B. (A) Endoscopic figure of Type A in elevated-type early cancer with depression at the rectum. (B) There were cancer glands on the "shoulder" of the tumor (H & E, ×2.4).

form of invasion. Lymphatic or venous invasion was observed in four of the five cases.

Residues of preexisting adenoma (carcinoma in adenoma) were observed in only three cases of the elevated type with depression, Type A.

*Flush type:* Two lesions had no elevation nor depression and did not exhibit submucosal invasion.

*Depressed type:* Three lesions were further depressed than the surrounding mucosa. In two cases without lymph nodes metastasis, one was well-differentiated and the other

was moderately differentiated adenocarcinoma. The height of the cancer glands was lower than the adjoining colonic mucosa. The third was signet-ring cell carcinoma with submucosal invasion and lymph node metastasis (Fig. 5).

## Discussion

The frequent use of the colonoscope and the progressive reformation of the idea that cancer can arise *de novo* in the human large intestine enable us to find many early
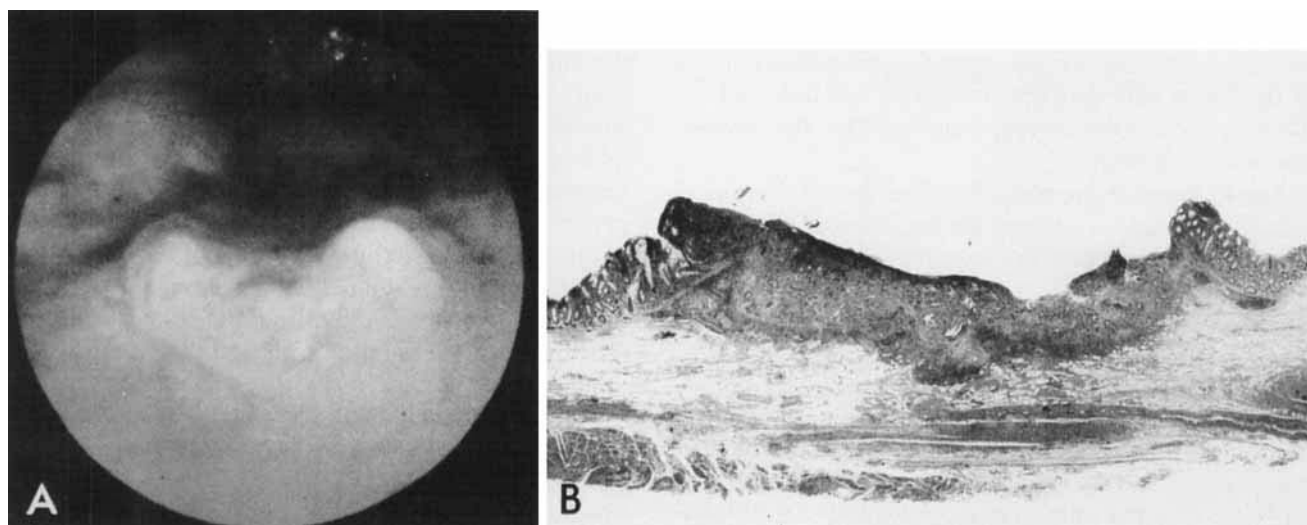


FIGS. 4A AND 4B. (A) Endoscopic feature of Type B in elevated-type early cancer with depression at the rectum. Normal colonic glands on the outer slope of the elevated ridge could be observed endoscopically. (B) Histologic examination showed massive submucosal invasion in Type B (H & E, ×3.2).
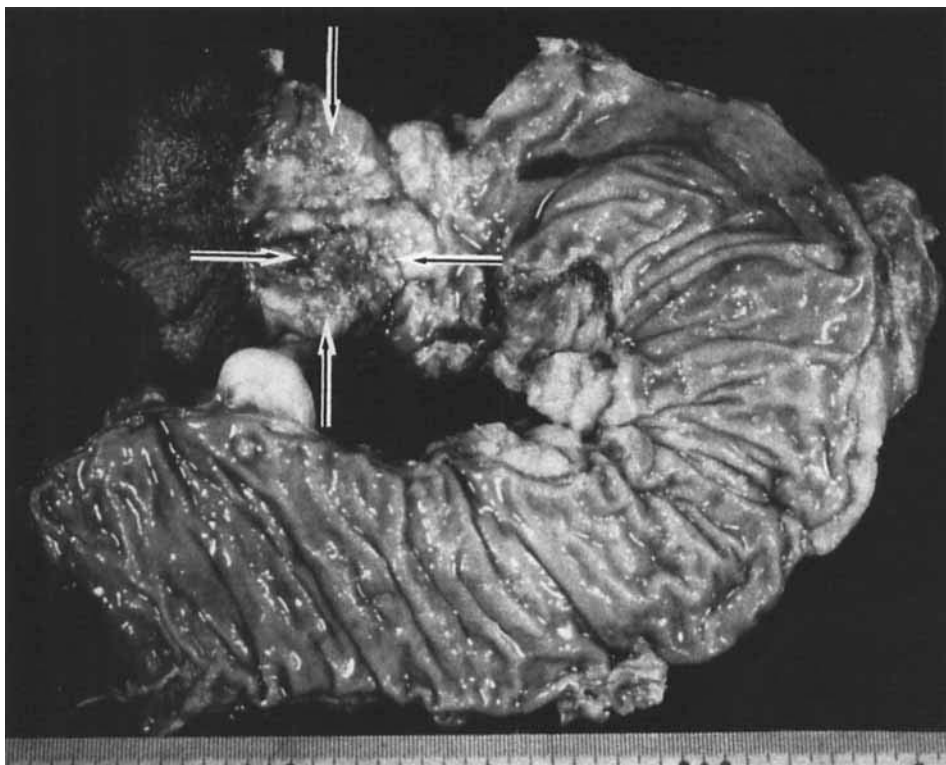
FIG. 5. Resected specimen of depressed-type early cancer. A depressed lesion (arrows), 35 × 23 mm, was seen at the lower rectum.

colorectal cancers of the flat type. Indeed, 29/37 of all flat early cancers and especially 13/15 of small flat cancers (less than 10 mm in diameter) were found after January 1984, when we found minute cancers *de novo* by step-sectioning study, and began to search for the small flat cancers clinically. Most of these flat early cancers (34/37) had no adenoma, and they were considered to be fully developed forms of minute cancers *de novo,* and to be transforming to advanced cancer. They could not be considered as polypoid cancers where the protruding portion of the polyp had sloughed away, because they had no ulceration with a few exception in Type B of the elevated type with depression.

The location of the early flat cancers and the differentiation of adenocarcinoma did not differ from those of the advanced cancers of the large intestine.

Flat cancers arising *de novo* had a tendency to infiltrate into the deeper layers at a smaller size. The submucosal invasion began at about 7 mm in diameter. There were 15 small cancers, and in 60% of them there was submucosal invasion. These submucosal invasions, differing from those of polypoid cancers, are extensive on the horizontal plane, and are vertically proximate to proper muscle. More care and caution must be exerted to treat these flat early cancers.

As a procedure for detecting small flat lesions, careful colonoscopy is preferable to barium enema, in conjunction with repeated inflation and deflation. Upon deflation,

flat early cancers tend to come within the field of vision, being unobscured by colonic folds. Even if the lesions which were resected accompanied with an advanced cancer were included, all lesions could have been diagnosed preoperative endoscopically, when they were not proximal to an obstructive advanced cancer.

The differential diagnosis of the flat early cancers is the adenoma of the flat type. To diagnose flat types of adenoma, biopsy can be conducted as a final resort. However, the softness of the intestinal wall and the flabbiness of the tumor are clues to diagnosing adenoma endoscopically. The endoscopic findings which suggest of cancer are solidity and stiffness of the tumor. Careful observation is necessary during repeated inflation and deflation. Palpation by biopsy forceps is also an useful method. Three findings, (1) absence of smoothness of the surrounding intestinal wall during inflation, deflation, and peristalsis, (2) large depressions, and (3) normal colonic mucosa at the "shoulder" of the tumor, suggest the submucosal invasion of carcinoma.

For the initial treatment, operative resection was carried out in nine lesions which were smaller than 15 mm in diameter. In 11 of them there was submucosal invasion. Preoperative diagnosis of the depth of invasion is possible and is important. Three elevated cancers, limited to the mucosa, were surgically resected, but they might be resected endoscopically. All colorectal cancers which were in the mucosal layer had no lymphtic or venous invasion.

When more accurate methods of diagnosis concerning the depths of tumors are developed, for example, endoscopic ultrasonography,[4] we will be able to resect cancers limited to the mucosa endoscopically with confidence.

We perform operations if there is evidence of submucosal invasion, and resort to polypectomy only when the tumor is under 10 mm across and is considered to remain within the mucosa. When snare polypectomy is decided upon for initial treatment, the tumors that underwent polypectomy must be retained and the cut end of the lesion must be marked in order to examine whether or not carcinoma is present at the cut end. We generally perform a subsequent operation if one or more of the following factors are present[5,6]: (1) massive tumor at or "near" the margin; (2) poorly differentiated adenocarcinoma; and (3) lymphatic or venous invasion.

Previous investigators definited that the height of flat-type lesions did not exceed 50% of the longer diameter.[7] In the current study, we collected specimens of flat lesions based on our own classification scheme and found that all specimens conformed to the above-mentioned rule. We are using the classification shown in Figure 1 in order to figure out treatment procedure. According to our experience, this classification has a very close relation with depth of carcinoma. Flat-type early cancers of the large intestine come in various forms, and classification of their macroscopic shapes is therefore open to discussion. When analyzing clinicopathologic characteristics, it is misleading to determine classification using histologic slides retrospectively. Histologic samples are usually cut longitudinally, and colorectal tumors are frequently present on the colonic fold, causing tumors to resemble a peduncular or semipeduncular polyp.

It is characteristic of flat early cancers that the elevation is conspicious during endoscopic observation, and becomes unobtrusive once the lesion has been resected. This difference is especially noticeable in Type B of the elevated type with depression. Type B is composed of the relatively poorly differentiated adenocarcinoma, and involves massive submucosal invasion. Viewed endoscopically, the elevation is striking, but nevertheless, the lesion must be treated as an ulcerated one. The biopsy from the "shoulder" of the elevation is important. If there is normal mucosa on the outer slope of the elevated ridge, the tumor should be resected operatively with the mesentery. Two Type B cancers were resected initially by wedge resection, but a subsequent radical operation was necessary because of vessel invasion or massive submucosal invasion. Segmental excision[8] (piecemeal polypectomy) is contraindicated, although the elevation is striking.

The depressed-type early cancers have been considered to be extremely rare in the human large intestine. Nevertheless, these lesions have begun to be found,[9] and small *de novo* adenocarcinoma has been reported.[10] As a result of widespread use and development of the colonoscope, early colonic cancers of the depressed-type will be detected more frequently.

Almost all flat-type cancers are considered to be the intermediate stage between minute cancers arising *de novo* and advanced colorectal cancers. Jass[11] has suggested that cancers arising within small flat foci of dysplasia are likely to be the exception rather than the rule, and that colonoscopic screening would make it clear. In contrast to this opinion, careful endoscopic observation has shown that many flat-type early cancers arise *de novo* in the human large intestine. Endoscopic observation must be carried out, paying attention not only to large polyps and advanced cancers but also to flat-type small lesions. Advanced colorectal cancers cannot be prevented only by polypectomy of adenomatous polyps and peduncular or semipeduncular cancer in adenoma, according to the adenoma–carcinoma sequence.

## Conclusion

In the human large intestine, there are many cancers which arise *de novo*, and most of them develop showing the flat shape. The progressive development of the idea of *de novo* genesis enables one to detect early flat colorectal cancers earlier. Advanced cancers of the large intestine cannot be prevented by polypectomy alone. Flat early cancers which invade the submucosal layers at a smaller size must be dealt with carefully. The elevated type with depression which has normal mucosa on the outer slope of the elevated ridge has a particularily invasive tendency. Piecemeal polypectomy is contraindicated even if it appears elevated endoscopically.

## REFERENCES

1. Morson BC. The polyp cancer sequence in the large bowel. *Proc R Soc Med* 1974; 67:451–457.
2. Muto T, Bussey HJR, Morson BC. The evolution of cancer of the colon and rectum. *Cancer* 1975; 36:2251–2270.
3. Kuramoto S, Oohara T. Minute cancers arising *de novo* in the human large intestine. *Cancer* 1988; 61:829–834.
4. Yasuda H, Johjima Y, Kaminishi M, Oohara T. Point of diagnosis on gastrointestinal lesions. *Rinsho Seijinnbyo* 1987; 17:634–644 (in Japanese).
5. Forde KA. The "malignant colonic polyp": A critique and opinion. *Surg Endosc* 1987; 1:55–57.
6. Japanese Research Society for Cancer of Colon and Rectum. General Rules for Clinical and Pathological Studies on Cancer of Colon, Rectum and Anus, ed. 3. Tokyo: Kanehara, 1983:14–15 (in Japanese).
7. Hasegawa K, Mikami T, Noguchi T et al. Colonoscopic diagnosis of flat tumors. *Gastroenterol Endosc* 1984; 26:1692–1699 (in Japanese with English Abstr).
8. Shinya H. Colonoscopy. New York: Igaku-Shoin, 1982; 184–190.
9. Kudo S, Takano Y, Tominaga T et al. IIc (depressed) type early carcinoma of the descending colon: Report of a case. *I Cho (Stomach Intestine)* 1987; 22:883–887 (in Japanese with English Abstr).
10. Jelinek GP, Nava HR, Nime F. Small primary *de novo* adenocarcinoma of the colon with mesenteric lymphatic metastasis. *J Surg Oncol* 1983; 23:185–188.
11. Jass JR. Commentary. *Colon Rec Surg Outlook* 1988; 1:3.