

Review

# Introduction of the General Rules for Clinical and Pathological Studies on Cancer of the Colon, Rectum and Anus : Evaluation of invasion distance and budding appearance in early colorectal cancer

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## SUMMARY

Indication of endoscopic treatment for colorectal cancer with submucosal invasion (called as early colorectal cancer) is expanding although such lesions have a high potential to metastasize. Therefore, pathological evaluation of early colorectal cancer is important. In practice, surgical resection is required after endoscopic treatment of early colorectal cancer when lymphovascular invasion is obvious, the treated lesion is a poorly differentiated adenocarcinoma or an undifferentiated carcinoma, or carcinoma is invading massively to the vicinity of the stump. However, lymph node metastasis is indeed found only at about 10%, nevertheless an additional colectomy is performed to exclude the risk of lymph node metastasis. From the viewpoint of pathology, the measurement of vertical invasion distance and/or the evaluation of tumor budding appearance in its invasive front may be useful for the precise prediction of lymph node metastasis in patients with early colorectal cancers. Then, the Project Committee for Handling Submucosal Carcinomas, the Japanese Society for Cancer of the Colon and Rectum, have recently collected 865 cases of early colorectal cancers and analyzed clinicopathological factors including the distance of submucosal invasion. Subsequently, the committee suggested the outline to determine the early colorectal cancer without lymph node metastasis and moreover clarified that budding appearance is important to predict lymph node metastasis in patients with early colorectal cancers. In the present article, we explain the detailed discussion in the process of establishment for the outline.

**Key Words** : early colorectal cancer, endoscopic treatment, lymphovascular invasion, budding

## INTRODUCTION

Colorectal cancer is a leading cause of mortality worldwide, and patients with colorectal cancers are

treated with endoscopic mucosal resection (EMR), surgery, or chemoradiation. EMR is applied for early colorectal cancer to ensure a good quality of life; its use is limited to intramucosal colorectal cancer. Although EMR may be applicable for early colorectal cancers with submucosal invasion, its application will not be accepted until pre-EMR diagnosis of lymph node metastasis is confirmed. In the present study, we described that the measurement of vertical invasion distance and/or the evaluation of tumor budding appearance in

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**Table 1** Relationship between lymph node metastases and invasion distance or morphological features in early colorectal cancers.

SM depth ( $\mu\text{m}$ )	Ip type		Non-Ip type	
	N (-)	N (+)	N (-)	N (+)
head invasion	50	3 (5.7%) <sup>**</sup>		
0 < X $\leq$ 500	10	0	65	0
500 $\leq$ X < 1,000	7	0	58	0
1,000 $\leq$ X < 1,500	10	1 (9.1%) <sup>**</sup>	46	6 (11.5%)
1,500 $\leq$ X < 2,000	6	1 (14.3%) <sup>**</sup>	72	10 (12.5%)
2,000 $\leq$ X < 2,500	9	1 (10.0%) <sup>**</sup>	71	13 (15.5%)
2,500 $\leq$ X < 3,000	4	0	63	8 (11.3%)
3,000 $\leq$ X < 3,500	7	2 (22.2%)	67	5 (6.9%)
3,500 $\leq$	28	2 (6.7%)	205	35 (14.6%)
Total	131	10 (7.1%)	647	77 (10.6%)

<sup>\*\*</sup>positive : positive for vessel invasion. This table is modified from reference No. 1.

its invasive front may be useful for the precise prediction of lymph node metastasis in patients with early colorectal cancers.

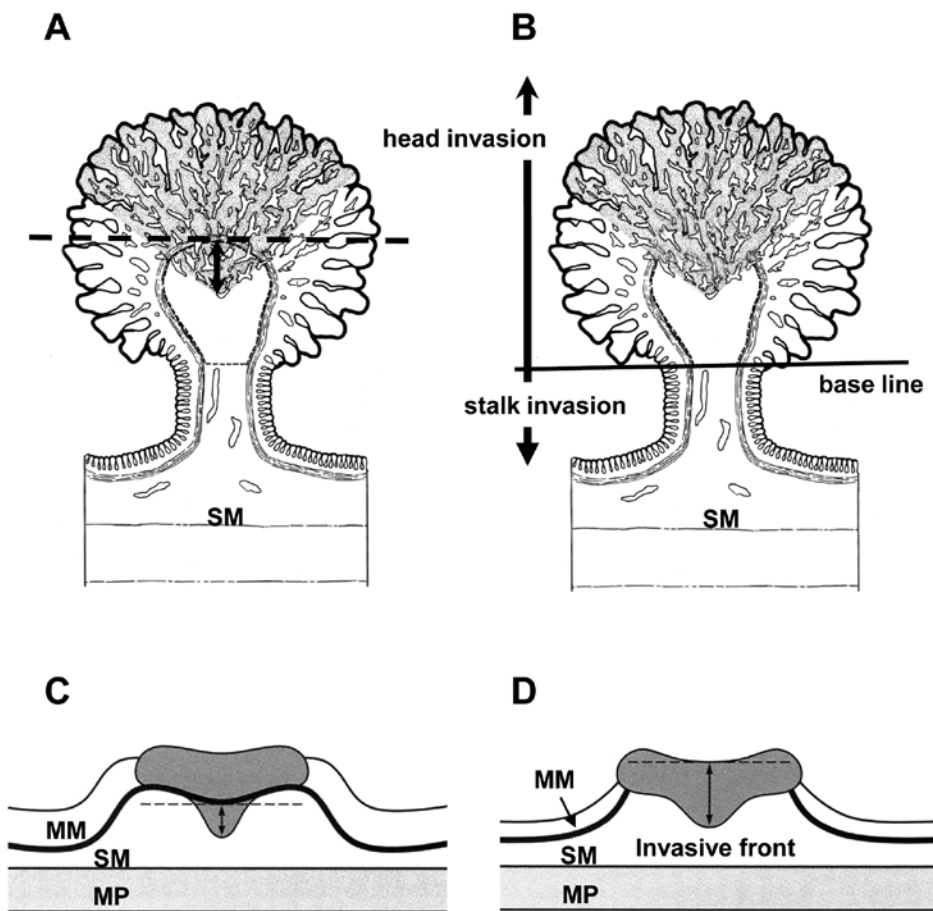
### I. Conditions for additional surgery after EMR

An additional colectomy with lymph node dissection after EMR is explained in the General Rules for Clinical and Pathological Studies on Cancer of the Colon, Rectum and Anus (the 6th edition). In brief, the additional colectomy should be done when the resected lesion fits to the conditions as follows : (i) an obvious lymphovascular carcinoma invasion ; (ii). poorly differentiated adenocarcinoma or undifferentiated carcinoma ; (iii). massive carcinoma invasion to the vicinity of the stump. However, even when an additional colectomy is performed based on these conditions, lymph node metastasis is actually found in only about 10% of the cases<sup>1~3)</sup>. Concerning (i) and (ii), consensus has almost been obtained although accurate histological evaluation of lymphovascular invasion still remained to be solved. In contrast, (iii) is quite an ambiguous description in General Rules for Clinical and Pathological Studies on Cancer of the Colon, Rectum and Anus (the 6th edition). Previously, many studies tried to find out the absolute depth of invasion with which early colorectal cancers never have lymph node metastasis. However, they had some problems such as "inappropriate baseline for measurement", "inconsistent" and "small number of cases examined".

The Project Committee for Handling Submucosal Carcinomas, the Japanese Society for Cancer of the Colon and Rectum, collected 865 cases of early colorectal cancers and analyzed clinicopathological factors including the depth of submucosal invasion<sup>1)</sup>. Early colorectal cancers were classified endoscopically into pedunculated (Ip) and non-pedunculated (non-Ip) types and the conditions in which early colorectal cancers never have lymph node metastasis were investigated (Table 1).

None of non-pedunculated early colorectal cancers had lymph node metastasis when the distance of submucosal invasion was 1000  $\mu\text{m}$  (1 mm) or less. None of pedunculated early colorectal cancers had lymph node metastasis, when the distance of submucosal invasion was 1000  $\mu\text{m}$  (1 mm) or less, and lymphatic vessel invasion was negative. The measurement of vertical invasion distance was recommended by the Japanese Society for Cancer of the Colon and Rectum and is applicable for the early colorectal cancers in which the muscularis mucosa is not clear.

Moreover, budding appearance has been considered as an important feature to evaluate the malignant potential of early colorectal cancer lesions<sup>4~6)</sup>. The budding appearance has been reported as a predictive marker of lymph node metastasis in colorectal cancer patients and named as the terms "sprouting", "single cell infiltration", or "dedifferentiation"<sup>4~6)</sup>. The evaluation of budding appearance is possible by ordinary HE



**Figure 1** Measurement of invasion distance in early colorectal cancers. (A) Pedunculated lesion. Muscularis mucosae are maintained. Dot line is a baseline. (B) Ip lesion with head invasion. Baseline is as indicated. (C) Non-pedunculated lesion. Muscularis mucosae are maintained. Dot line is a baseline. (D) Non-pedunculated lesion with destructed muscularis mucosae. Invasion distance is measured from the surface of tumor. MM, muscularis mucosa ; SM, submucosa ; MP, muscularis propria.

staining alone, and moreover, budding appearance was indeed useful to predict lymph node metastasis in patients with early colorectal cancers.

## 2. Budding

### A. Definition of budding

The budding was defined according to the Ueno's criteria as follows (6) : One budding lesion is an invasive lesion consisting of 4 or less individual carcinoma cells, or small cells or tubules with no obvious lymphatic vessel invasion and those difficult to judge whether or not they are carcinoma cells are excluded.

### B. Evaluation of budding

- (1) Observations of the invasive front were made.
- (2) One field where budding was most intensive was

selected. (3) Budding foci in 1 field were counted in a field measuring  $0.385 \text{ mm}^2$  using objective lens ( $\times 25$ ). (4) Cases were graded into 3 groups, grade 1 (budding count 0-4) , grade 2 (budding count 5-9) and grade 3 (budding count 10 or more) on the basis of the budding count. (5) Correction was considered because the actual area of each visual field differed due to the difference in the number of visual fields of 1 microscopic eyepiece used.

### C. Significance of budding

Significance of budding as a risk factor for lymph node metastasis was evaluated in patients with colorectal submucosal carcinoma. The early colorectal cancers collected were divided by the distance of submucosal invasion. The lesion whose distance of submu-

cosal invasion is 1000  $\mu\text{m}$  or more had lymph node metastasis at about 35% and was positive for budding appearance.

### 3. Measurement of submucosal invasion distance in early colorectal cancers

The following two lesions must be handled carefully : 1) Non-pedunculated early colorectal cancer whose muscularis mucosae are not continuous ; 2) Pedunculated early colorectal cancer. In the case of 1), cancer cells destroy the muscularis mucosae and subsequently, pathologists cannot measure the distance of submucosal invasion. For such lesions, pathologists must not image the line of muscularis mucosae. When muscularis mucosae are destroyed in early colorectal cancers, the rate of lymph node metastasis is high (Figure 1).

### 4. Confused terms related to the level of submucosal invasion in early colorectal cancer

Early colorectal cancers have previously been classified by Kudo et al., Haggitt et al. and Kikuchi et al. Their classification is so-called "relative classification". On the other hand, the evaluation by measuring invasion distance is called "absolute classification". In this section, we explain "relative classification".

#### A. Kudo's classification and Kikuchi's classification

Kudo et al. divided the length between muscularis mucosa and muscularis propria into three parts. According to the position of invasive front of cancerous lesion, they classified early colorectal cancer as follows<sup>7)</sup> : sm1, the front of invasion is in the upper third ; sm2, middle third ; sm3, lower third.

Kikuchi et al. classified early colorectal cancers with submucosal invasion as follows<sup>8)</sup> : sm1, the distance of submucosal invasion is small (they stated 200–300  $\mu\text{m}$ ) ; sm3, invasive front of cancerous lesion reaches upper end of muscularis propria ; sm2, others.

#### B. Haggitt's classification

Haggitt et al. determined the borderline by referring to the anatomical positions and evaluated the level of invasion according to the position of invasive front of early colorectal cancers<sup>9)</sup>. Haggitt's classification has a

problem that pedunculated lesion and non-pedunculated lesion is not distinguished. According to the Haggitt's classification, the early colorectal cancers with slight submucosal invasion are classified into level 4. In addition, the area named as level 2 remained to be defined clearly.

## CONCLUSION

The evaluation of invasion distance and budding appearance is important to predict lymph node metastasis in patients with early colorectal cancers.

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