

SPECIAL REPORT

MID-TERM PROGNOSIS AFTER ENDOSCOPIC RESECTION FOR SUBMUCOSAL COLORECTAL CARCINOMA: SUMMARY OF A MULTICENTER QUESTIONNAIRE SURVEY CONDUCTED BY THE COLORECTAL ENDOSCOPIC RESECTION STANDARDIZATION IMPLEMENTATION WORKING GROUP IN JAPANESE SOCIETY FOR CANCER OF THE COLON AND RECTUM

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We carried out a retrospective questionnaire survey of 792 submucosal colorectal carcinoma (CRC) cases from 15 institutions affiliated with the Colorectal Endoscopic Resection Standardization Implementation Working Group in Japanese Society for Cancer of the Colon and Rectum. In these cases, endoscopic resection (ER) and surveillance was carried out without additional surgical resection. Local recurrence or metastasis was observed in 18 cases. Local submucosal recurrence was observed in 11 cases, and metastatic recurrence was observed in 13 cases. Among the 15 cases in which the depth of submucosal invasion was measured, two cases showed depth less than 1000 μm , which has other risk factors for metastasis. Metastatic recurrence was observed in the lung, liver, lymph node, bone, adrenal glands, and the brain; in some cases, metastatic recurrence was observed in multiple organs. Death due to primary disease was observed in six cases. The average interval between ER and recurrence was 19.7 ± 9.2 months. In 16 cases, recurrence was observed within 3 years after ER. Thus, validity of ER without additional surgical resection for cases with the conditions that the depth of submucosal invasion is less than 1000 μm and the histological grade is well or moderately differentiated adenocarcinoma with no lymphatic and venous involvement was proven.

Key words: endoscopic resection, prognosis, recurrence, submucosal colorectal carcinoma.

INTRODUCTION

In the Guidelines for Colorectal Cancer Treatment, 1st Edition, 2005 by Japanese Society for Cancer of the Colon and Rectum (JSCCR),¹ the curative conditions after endoscopic resection (ER) for submucosal colorectal carcinoma (CRC) state that 'if a lesion is completely resected by ER, the depth of submucosal invasion is less than 1000 μm , and the histological grade is well or moderately differentiated adenocarcinoma with no lymphatic and venous involvement, the possibility of lymph node (LN) metastasis will be extremely low so that the surveillance is allowed without additional surgical resection.' This statement has generated a certain consensus. However, these conditions were established on

the basis of the analysis of submucosal CRC cases obtained from surgical resection,² and there are very few reports of cases in which surveillance after ER for submucosal CRC was carried out extensively.

In the present study, we obtained information on the non-surgical submucosal CRC cases with surveillance after ER; this information was obtained from the institutions affiliated with the Colorectal Endoscopic Resection Standardization Implementation Working Group in JSCCR. Using the information for these cases, we analyzed the risk factors for recurrence, the interval between ER and recurrence, and the recurrence pattern (local or metastatic). In this report, we have introduced data that can be used to verify the validity of the curative conditions after ER for submucosal CRC.

QUESTIONNAIRE SURVEY METHOD

The retrospective questionnaire survey was carried out for submucosal CRC cases obtained from the institutions affiliated with the Colorectal Endoscopic Resection Standardization Implementation Working Group in JSCCR. In these

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Table 1. Facilities that answered the questionnaire

Kitasato University East Hospital
Hiroshima University Hospital
National Cancer Center East Hospital
Asahikawa City Hospital
Jichi Medical University Hospital
National Cancer Center Hospital
Osaka Medical Center for Cancer and Cardiovascular Diseases
Nagoya City University Hospital
Kobe University Hospital
Fukuoka University Chikushi Hospital
Showa University Northern Yokohama Hospital
Cancer Institute Hospital Ariake
Tokyo University Hospital
Kyusyu University Hospital
Juntendo University Hospital

cases, surveillance had been carried out after ER without additional surgical resection for various reasons.

The following factors were surveyed: age of the patient at the initial ER, gender, tumor size, location, macroscopic type, ER technique (en bloc or piecemeal resection), histological margin (lateral or vertical), histological grade, histological grade at the deepest invasive portion, depth of submucosal invasion (μm), lymphatic/venous involvement, follow-up period after ER, existence of recurrence, recurrence pattern, and vital prognosis. Tumor size, location, macroscopic type, histological margin, histological grade, depth of submucosal invasion and lymphatic/venous involvement were recorded according to the General Rules for Clinical and Pathological Studies on Cancer of the Colon, Rectum, and Anus, 7th Edition, Revised Version by JSCCR³. Further, we directly used the clinical and histopathological findings stated in the questionnaire.

QUESTIONNAIRE SURVEY RESULTS

Among the 28 institutions affiliated with the Colorectal Endoscopic Resection Standardization Implementation Working Group in JSCCR, 15 institutions participated in this questionnaire survey (response rate, 53.6%) (Table 1). The information for 792 patients (556 male and 236 female) was collected from these 15 institutions. The average age of the patients was 72.9 ± 12.3 years (range, 19–93 years). The lesions were located in the cecum (25 cases), ascending colon (91 cases), transverse colon (77 cases), descending colon (56 cases), sigmoid colon (339 cases), and rectum (204). The average size of the lesions was 16.2 ± 8.2 mm (3–60 mm). The macroscopic type of the lesions showed that there were 0-Ip (209 cases), 0-Isp (197 cases), 0-Is (142 cases), 0-IIa (141 cases), 0-IIa + IIc (76 cases) and 0-IIc (27 cases). En bloc resection was carried out in 569 cases, and piecemeal resection was carried out in 114 cases; the ER technique was not mentioned in 109 cases. The histological lateral margin-positive was reported in 50 cases and was negative in 504 cases; the lateral margin was not mentioned in 238 cases. The histological vertical margin-positive was reported in 34 cases and was negative in 563 cases; the vertical margin was not mentioned in 195 cases. With regard to the histological grade,

724 lesions were graded as well differentiated adenocarcinoma, 63 were graded as moderately differentiated adenocarcinoma, two were graded as poorly differentiated adenocarcinoma, and the histological grade was not mentioned in three cases. The average depth of submucosal invasion was 1388 ± 1546 μm (5–10 000 μm); submucosal invasion less than 1000 μm was observed in 324 cases; deeper than 1000 μm was observed in 315 cases; and the depth of submucosal invasion was not mentioned in 153 cases. The average follow-up period was 38.7 ± 83.0 months, and recurrence was observed in 18 cases (2.3%). The recurrence rate for the cases that underwent en bloc resection was 2.5% (14/569) and that for the cases that underwent piecemeal resection was 3.5% (4/114); there was no significant difference between these two techniques. In 368 cases, the lesion satisfied the curative conditions after ER for submucosal CRC, whereas the lesion did not satisfy the curative conditions after ER for submucosal CRC in 302 cases; the relationship between the lesion and the curative conditions after ER for submucosal CRC was not mentioned in 122 cases.

HISTOPATHOLOGICAL RISK FACTORS FOR RECURRENCE

Among the 792 cases with surveillance after ER for submucosal CRC, information on all factors related to the histopathological findings was obtained in 387 cases (48.9%). These cases were re-examined to determine the relationship between the following factors and recurrence: histological grade, histological grade at the deepest invasion portion, existence of budding,⁴ submucosal invasive depth of 1000 μm , lymphatic involvement, and venous involvement.

Among these 387 patients, there were 275 males and 112 females. The average age of the patients was 64.4 ± 11.2 years (19–93 years). The average tumor size was 15.7 ± 8.3 mm (4–60 mm). The lesions were located in the cecum (6 cases), ascending colon (47 cases), transverse colon (37 cases), descending colon (40 cases), sigmoid colon (174 cases), and rectum (83 cases). Macroscopic type of the lesions revealed 0-Ip (138 cases), 0-Isp (105 cases), 0-Is (43 cases), 0-IIa (45 cases), 0-IIa+IIc (24 cases), 0-IIc (9 cases), and other type (23 cases). The average follow-up period after ER was 39.5 ± 36.7 months (3–174 months). Further, recurrence was observed in 10 cases. There were no intramucosal recurrent cases.

Using univariate analysis, each of the following factors was confirmed to be significantly related to recurrence: existence of budding,⁴ submucosal invasion depth deeper than 1000 μm , and lymphatic/venous involvement (Table 2). Multivariate analysis using logistic-regression analysis was carried out using these four factors. Consequently, submucosal invasion depth deeper than 1000 μm and lymphatic involvement were indicated as the factors with high odds ratios, and only lymphatic involvement was considered as an independent risk factor for recurrence (Table 3).

CLINICOPATHOLOGICAL CHARACTERISTICS OF THE CASES SHOWING RECURRENCE

The 18 cases (11 male and 7 female) of recurrence are shown in Table 4. The average age of the patients was

Table 2. Recurrence rate after ER for submucosal CRC in relation to pathological features ($n = 387$)

Pathological features	<i>n</i>	Recurrence positive (%)	<i>P</i> value
Histological grade			
well or mod	387	10 (3)	
por or muc	0		–
Histological grade at the deepest invasive portion			
well or mod	367	9 (2)	
por or muc	11	1 (9)	0.2756
Budding			
Positive	42	4 (10)	
Negative	345	6 (2)	0.0015
Depth of submucosal invasion (μm)			
<1000	220	1 (0.5)	
≥ 1000	167	9 (5)	0.0016
Lymphatic involvement			
Positive	29	5 (17)	
Negative	358	5 (1)	0.0002
Venous involvement			
Positive	18	3 (17)	
Negative	369	7 (2)	0.0070

CRC, colorectal carcinoma; ER, endoscopic resection; mod, moderately differentiated adenocarcinoma; por, poorly differentiated adenocarcinoma; well, well differentiated adenocarcinoma.

Table 3. Multivariate analysis of risk factors for recurrence after ER for submucosal CRC ($n = 387$)

Risk factors	Odds ratio	(<i>P</i> -value)	95% CI
Depth of submucosal invasion $\geq 1000 \mu\text{m}$	7.014	(0.0753)	0.820–60.01
Lymphatic involvement positive	6.363	(0.0139)	1.457–27.79
Budding positive	2.258	(0.3466)	0.414–12.31
Venous involvement positive	2.275	(0.3446)	0.634–11.64

CRC, colorectal carcinoma; ER, endoscopic resection.

69.2 \pm 7.2 years. The lesions were located in the cecum (2 cases), ascending colon (2 cases), sigmoid colon (6 cases), and the rectum (8 cases). The average size of the lesions was 19.7 \pm 9.2 mm. The macroscopic type of the lesions revealed 0-Ip (6 cases), 0-Isp (4 cases), 0-Is (3 cases), 0-IIa (3 cases), 0-IIa+IIc (1 case), and another type (1 case). En bloc resection was carried out in 14 cases, and piecemeal resection was carried out in four cases. Histological lateral margin-positive was reported in eight cases, and histological vertical margin-positive was reported in eight cases. Among the 15 cases in which the depth of submucosal invasion was reported, the depth was $<1000 \mu\text{m}$ in one case and $\geq 1000 \mu\text{m}$ in 14 cases.

Local intramucosal recurrence was observed in four cases with a histological positive lateral margin. Among these four cases, metastatic recurrence was observed in two cases (lung metastasis was observed in one case, and the details were unknown in one case). However, as the details of the vertical margin were unknown, the exact depth of submucosal invasion could not be measured. Among the 18 cases in which the submucosal invasive carcinoma showed recurrence, local recurrence in the form of submucosal carcinoma was observed in 11 cases, and metastatic recurrence was observed in 13 cases. Among the 15 cases in which the depth of submucosal invasion was measured, two cases showed depth $<1000 \mu\text{m}$; however, these cases had lymphatic involvement

and a positive vertical margin. Among the cases in which metastatic recurrence was observed in the organs, recurrence was observed in the lung (5 cases), liver (4 cases), LN (4 cases), bone (2 cases), adrenal gland (1 case), and brain (1 case); in some cases, metastatic recurrence was observed in multiple organs. Among the eight cases in which the patients died, death due to the primary disease was observed in six cases, death due to other diseases was observed in one case, and there were no details regarding the death in one case.

The average interval between ER and recurrence was 19.7 \pm 9.2 months. Among the 18 cases in which recurrence was observed, 16 cases showed recurrence within 3 years after ER. Among the 18 cases in which recurrence was observed, in all cases the lesions did not satisfy the curative conditions after ER for submucosal CRC.

RELATIONSHIP BETWEEN DEPTH OF SUBMUCOSAL INVASION AND POSITIVE RATE OF VERTICAL MARGIN IN EACH MACROSCOPIC TYPE OF SUBMUCOSAL CRC

We examined the relationship between depth of submucosal invasion and positive rate of vertical margin according to the

Table 4. Cases with recurrence after ER for submucosal CRC

No.	Gender	Age	Location	Macroscopic type	Size (mm)	ER technique	Vertical margin	Lateral margin	Depth of SM (µm)	Lymphatic/venous involvement	Histological grade	Budding	Local recurrence	Metastatic recurrence	Alive/death	Interval after ER (month)
1	F	68	C	Protruded	≥20	Piecemeal	?	+	240	-	well	-	IM	+	Alive	4
2	M	68	S	Superficial	≥20	Piecemeal	+	?	250	-	mod	-	SM	+	Alive	15
3	M	62	S	Protruded	<20	En bloc	-	+	SM scanty	?	well	-	IM	-	Alive	14
4	M	63	S	Protruded	≥20	En bloc	-	+	1000	+	mod	+	SM	+	Death	16
5	F	69	R	Superficial	<20	En bloc	-	-	1024	-	well	-	?	+	Alive	14
6	M	73	R	Protruded	<20	En bloc	-	-	1300	-	well	-	SM	+	Death	20
7	F	60	S	Protruded	<20	En bloc	-	-	1572	-	well	-	SM	+	Alive	89
8	M	61	R	Protruded	≥20	En bloc	+	-	1800	-	mod	-	?	+	Death	12
9	F	71	A	?	≥20	Piecemeal	-	+	2200	+	mod	+	SM	+	Alive	24
10	F	78	C	Superficial	<20	Piecemeal	?	?	2433	-	well	-	SM	-	Alive	16
11	M	59	A	Protruded	<20	En bloc	-	-	3000	+	por	+	?	+	Death	18
12	F	80	R	Protruded	<20	En bloc	-	-	3500	-	well	-	SM	+	Alive	60
13	M	68	S	Protruded	≥20	En bloc	?	?	3800	+	well	+	IM	-	Alive	8
14	M	74	S	Protruded	<20	En bloc	-	-	4200	-	mod	-	SM	+	Death	0
15	M	66	R	Protruded	<20	En bloc	?	-	5300	+	well	+	SM	-	Death	26
16	M	65	R	Protruded	≥20	En bloc	-	-	6886	+	mod	+	SM	+	Death	22
17	M	81	R	Protruded	<20	En bloc	+	-	SM3	-	?	-	SM	-	Death	10
18	F	80	R	Superficial	≥20	En bloc	?	+	?	-	?	-	IM	+	Alive	10

A, ascending colon; C, cecum; F, female; IM, intramucosa; M, male; mod, moderately differentiated adenocarcinoma; por, poorly differentiated adenocarcinoma; R, rectum; S, sigmoid colon; SM, submucosa; well, well-differentiated adenocarcinoma.

Table 5. Relationship between the depth of submucosal invasion and positive rate of vertical margin in each macroscopic type of submucosal CRC

Depth of submucosal invasion (µm)	Macroscopic type	
	Protruded type <i>n</i> = 286	Superficial type <i>n</i> = 82
~1000	7.1% (11/156)	2.9% (2/68)
1001~2000	10.2% (6/59)	8.3% (1/12)
2001~3000	14.7% (5/34)	0% (0/7)
3001~4000	18.8% (3/16)	
4001~	9.5% (2/21)	0% (0/2)
Total	9.4% (27/286)	3.7% (3/82)

CRC, colorectal carcinoma.

Table 6. Relationship between vertical margin and recurrence in endoscopically resected submucosal CRC without additional surgical resection

Vertical margin	Recurrence		Total
	Positive	Negative	
Positive	1 (3.2)	31 (96.8)	32 (100)
Negative	9 (2.5)	347 (97.5)	356 (100)

There were no intramucosal recurrent cases.
CRC, colorectal carcinoma.

macroscopic type (protruded or superficial type) in the 368 cases in which the depth of submucosal invasion was reported (Table 5). The overall positive rate of vertical margin was 8.2% (30/368), and the positive rate of protruded and superficial type lesions was 9.4% (27/286) and 3.7% (3/82), respectively. There were no significant differences between each macroscopic type. The positive rate of vertical margin of the protruded and superficial type lesions with submucosal invasion ≤1000 µm was 7.1% (11/156) and 2.9% (2/68), respectively. The positive rate of vertical margin of the protruded and superficial type lesions with submucosal invasion >1000 µm was 6.2% (16/259) and 4.8% (1/21), respectively. With regard to the relationship between vertical margin and recurrence, the recurrence rate for the vertical margin-positive cases was 3.1% (1/32) and that for the vertical margin-negative cases was 2.5% (9/356). There were no significant differences between the values for these two groups (Table 6).

DISCUSSION

This multi-institution questionnaire survey had several limitations. Owing to the retrospective-examination model, the average follow-up period was 38.7 months, and a central review was not carried out on the pathological specimens. However, valuable data were obtained by analyzing the prognoses of non-surgical submucosal CRC cases after ER, which were provided by multiple institutions. Our data showed that all non-surgical submucosal CRC cases with recurrence after

ER did not satisfy the curative conditions according to the Guidelines for Colorectal Cancer Treatment, 1st Edition by JSCCR.¹ As the curative conditions after ER for submucosal CRC stated in the currently used Guidelines for Colorectal Cancer Treatment, 2nd Edition by JSCCR, 2009⁵ (a factor of budding grade was added to the curative condition of the 1st Edition) were derived from examinations of the cases in which surgical resection was accompanied by LN metastasis, micrometastasis was not taken into consideration. Clinical verification of the curative conditions can be proved by the prognosis of the non-surgical submucosal CRC cases after ER. However, as these results were obtained on the basis of the histopathological diagnosis in different institutions, we presumed that a certain amount of scattering existed among the data from different institutions.

ER is a therapeutic technique as well as an important diagnostic method that can be used as the total incisional biopsy. Complete resection of the lesions, including vertical margin-negative, is indispensable for curative conditions after ER for submucosal CRC. Currently, among the factors in the curative conditions, only the depth of submucosal invasion can be diagnosed prior to the surgical operation. LN metastasis of submucosal CRC with invasion depth deeper than 1500 μm and 2000 μm was not observed under certain conditions when the histological grade at the deepest invasive portion was taken into consideration.⁶ Our data showed that the incidence of the histopathological vertical margin-positive was 8.2%, and there was no significant relationship between the vertical margin-positive and recurrence. This result may show that there is a difference between the histologically vertical margin-positive and submucosal residual tumors on the colorectal wall. To avoid local recurrence after ER, it is important to observe an ulcer in detail using colonoscopy. A previous report has described that residual tumors caused by incomplete ER have a higher growth potential than tumors before ER.⁷ Therefore, to avoid a potential disadvantage to the patients, the preoperative diagnosis must be carried out precisely, and an appropriate therapy must be selected.

Regarding surveillance for non-surgical submucosal CRC cases after ER, the results obtained in this study revealed that distant metastasis or death due to primary disease within 3 years after ER was observed in 89% of the patients showing recurrence. Therefore, surveillance must be strictly carried out for 3 years after ER for submucosal CRC with non-curative condition. The examinations conducted in other institutions revealed that in many cases, recurrence took place within 5 years after ER.⁸⁻¹⁰ Currently, there is no consensus as to the ideal surveillance method and period after ER for submucosal CRC.

This unstable questionnaire survey had several limitations. However, the current status regarding the mid-term prognosis after ER for submucosal CRC without additional surgical operation in Japan is not available. To investigate curative condition after ER for submucosal CRC and the appropriate interval between surveillances, a long-term prognosis survey from a large number of cases must be analyzed in the near future.

CONCLUSION

This questionnaire survey was conducted in institutions affiliated with the Colorectal Endoscopic Resection Standardization Implementation Working Group in JSCCR. The results obtained by analysis of the prognosis of the non-surgical submucosal CRC cases after ER proved that there is no risk of recurrence, and that surveillance could be carried out without additional surgical resection when the lesions satisfied the curative conditions after ER for submucosal CRC according to the Guidelines for Colorectal Cancer Treatment, 1st Edition by JSCCR,¹ and recurrence was observed within 3 years after ER.

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