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# Histoclinical Analysis of Early Colorectal Cancer

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Abstract. To evaluate the clinicopathologic characteristics of early colorectal cancer (ECC), histopathologic and clinical features of 90 ECC patients who underwent surgical resection (not including the endoscopic polypectomized cases) and 1704 patients with advanced colorectal cancer were analyzed. Smaller size, better histologic differentiation, less lymph node (LN) metastasis, and better clinical outcome were observed in those with ECC than in patients with more advanced lesions. LN metastasis was found in 5 patients with ECC among the 56 patients who underwent bowel resection (8.9%). Tumors with LN metastasis were more frequently associated with deep submucosal invasion, absence of an adenomatous component within the tumor, sessile configuration, and lymphovascular invasion. Tumors showing deep submucosal layer invasion were associated with a more unfavorable histologic grade, lymphovascular invasion, LN metastasis, sessile morphology, and absence of an adenomatous component within the tumor. Recurrence was observed in two patients who underwent local excision for their submucosal cancer. One of the patients was salvaged after bowel resection, but one patient died of distant metastasis. From our data analysis and literature review, extensive submucosal invasion, lymphovascular invasion, sessile configuration, and tumors with no adenomatous component should be considered high risk factors for LN metastasis and recurrence after limited therapy.

Despite recent advances in the knowledge of tumor biology and treatment modalities, a remarkable improvement in the clinical outcomes of colorectal cancer patients has not yet been achieved. Currently, various clinical, biologic, and histologic variables are claimed to be related to the prognosis of colorectal cancer, but the pathologic stage of disease at the time of operation remains the most reliable indicator of clinical outcome. Thus the early detection of cancer is the most efficient way to improve the survival of patients with colorectal cancer. Early colorectal cancer (ECC), which is defined as cancer where the depth of invasion is limited to the mucosa or submucosa regardless of the presence or absence of lymph node (LN) metastasis [1], clearly exhibits better prognosis than advanced-stage cancer.

Many studies, mainly undertaken in Japan, show that an ECC rate as high as 20% of all colorectal cancer [2–4] is mainly due to the wider distribution of mass screening. It provides a successful model for mass screening for colorectal cancer. However, even in Japan, the detection rate of colorectal cancer at an early stage is

much lower than that for gastric cancer, indicating that more extensive efforts should be invested in detecting ECC to improve the prognosis.

Both ECC and advanced colorectal cancers exhibit many different features in the clinical spectrum and in treatment and prognosis. Complete cure is usually expected not only after bowel resection but also after much less invasive treatment, such as endoscopic polypectomy, local resection, and laparoscopic colectomy if the patients are selected under strict criteria [5–7]. There are some patients who show treatment failure during the follow-up, and the risk factors for recurrence are not yet clearly defined. Furthermore, the difficulty of detecting LN metastasis or deep invasion beyond the muscularis propria before the operation make surgeons hesitate when choosing the less invasive modality. The present study was undertaken in an attempt to delineate the unique features of ECC that are distinct from advanced cases and the clinicopathologic features of ECC that correlate with LN metastasis and a worse clinical outcome.

## **Materials and Methods**

The records of 1804 patients with colorectal cancer who underwent operations at the Seoul National University Hospital between 1988 and 1996 were retrospectively reviewed, and their detailed clinical and pathologic data were recorded. Among them, 90 patients (5.0%) were diagnosed as having ECC (tumor invasion limited to the mucosa or submucosa regardless of the status of LN metastasis) after pathologic examination of the postoperative surgical specimens. Patients who underwent endoscopic polypectomy only and those with inflammatory bowel disease or familial polyposis were not included in this study. In patients who underwent local resections (34 patients), the exact status of LN metastasis was not available and was excluded from the LN metastasis analysis.

Lesions were subclassified according to the level of bowel wall invasion as mucosal (m) and submucosal (sm) lesions. The submucosal lesions were further subdivided as follows: sm1, slight submucosal invasion from the muscularis mucosa; sm2, intermediate invasion; sm3, deep invasion near the inner surface of the muscularis propria. The lesions were divided into pedunculated,

intermediate, and sessile forms according to their gross morphology. They were also divided into polypoid growth (PG), which was accompanied by an adenomatous component, and nonpolypoid growth (NPG), which does not contain the adenomotous component within the tumor, based on their histologic findings as described by Shimoda et al. [4].

The statistical analyses were performed using the chi-square test. The statistical analyses associated with survival were performed using Kaplan-Meier methods.

#### Results

Clinicopathologic Findings in Regard to Advanced Colorectal Cancer

The macroscopic appearance of the ECCs most frequently revealed tumors with a pedunculated configuration. The tumor was smaller for ECCs than for advanced colorectal cancer; more than half of the ECCs were less than 2 cm in diameter; whereas most of the advanced colorectal cancers exceeded 2 cm in diameter. Most of the ECCs were located in the rectosigmoid area (Table 1). Histologic examination revealed more favorable histologic features in ECCs than advanced cases. Most tumors were well differentiated, and tumors with adverse histology were observed only in two mucinous-type tumors.

Of the 90 ECCs, 40 were confined to the mucosal layer, and 50 were submucosal cancers. Among the advanced colorectal cancers, only 18% of the lesions were confined to the muscularis propria; and most of the tumors invaded beyond the muscularis propria. LN metastasis and lymphatic or vascular invasion were much more prevalent in advanced colorectal cancer than in ECCs (p = 0.001). Of the 56 bowel-resected ECC cases, 19 of the lesions were mucosal and 32 were submucosal. LN metastasis was observed in five patients whose tumors invaded the submucosal layer. Thus LN metastasis was observed in 8.9% of all ECC cases and in 15.6% of these with submucosal cancers. Associated clinical symptoms of ECC, in order of decreasing frequency, included blood-tinged stool or hematochezia, changes in bowel habits (diarrhea, constipation, obstruction symptom), and altered feces (change in stool caliber, mucoid stool). There were no significant differences in the associated symptoms between ECC and advanced colorectal cancer patients, although bleeding and bowel habit changes were more frequent with the advanced cancers.

## Factors Associated with Depth of Invasion and LN Metastasis

The relations of various pathologic factors to the invasion level of ECC are shown in Table 2. Among the factors, a low degree of differentiation, the presence of lymphovascular invasion, the presence of LN metastasis, sessile tumor, and no association of an adenomatous component (NPG tumor) were significantly associated with a deeper level of invasion. Tumor size and location were not significant factors.

Among the 56 ECC patients who underwent bowel resection, five patients had LN metastases. All the patients with LN metastases had sm2 or sm3 lesions (Table 3). In addition to the level of submucosal invasion, the existence of lymphovascular invasion and the absence of an adenomatous component within tumor were more frequently associated with LN metastasis. Larger size,

Table 1. Clinicopathologic variables for early and advanced colorectal cancer.

|                                    | ECC                              | ACC              |         |
|------------------------------------|----------------------------------|------------------|---------|
| Variable                           | ECC (n = 90)                     | ACC  (n = 1,714) | p       |
| Gender (M/F)                       | 1:1                              | 1.4:1            |         |
| ECC `                              |                                  |                  |         |
| Pedunculated                       | 45 (50.0)                        |                  |         |
| Subpeduculated                     | 21 (23.3)                        |                  |         |
| Sessile                            | 24 (26.7)                        |                  |         |
| ACC                                | , ,                              |                  |         |
| Bormann I                          |                                  | 281 (16.4)       |         |
| Bormann II                         |                                  | 775 (45.2)       |         |
| Bormann III                        |                                  | 595 (34.7)       |         |
| Bormann IV                         |                                  | 6 (0.3)          |         |
| Others                             |                                  | 60 (3.4)         |         |
| Tumor size                         |                                  | ` /              |         |
| Mean $\pm$ SD (cm)                 | $2.3 \pm 1.5$                    | $5.1 \pm 2.7$    |         |
| <1 cm                              | 16 (17.8)                        | 15 (0.9)         | 0.001   |
| 1–2 cm                             | 38 (42.2)                        | 61 (3.6)         |         |
| 2–3 cm                             | 21 (23.3)                        | 206 (12.0)       |         |
| 3–4 cm                             | 9 (10.0)                         | 631 (36.8)       |         |
| >4 cm                              | 6 (6.7)                          | 801 (54.5)       |         |
| Location                           | • (•••)                          | (* 110)          |         |
| Nonrectosigmoid                    | 13 (14.5)                        | 455 (26.5)       | 0.004   |
| Rectosigmoid                       | 77 (85.5)                        | 1259 (73.5)      |         |
| Histology                          | ,, (00.0)                        | (,)              |         |
| Well                               | 60 (66.7)                        | 574 (33.5)       | 0.001   |
| Moederate                          | 28 (31.1)                        | 897 (52.3)       | 0.001   |
| Poor and mucinous                  | 2 (2.2)                          | 243 (14.2)       |         |
| Depth of invasion                  | <i>=</i> ( <i>-</i> : <i>-</i> ) | 2 10 (1 112)     |         |
| Mucosa                             | 40 (44.4)                        |                  |         |
| Submucosa                          | 50 (55.6)                        |                  |         |
| Proper muscle                      | 20 (22.0)                        | 308 (18.0)       |         |
| More than proper muscle            |                                  | 1406 (82.0)      |         |
| Lymph node metastasis <sup>a</sup> |                                  | 1.00 (02.0)      |         |
| Positive                           | 5 (8.9)                          | 747 (46.2)       | 0.001   |
| Negative                           | 51 (91.1)                        | 852 (53.8)       | 0.001   |
| Unknown                            | 34                               | 115              |         |
| Lymphovascular invasion            |                                  | 110              |         |
| Positive                           | 15 (16.7)                        | 977 (57.0)       | 0.001   |
| Negative                           | 75 (83.3)                        | 737 (43.0)       | 0.001   |
| Clinical symptom                   | 70 (00.0)                        | 707 (1010)       |         |
| Rectal bleeding                    | 65 (72.2)                        | 1,126 (65.9)     | 0.109   |
| Altered feces                      | 14 (15.6)                        | 249 (14.5)       |         |
| Change in bowel habit              | 19 (21.1)                        | 586 (34.3)       |         |
| Asymptomatic and others            | 15 (16.6)                        | 218 (12.7)       |         |
| Operation                          | ()                               | (                |         |
| Bowel resection                    | 56 (62.2)                        | 1563 (91.2)      | < 0.001 |
| Local excision                     | 34 (37.8)                        | 24 (1.4)         |         |
| Surgical outcome                   | 2 . (2 )                         | - · ( · )        |         |
| Minor complication                 | 8 (8.9)                          | 201 (11.7)       |         |
| Major complication                 | 3 (3.3)                          | 96 (5.6)         |         |
| Postoperative mortality            | 1 (1.1)                          | 36 (2.1)         |         |
| Long-term survival rate            | 98%                              | 67%              |         |

Numbers in parentheses are percents.

ECC: early colorectal cancer; ACC: advanced colorectal cancer.

<sup>a</sup>Only bowel-resected cases are included.

sessile type, and tumor location other than the rectosigmoid portion had a higher tendency toward LN metastasis, but not at a significant level.

# Surgical Procedure and Outcome

Of the 90 patients with ECC, 34 patients (37.8%) were treated by local resection of the tumor. All the lesions removed by local resection were located at the rectum, and the operations were

Table 2. Relation of clinicopathologic factors to level of invasion.

|                         | Depth of | invasion | $\mathbf{n}^a$ |     |       |
|-------------------------|----------|----------|----------------|-----|-------|
| Variables               | Mucosa   | sm1      | sm2            | sm3 | p     |
| Tumor size (cm)         |          |          |                |     |       |
| 0-1                     | 8        | 2        | 2              | 3   | 0.548 |
| 1–2                     | 20       | 7        | 4              | 5   |       |
| 2–3                     | 7        | 6        | 6              | 4   |       |
| 3-4                     | 2        | 2        | 2              | 4   |       |
| >4                      | 2 3      | 0        | 0              | 1   |       |
| Average                 | 2.2      | 2.1      | 2.3            | 2.8 |       |
| Histopathologic grade   |          |          |                |     |       |
| Well                    | 32       | 14       | 8              | 7   | 0.034 |
| Moderate                | 8        | 4        | 6              | 9   |       |
| Poor                    |          |          |                |     |       |
| Mucinous                |          |          |                | 2   |       |
| Lymphovascular invasion |          |          |                |     |       |
| Yes                     | 3        | 2        | 4              | 6   | 0.049 |
| No                      | 37       | 16       | 10             | 12  |       |
| Morphology of tumor     |          |          |                |     |       |
| Polypoid                | 28       | 7        | 5              | 5   | 0.006 |
| Sessile-polypoid        | 7        | 7        | 4              | 3   |       |
| Sessile                 | 5        | 4        | 5              | 10  |       |
| Location                |          |          |                |     |       |
| Rectosigmoid            | 33       | 15       | 13             | 17  | 0.536 |
| Nonrectosigmoid         | 7        | 3        | 1              | 1   |       |
| Lymph node metastasis   |          |          |                |     |       |
| Yes                     | 0        | 0        | 2              | 3   | 0.033 |
| No                      | 24       | 13       | 7              | 9   |       |
| Association with        |          |          |                |     |       |
| adenomatous component   |          |          |                |     |       |
| Yes                     | 37       | 15       | 9              | 12  | 0.034 |
| No                      | 3        | 3        | 4              | 7   |       |
| Total                   | 40       | 18       | 14             | 18  |       |

<sup>a</sup>sm1: slight submucosal invasion from the muscularis mucosa; sm2: intermediate invasion; sm3: deep invasion near the inner surface of the muscularis propria.

performed using the transanal approach. The surgical complication and postoperative mortality rates were lower for the ECC patients than for those with advanced colorectal cancer, though there was no statistical significance. The long-term survival rate was far better for the ECC patients (Table 1).

Local recurrence or distant metastasis was observed in two patients who underwent local excision. In these patients, the tumors were classified as sm2 and sm3 lesions, respectively; and the resection margins were free of tumor cells. A local recurrence was detected in one female patient 28 months after the initial operation, and a transsacral resection was performed. The tumor had invaded up to the muscularis propria layer, but no lymph node metastasis was observed during the second operation. To date, she has survived for 51 months since the second operation with no evidence of recurrence. Multiple liver metastases without local recurrence were detected in other female patient 40 months after the initial operation, and she died 9 months later after detection of metastasis (Table 4).

## Discussion

The clinical outcome of the patients with ECC who underwent surgical treatment is excellent. As shown in Table 5, most authors [2, 5, 8–13] have reported long-term survival rates of more than 95%. Furthermore, some patients with ECC were cured by less aggressive therapeutic modalities, such as endoscopic polypec-

Table 3. Relation of clinicopathologic factors to lymph node metastasis.

|                          | No. of | Cases<br>LN me |      |       |
|--------------------------|--------|----------------|------|-------|
| Variable                 | cases  | No.            | %    | p     |
| Size (cm)                |        |                |      |       |
| 0-1                      | 5      | 0              |      |       |
| 1–2                      | 21     | 1              | 4.8  | 0.413 |
| 2–3                      | 15     | 1              | 6.7  |       |
| 3–4                      | 8      | 2              | 25.0 |       |
| >4                       | 6      | 1              | 16.7 |       |
| Histopathologic grade    |        |                |      |       |
| Well                     | 37     | 3              | 8.1  |       |
| Moderate                 | 15     | 2              | 13.2 | 0.566 |
| Poor                     | 0      |                |      |       |
| Mucinous                 | 2      |                |      |       |
| Lympho vascular invasion |        |                |      |       |
| Yes                      | 8      | 3              | 37.5 | 0.003 |
| No                       | 46     | 2              | 4.3  |       |
| Morphology of polyp      |        |                |      |       |
| Pedunclated              | 22     | 1              | 4.5  | 0.416 |
| Subpedunclated           | 14     | 1              | 7.1  |       |
| Sessile                  | 18     | 3              | 16.7 |       |
| Location                 |        |                |      |       |
| Rectosigmoid             | 46     | 4              | 8.7  | 0.567 |
| Nonrectosigmoid          | 8      | 1              | 12.5 |       |
| Depth of invasion        |        |                |      |       |
| Mucosa                   | 23     | 0              | 0    | 0.023 |
| sm1                      | 10     | 0              | 0    |       |
| sm2                      | 9      | 2              | 22.2 |       |
| sm3                      | 11     | 3              | 27.3 |       |
| Association with         |        |                |      |       |
| adenomatous component    |        |                |      |       |
| Yes                      | 44     | 2              | 4.5  | 0.039 |
| No                       | 10     | 3              | 30   |       |

LN: lymph node.

tomy and local excision, which not only reduce the postoperative morbidity and mortality but also result in a better quality of life than traditional operations. As the number of patients with ECC has increased, there have been many reports about the clinicopathologic characteristics of this disease. As shown by Kitamura et al. and our series, ECCs exhibit features different from those of advanced lesions, including smaller size, different shape, relatively rare lymphatic or vascular invasion, and more favorable histologic grade (Y.J. Park et al., unpublished observations) [2]. The precise analysis of factors related to the poor outcome of patients with ECC is usually difficult because local recurrence or distant metastases develop in only a small portion of the patients after treatment, and thus the discrimination based on statistical analysis is sometimes impossible. However, based on accumulated reports on this issue, general agreement has been reached about several possible risk factors.

The existence of LN metastases upgrades the pathologic staging of ECC and implies that the disease is already a systemic disease for which the application of less invasive therapies is not justified. There is little controversy that LN metastasis is the most important indicator of unfavorable clinical outcome, and determination of the clinicopathologic characteristics associated with LN metastasis is one of the most interesting topics concerning the treatment of ECC. However, it cannot be precisely determined whether LN metastasis is present unless a colectomy is performed. Although endorectal ultrasonography is occasionally helpful, its capacity for

Table 4. Detailed data for recurrent ECC after treatment.

| P | atient | Age/<br>gender | Diameter<br>of tumor<br>(cm) | Depth of invasion | Lymph<br>node<br>metastasis | Grade | Lymphovascular invasion | Gross<br>feature | Type of operation | Pattern of treatment failure | Interval<br>between<br>resection and<br>recurrence<br>(months) | Result                   |
|---|--------|----------------|------------------------------|-------------------|-----------------------------|-------|-------------------------|------------------|-------------------|------------------------------|--|--------------------------|
| 1 |        | F/67           | 2                            | sm2               | Unknown                     | W     | No                      | Polypoid         | LE                | Local recurrence             | 28   | Resesection,<br>survival |
| 2 |        | F/40           | 1.5                          | sm3               | Unknown                     | M     | Yes                     | Sessile          | LE                | Lung metastasis              | 40   | Death                    |

W: well differentiated; M: moderately differentiated; LE: local excision.

Table 5. Clinical outcome of patients with ECC.

| Authors        | No. of cases | Treatment | Recurrence                   | Deaths due to cancer            | Comment  |
|----------------|--------------|-----------|------------------------------|---------------------------------|--|
| Fried [8]      | 16           | P, LE, C  | None                         | $0 (100\%)^a$                   |  |
| Christie [9]   | 106          | P, C      | 1 DM                         | 1 (99.1%)                       | Recurrence occurred from a polypectomy case where residual tumor was observed                                    |
| Moreira [10]   | 24           | C         | None                         | 0 (100%)                        |  |
| Bailey [5]     | 35           | LE        | 1 LR                         | 1 (97.1%)                       |  |
| ,              |              |           | 1 Pelvic recurrence          | , ,                             |  |
| Kikuchi [11]   | 182          | P, LE, C  | 4 LR                         | 5 (97.3%)                       | Only submucosal cancer included in analysis  |
|                |              |           | 5 DM                         | , ,                             | •  |
| Bleday [12]    | 21           | LE        | 1 LR<br>1 DM                 | 1 (95.2%)                       | Both recurrence patients had lymphatic<br>invasion and one patient had residual tumor<br>at the resection margin |
| Netzer [13]    | 35           | Р, С      | 1 LR<br>1 DM<br>1 LR with DM | 2 (95.3%)                       | Three recurrences: two had suspicious resection margins and one had lymph node metastasis                        |
| Kitamura [2]   | 90           | С         | Not specified                | 97.5% (colon)<br>93.5% (rectum) | Only submucosal cancer included in analysis  |
| Present series | 90           | C, LE     | 1 LR<br>1 DM                 | 1 (98.9%)                       |  |

C: colectomy; LE: local excision; P: polypectomy; DM: distant metastasis; LR: local recurrence.

**Table 6.** Series of lymph node metastases from ECC when the submucosal layer is invaded.

| Author          | Year | LN/total cases |
|-----------------|------|----------------|
| Fried [8]       | 1984 | 1/8 (12.5%)    |
| Hojo [19]       | 1985 | 6/98 (6.1%)    |
| Coverlizza [17] | 1989 | 5/31 (16.1%)   |
| Fujiyoshi [20]  | 1991 | 3/42 (7.1%)    |
| Ouchi [21]      | 1991 | 3/22 (13.6%)   |
| Brodsky [22]    | 1992 | 3/26 (11.5%)   |
| Kikuchi [11]    | 1995 | 13/90 (14.4%)  |
| Kudo [23]       | 1996 | 14/139 (10.0%) |
| Kitamura [2]    | 1997 | 7/66 (10.6%)   |
| Present series  |      | 5/32 (15.6%)   |
| Total           |      | 60/554 (10.8%) |
|                 |      |                |

No patients with LN metastasis were reported where the lesions were confined to the mucosal layer.

detecting LN metastasis is still unsatisfactory. Furthermore, the ability to detect LN metastases using ultrasonography varies greatly among operators, and it takes a long time to become proficient [14–16]. Furthermore, the diameter of LNs that contain metastases is frequently not large enough to be detected by a preoperative imaging study. Coverlizza et al. and Jinnai have reported that 50% of the LN metastases encountered in their series were between 0.2 and 0.6 cm, which is hardly detectable by

**Table 7.** Series of high risk factors for lymph node metastasis.

| Risk factors                             | References             |
|--|------------------------|
| Depth of invasion                        | 6, 8, 11, 24–27, P     |
| Lymphatic or vascular invasion (or both) | 6, 8, 17, 25, 27, 28 P |
| Poor histologic grade                    | 6, 8, 17, 24, 25, 28   |
| Sessile configuration                    | 8, 11, 24, 26          |
| Residual tumor at resection margin       | 6, 17, 28              |
| Flat carcinoma (type IIa or IIa+IIc)     | 25, 27                 |
| Located at rectum                        | 11                     |
| Accompanied by villous adenoma           | 24                     |
| Unaccompanied by adenomatous component   | 4, P                   |

P: present series.

imaging studies [17, 18]. In practice, the difficulty of determining the exact nodal status before operation makes surgeons hesitate when choosing the less aggressive modalities such as endoscopic polypectomy and local excision.

It is generally agreed that lesions confined to the mucosal layer rarely metastsize, and the incidence of metastasis increases in proportion to the level of invasion into the submucosal layer. LN metastasis is present with approximately 10% of submucosal cancers, although the percentage varies from 6% to 16% depending on the source reviewed (Table 6) [2, 8, 11, 17, 19–23].

Several pathologic variables have been reported to predict LN metastasis of submucosal cancer. Literature reviews (Table 7)

<sup>&</sup>lt;sup>a</sup>Corrected survival rate.

LN: lymph node metastasis.

| Author       | Year | No. of cases | Reason for colectomy                                     | Results  |
|--------------|------|--------------|--|--|
| Langer [33]  | 1983 | 6            | Suspicious resection margin                              | Residual tumor, 5 cases; LN metastasis negative            |
| Morson [34]  | 1984 | 14           | Suspicious resection margin                              | Residual tumor, 2 cases; LN metastasis negative            |
| Fried [8]    | 1984 | 12           | Submucosal tumor   | Residual tumor negative; LN metastasis negative; one death |
| Christie [9] | 1987 | 15           | Invasion to submucosa; residual tumor                    | Residual tumor; negative LN metastasis one case; no death  |
| Kitamura [2] | 1997 | 15           | Suspicious resection margin; massive submucosal invasion | Residual tumor negative                                    |
| Kikuchi [11] | 1995 | 23           | Suspicious resection margin; sm3 layer                   | Residual tumor negative; LN metastasis                     |

invasion; lymphovascular invasion

**Table 8.** Patients treated by subsequent surgery (colectomy after polypectomy).

revealed that deep submucosal invasion is a definite high risk factor [6, 11, 17, 24–28], and there is little controversy about this. In addition to the depth of invasion, the presence of lymphatic or vascular channel invasion, a sessile or flat configuration, low grade differentiation, and residual tumors after polypectomy or local resection were suggested to be associated with lymph node metastasis. However, Kikuchi et al. [11] suggested that lymphovascular invasion is not an independent risk factor for LN metastasis, but its high association with LN metastasis is a secondary phenomenon closely related to the depth of bowel wall invasion. This issue is clearly not yet defined, and further data are needed to delineate it. Our data also show that the degree of submucosal invasion is most significantly associated with LN metastasis. The so-called NPG lesions, which do not contain an adenomatous component within the tumor mass as described by Shimoda et al. [4], have been reported to be highly associated with LN metastasis, and our data support their results. The LN metastasis rate was also increased in patients with lymphatic or vascular channel invasion. Sessile forms of ECC have been reported to be associated with adverse prognostic factors, such as LN metastasis and more severe invasion of the deeper submucosal layer, and thus are regarded as requiring more aggressive therapy. In our series, tumors with sessile configurations were associated with LN metastasis, although statistical significance was not observed owing to the small number of such cases.

Traditionally, most colorectal cancers were considered to develop from colonic polyps (adenoma-carcinoma sequence), and consequently the configurations of ECC have been considered to have a polypoid shape, whether it is pedunculated or sessile. Many flat adenomas were reported after the first description of a case by Muto et al. [29]. Many Japanese authors have also reported depressed (IIc/IIa + IIc by the Japanese classification) and flat forms (IIb) of ECC that might not have developed from adenoma but are considered to be directly developed from the colonic mucosa (de novo pathway) or derived from the flat adenoma [2, 4, 21, 23]. According to Kudo et al., the de novo pathway might be a more common pathway of colorectal cancer development than the traditional adenoma-carcinoma route, and the relative low incidence of such lesions is mainly due to the difficulty of detection. The lesions with type IIc or IIc + IIa are known to invade deeply at an early stage and to be more frequently associated with LN metastasis [23]. According to the recent molecular biologic study on this topic, the flat-form tumor manifests a lack of K-ras

mutation, suggesting a different pathway of carcinogenesis [30, 31].

negative

Another interesting study is that the flat-form adenoma may be the precursor lesion of the tumors occurred in hereditary nonpolyposis colorectal carcinoma (HNPCC) based on the finding that flat adenomas have a proclivity for the proximal colon and high expression of replication errors [32]. However, the reports on this disease are rare except in Japan, and further studies should be done to delineate the epidemiology and its role in the pathogenesis of colorectal cancer.

Which subclass of ECC patients can be treated by endoscopic resection or local excision alone and which patients require subsequent surgical resection after local therapy continues to be controversial. A clear guideline for this question does not yet exist, and the decision must be based on knowledge of the long-term clinical outcome of the patients and careful examination of the pathologic features of the resected specimens. The previously discussed risk factors for LN metastasis may provide a guideline for solving this problem.

The ECCs confined to the mucosal layer can be safely treated by endoscopic resection or local excision alone. This conclusion is based on the fact that only a few cases of LN metastasis from mucosal cancer have been reported throughout the world. However, even with mucosal cancer, the resection margin should be carefully selected to avoid leaving any residual tumor. It is impossible to select precisely cases with mucosal cancer by preoperative investigation. With rectal cancer, endorectal ultrasonography, despite having some limits when detecting LN metastasis, provides relatively accurate information in this regard [14–16]. Kudo et al. suggested some endoscopic findings that indicate submucosal cancer. They include ulceration, a small Buddha-like appearance formation, a polyp-on-polyp appearance in protruded-type lesions, and the so-called type V pit pattern seen with magnifying endoscopy [23].

Some patients with submucosal cancer are good candidates for colonoscopic resection or local resection if they have low or mid-rectal cancers. Table 8 shows the patients for whom subsequent colectomy was performed after endoscopic resection of malignant colonic polyps due to unfavorable pathologic findings [2, 8, 9, 11, 33, 34]. Even in such cases the LN metastasis rate is not high and causes us to question the need for the subsequent colectomies. Furthermore, in a large proportion of patients, residual viable malignant cells were not observed in the surgical

specimens removed during colectomy performed owing to resection margin involvement, as shown in Table 8, although these findings may have resulted from the destruction of tumor cells by heat during the electrocautery or from misdiagnosis of the endoscopically resected specimen due to improper handling of specimen, which can cause disorientation.

Although the less aggressive therapeutic modalities are acceptable in some patients with ECC, surgical resection should also be considered when adverse findings exist if the patient is not a poor candidate for surgical resection because an exceptionally excellent prognosis is expected with this disease.

The local excision of early, mid, or low rectal cancer is attractive in that it can salvage sphincter function. Many successful results were reported even for patients with muscularis propria involvement. However, according to Willett et al. the overall results were obviously worse than those for Miles' operation when adverse findings (deep invasion, poor differentiation, venous/lymphatic invasion) were present [35]. When adverse findings are present in pathologic specimens, further therapy should be considered. Whether abdominoperineal resection should be done is not clear in circumstances where LN metastasis is not definite. Our opinion, based on our data and a review of the literature, is that sm3 lesions, poor histologic grade, sessile form, lymphovascular invasion, cancer not associated with an adenomatous component (the so-called NPG), and possibly the flat carcinoma proposed by the Japanese are serious risk factors for LN metastasis. Hence further therapy should be considered when these characteristics are present.

# Résumé

Afin d'évaluer les caractères clinicopathologiques du cancer colorectal dit «au début» (CCD), on a analysé les données histopathologiques et cliniques de 90 patients qui ont eu une résection chirurgicale d'un CCD (en dehors des patients ayant eu une polypectomie endoscopique) et 1704 patients ayant un cancer colorectal évolué. Par rapport aux cancers évolués, on a observé que les CCD étaient plus petits, et qu'ils avaient une meilleure dédifférenciation histologique, moins de ganglions envahis et une meilleure évolution clinique. Parmi les 56 patients ayant eu une résection intestinale, on a trouvé un envahissement des ganglions lymphatiques chez cinq d'entre eux (8.9%). Parmi les tumeurs avec envahissement ganglionnaire, il y avait plus de cas d'invasion de la sous-muqueuse profonde, d'absence de composante adénomateuse à l'intérieur de la tumeur, de configurations sessiles et plus d'invasion des vaisseaux lymphatiques. Les tumeurs ayant un envahissement de la sous-muqueuse profonde avaient un stade histologique moins favorable, un envahissement des vaisseaux lymphatiques, des métastases ganglionnaires, une morphologie sessile et une absence de composante adénomateuse à l'intérieur de la tumeur. Deux cas d'excision locale de cancer de la sous-muqueuse ont récidivé. Un de ces patients a pu être guéri par une résection colique, mais l'autre est décédé de métastases à distance. A partir de l'analyse de nos données et celles de la littérature, on pense qu'il existe un groupe de tumeurs à haut risque de métastases ganglionnaires et de récidive en l'absence de thérapeutique agressive: tumeur avec envahissement de la sousmuqueuse, envahissement des vaisseaux lymphatiques, une configuration sessile, et les tumeurs sans composante adénomateuse.

#### Resumen

Con objeto de evaluar las principales características anatomoclínicas del cáncer colorrectal precoz (ECC), se analizaron las peculiaridades clínicas e histopatológicas de 90 pacientes, sometidos a resección quirúrgica, por padecer un ECC (no se incluyeron los casos polipectomizados por endoscopia) y de 1,704 enfermos con carcinoma colorrectal avanzado. En casos de ECC se constató un menor tamaño, mejor diferenciación histológica y menor numero de metástasis ganglionares (LN) y a distancia, así como resultados clínicos más satisfactorios, que en los cánceres colorrectales avanzados. Sólo en 5 casos (8.9%) de 56 pacientes, que sufrieron una resección intestinal por ECC, se observaron metástasis linfáticas (LN). Las LN acompañaban con más frecuencia a tumores que invadían la submucosa, no presentaban componente adenomatoso alguno, tenían aspecto sesil e invasión linfo-vascular. Las neoplasias que muestran un crecimiento profundo, invadiendo las capas submucosas, se caracterizan por presentar un mayor grado de malignidad histológica, infiltración linfo-vascular, metástasis ganglionares (LN), morfología sesil y ausencia de componente adenomatoso alguno en el interior del tumor. Dos pacientes, cuyo cáncer submucoso fue tratado mediante resección local, recidivaron. Uno de ellos, tras resección intestinal sobrevivió; el otro murió de metástasis a distancia. Del análisis de nuestros datos y de la revisión bibliográfica al respecto podemos concluir diciendo que: tumores que invaden ampliamente la submucosa, con irrupción linfo-vascular, morfología sesil y sin componente adenomatoso alguno, constituyen el grupo con mayor riesgo de producir LN y recidivas, tras extirpación local.

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