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Retrospective Study

Clinicopathological features of small T1 colorectal cancers

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Abstract

BACKGROUND

Although small colorectal neoplasms (< 10 mm) are often easily resected endoscopically and are considered to have less malignant potential compared with large neoplasms (≥ 10 mm), some are invasive to the submucosa.

AIM

To clarify the clinicopathological features of small T1 colorectal cancers.

METHODS

Of 32025 colorectal lesions between April 2001 and March 2018, a total of 1152 T1 colorectal cancers resected endoscopically or surgically were included in this study and were divided into two groups by tumor size: a small group (< 10 mm) and a large group (≥ 10 mm). We compared clinicopathological factors including lymph node metastasis (LNM) between the two groups.

RESULTS

The incidence of small T1 cancers was 10.1% (116/1152). The percentage of initial

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endoscopic treatment in small group was significantly higher than in large group (< 10 mm 74.1% *vs* \geq 10 mm 60.2%, $P < 0.01$). In the surgical resection cohort ($n = 798$), the rate of LNM did not significantly differ between the two groups (small 12.3% *vs* large 10.9%, $P = 0.70$). In addition, there were also no significant differences between the two groups in pathological factors such as histological grade, vascular invasion, or lymphatic invasion.

CONCLUSION

Because there was no significant difference in the rate of LNM between small and large T1 colorectal cancers, the requirement for additional surgical resection should be determined according to pathological findings, regardless of tumor size.

Key Words: Colorectal neoplasms; Lymphatic metastasis; Biological phenomena; Polyps; Colorectal cancers

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Core Tip: This is a retrospective study to evaluate the clinicopathological features in T1 colorectal cancers. We compared clinicopathological factors including lymph node metastasis (LNM) between the two groups: A small group (< 10 mm) and a large group (\geq 10 mm). Since there was no significant difference in the rate of LNM followed by histological grade, vascular invasion, or lymphatic invasion, between small and large T1 colorectal cancers, the requirement for additional surgical resection should be determined according to pathological findings, regardless of tumor size.

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INTRODUCTION

Colorectal cancer (CRC) is the third most common cancer and the fourth most common cancer cause of death worldwide[1]. Lymph node metastasis (LNM) is present in approximately 10% of T1 CRCs that require surgical resection with lymph node dissection[2,3]. Therefore, risk stratification for LNM in T1 CRC is necessary. According to the current guidelines, the risk factors for LNM are lymphovascular invasion, histological differentiation, depth of submucosal invasion, and tumor budding. Surgical treatment is recommended if any of these factors are identified in the pathological diagnosis of endoscopically resected specimens[4-8], whereas follow-up by endoscopic resection alone would be acceptable when there are no risk factors. However, tumor size is not mentioned in these guidelines. Although tumor size was reported to be a risk factor for prognosis in advanced cancers, few reports have investigated the correlation between tumor size and clinicopathological features including the presence of LNM in T1 CRC[9,10]. Recently, the "resect and discard" strategy has emerged. In this approach, polyps smaller than 10 mm that are preoperatively diagnosed by magnifying narrow-band imaging do not need to be sent for pathological examination because of its high diagnostic performance despite the potential risk of small invasive cancer, which should be assessed to determine the additional surgical resection[11]. In this study, we aimed to investigate the clinicopathological characteristics of small (less than 10 mm) T1 CRC compared to large (10 mm or more) tumor groups.

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MATERIALS AND METHODS

Patients

A total of 32025 colorectal lesions (< 10 mm 21620 lesions, ≥ 10 mm 10405 lesions), excluding advanced cancers, were endoscopically or surgically resected at Showa University Northern Yokohama Hospital (Yokohama, Japan) between April 2001 and March 2018. Of these, 1272 were T1 CRCs. We excluded 45 patients who had synchronous advanced CRC, three patients with Lynch syndrome, six patients with inflammatory bowel disease, and 66 patients whose specimens were impossible to evaluate pathologically in detail because of damage or loss. In total, 1152 cases were included (Figure 1). Patient characteristics analyzed included age, sex, tumor location, tumor size, polypoid/non-polypoid growth, adenoma component, tumor morphology, initial treatment, depth of submucosal invasion, histological grade, vascular invasion, lymphatic invasion, tumor budding, and LNM. Surgical specimens were used as the gold standard for the presence of LNM. We classified tumor morphology into three types according to the Paris classification and Kudo's classification: flat type (IIa, laterally spreading tumor), protruded type (Is, Ip, and Isp), and depressed type (IIc, IIa + IIc, IIc + IIa, Is + IIc, and Ip + IIc)[12].

Histological examination

All resected specimens were retrieved and immediately fixed in 10% buffered formalin and were observed with a focus on the pit pattern using a stereomicroscope. They were then cut at the point where the deepest invasion area could be exposed on the cut end surface. The other histological specimens were cut into parallel 2- to 3-mm-thick sections and stained with hematoxylin and eosin (H&E). Tumor size was measured after formalin fixation. All specimens were diagnosed on the basis of the 2019 World Health Organization Classification of Tumors[13] and the current Japanese Society for Cancer of the Colon and Rectum (JSCCR) guidelines[6]. Histological grade was classified in view of the World Health Organization criteria as follows: well-differentiated adenocarcinoma, moderately differentiated adenocarcinoma, poorly differentiated adenocarcinoma (Por), and mucinous carcinoma (Muc). In this study, a Por/Muc component was considered present if any part of the lesion contained any of these features. The depth of submucosal invasion was classified according to the JSCCR classification as < 1000 μm (T1a) and ≥ 1000 μm (T1b)[6]. Vascular invasion was diagnosed by double staining with H&E and Victoria blue (Muto Pure Chemicals Co., Ltd., Tokyo, Japan) and lymphatic invasion was diagnosed by H&E staining and immunostaining with D2-40 antibody (Dako North America Inc., Carpinteria, CA, United States). Tumor budding is defined as a cancer cell nest consisting of one or fewer than five cells that infiltrate the interstitium at the invasive margin of the cancer. On selecting the region where tumor budding is the greatest, the front of the tumor growth is observed at 200 × magnification to count the number of tumor buds: BD1, 0-4; BD2, 5-9; and BD3, ≥ 10[14].

Statistical analysis

Nominal and ordinal variables are expressed as frequencies and percentages. Continuous variables are reported as mean ± SD. Continuous variables were compared using Student *t*-tests, while dichotomous variables were compared using chi-squared or Fisher's exact tests, as appropriate. All statistical analyses were performed using R for Windows 4.0.3. All *P* values were two sided, and *P* < 0.05 was considered statistically significant.

Ethical considerations

This study was approved by the institutional review board of Showa University Northern Yokohama Hospital (approval No. 19H057) and was registered with the University Hospital Medical Network Clinical Trials Registry (UMIN000043922). Written informed consent was obtained from all patients before treatment.

RESULTS

Patients' characteristics

Patients' characteristics are shown in Table 1. Of the included patients, 116 cases (10.1%) were included in the small group (tumors of less than 10 mm) and 1036 cases (89.9%) were included in the large group (tumors of 10 mm or larger). The mean age

Table 1 Clinicopathological characteristics of the study patients (n =1152)

Age, yr	66.4 ± 11.6
Sex (male/female)	729 (63.3)/423 (36.7)
Location (left-sided/right-sided)	788 (68.4)/364 (31.6)
Tumor size (mm)	21.2 ± 13.3
Polypoid/non-polypoid growth (polypoid/non-polypoid)	714 (62.0)/438 (38.0)
Adenomatous component (±)	466 (40.5)/686 (59.5)
Morphology (flat/ protruded/ depressed)	397 (34.5)/475 (41.2)/280 (24.3)
Initial treatment (endoscopic/surgical)	710 (61.6)/442 (38.4)
Surgical resection ¹	798 (69.3)/354 (30.7)
Depth of invasion (T1b/T1a)	826 (71.7)/326 (28.3)
Histological grade (Por or Muc ² /tub1 or tub2)	58 (5.0)/1094(95.0)
Vascular invasion (±)	322 (28.0)/830 (72.0)
Lymphatic invasion (±)	342 (29.7)/810 (70.3)
Tumor budding (BD 2 or 3/BD 1)	242 (21.0)/910 (79.0)

¹Surgical resection: Initial and additional surgical resection.

²Por or Muc, poorly differentiated adenocarcinoma or mucinous carcinoma. Results are expressed as mean ± SD or number of patients (%), as appropriate.

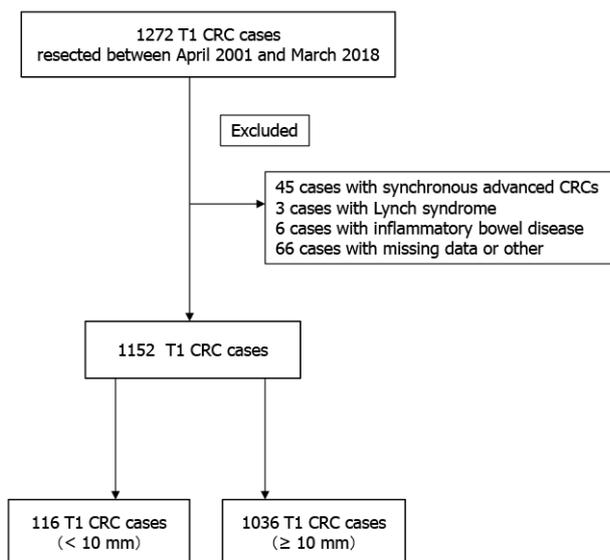


Figure 1 Patient flow chart. CRC: Colorectal cancer.

was 66.4 years. Seven hundred twenty-nine patients (63.2%) were male, and 788 patients (68.4%) had left-sided CRC. The number of patients with depressed type morphology was 280 (24.3%). The number of lesions that were initially selected for endoscopic treatment was 710 (61.6%). Seven hundred ninety-eight (69.3%) T1 CRCs were surgically resected. Vascular invasion was observed in 322 (28.0%) cases, and lymphatic invasion was observed in 342 (29.7%) cases. Among the operated cases, 11.0% (88/798) had LNM.

Small vs large in total cohort

Comparison of clinicopathological characteristics between < 10 mm and ≥ 10 mm tumors in total cohort T1 CRCs are shown in **Table 2**. Compared with T1 CRCs of ≥ 10 mm, T1 CRCs of < 10 mm had a significantly higher percentage of depressed type morphology (< 10 mm 51.7% *vs* ≥ 10 mm 21.2%, *P* < 0.01), a significantly lower percentage of polypoid growth (PG) (< 10 mm 43.1% *vs* ≥ 10 mm 64.1%, *P* < 0.01), and

Table 2 Comparison of clinicopathological characteristics between < 10 mm and ≥ 10 mm tumors in total cohort T1 colorectal cancers (n = 1152)

	< 10 mm (n = 116)	≥ 10 mm (n = 1036)	P value
Age, yr	66.8 ± 11.5	66.4 ± 11.6	0.72
Sex (male/female)	84 (72.4)/32 (27.6)	645 (62.3)/391 (37.7)	0.03
Location (left-sided/right-sided)	77 (66.4)/39 (33.6)	710 (68.5)/326 (31.5)	0.67
Tumor size (mm)	7.5 ± 1.2	22.5 ± 12.6	0.08
Polypoid/non-polypoid growth (polypoid/non-polypoid)	50 (43.1)/66 (56.9)	664 (64.1)/372 (35.9)	< 0.01
Adenomatous component (±)	34 (29.3)/82 (70.7)	432 (41.7)/604 (58.3)	< 0.01
Morphology (flat/ protruded/ depressed)	10 (8.6)/46 (39.7)/60 (51.7)	387 (37.4)/429 (41.4)/220 (21.2)	< 0.01
Initial treatment (endoscopic/surgical)	86 (74.1)/30 (25.9)	624 (60.2)/412 (39.8)	< 0.01
Surgical resection ¹	73 (62.9)/43 (37.1)	725 (70.0)/311 (30.0)	0.14
Depth of invasion (T1b/T1a)	72 (62.1)/44 (37.9)	754 (72.8)/282 (27.2)	0.02
Histological grade (Por or Muc ² /tub1 or tub2)	3 (2.6)/113 (97.4)	55 (5.3)/981 (94.7)	0.26
Vascular invasion (±)	35 (30.2)/81 (69.8)	287 (27.7)/749 (72.3)	0.59
Lymphatic invasion (±)	38 (32.8)/78 (67.2)	304 (29.3)/732 (70.7)	0.45
Tumor budding (BD 2 or 3/BD 1)	24 (20.7)/92 (79.3)	218 (21.0)/818 (79.0)	1.00

¹Surgical resection: initial and additional surgical resection.

²Por or Muc, poorly differentiated adenocarcinoma or mucinous carcinoma. Results are expressed as mean ± SD or number of patients (%), as appropriate.

a significantly lower proportion of adenomatous component (< 10 mm 29.3% *vs* ≥ 10 mm 41.7%, *P* < 0.01). In terms of the initial treatment modality, the percentage of patients with T1 CRCs of less than 10 mm opting for endoscopic treatment was significantly higher (< 10 mm 74.1% *vs* ≥ 10 mm 60.2%, *P* < 0.01). Furthermore, the rate of T1b was higher in the large group than in the small group (< 10 mm 62.1% *vs* ≥ 10 mm 72.8%, *P* = 0.02). There were no significant differences in the rate of histological grade, vascular invasion, lymphatic invasion, or tumor budding.

Small vs large tumors in the surgery group

Comparison of clinicopathological characteristics between < 10 mm and ≥ 10 mm tumors in surgical resection cohort T1 CRCs are shown in Table 3. Of these 1152 Lesions, 798 T1 CRCs underwent initial or secondary surgical resection. There was no significant difference in the LNM rate between the two groups (< 10 mm 12.3% *vs* ≥ 10 mm 10.9%, *P* = 0.70). The small group showed a higher rate of depressed type morphology, a lower rate of polypoid growth, and a lower rate of smaller adenomatous component. However, there were also no significant differences in the rate of depth of invasion, histological grade, vascular invasion, lymphatic invasion, vascular invasion, or tumor budding.

A case of small T1 CRC with LNM positivity

We present a typical case of small T1 CRC with LNM positivity in Figure 2. An 8-mm lesion with depressed type morphology was identified in the sigmoid colon. According to the magnification endoscopy findings, we predicted that the depth of invasion was T1b. Therefore, we selected surgical resection with lymph node dissection as the first-line treatment for this lesion. The final pathological findings were well to moderately differentiated adenocarcinoma, positive lymphovascular invasion, positive vascular invasion, 3750-μm depth of invasion, grade 2 tumor budding, and positive LNM. Despite the small lesion, it had risk factors for LNM and showed LNM positivity, and thus required surgical resection to achieve a cure. Of course, pre-treatment endoscopic diagnosis was important; however, if endoscopic resection was selected for this type of lesion, we should resect it with a negative margin and properly stratify the risk for LNM on the basis of the histopathological diagnosis.

Table 3 Comparison of clinicopathological characteristics between < 10 mm and ≥ 10 mm tumors in surgical resection cohort T1 colorectal cancers (n = 798)

	< 10 mm (n = 73)	≥ 10 mm (n = 725)	P value
Age, yr	66.0 ± 11.8	65.5 ± 11.2	0.71
Sex (male/female)	55 (75.3)/18 (24.7)	438 (60.4)/287 (39.6)	0.01
Location (left-sided/right-sided)	51 (69.9)/22 (30.1)	516 (71.2)/209 (28.8)	1.00
Tumor size (mm)	7.6 ± 1.1	22.3 ± 12.0	< 0.01
Polypoid/non-polypoid growth (polypoid/non-polypoid)	26 (35.6)/47 (64.4)	473 (65.2)/252 (34.8)	< 0.01
Adenoma component (±)	15 (20.5)/58 (79.5)	236 (32.6)/489 (67.4)	0.04
Morphology (flat/ protruded/ depressed)	4 (5.5)/ 24 (32.9)/ 45 (61.6)	307 (42.3)/214 (29.5)/204 (28.1)	0.03
Initial treatment (endoscopic/surgical)	43 (58.9)/30 (41.1)	316 (43.6)/409 (56.4)	0.01
Depth of invasion (T1b/T1a)	67 (91.8)/6 (8.2)	631 (87.0)/94 (13.0)	0.35
Histological grade (Por or Muc ¹ /tub1 or tub2)	3 (4.1)/70 (95.9)	47 (6.5)/678 (93.5)	0.61
Vascular invasion (±)	32 (43.8)/41 (56.2)	261 (36.0)/464 (64.0)	0.20
Lymphatic invasion (±)	34 (46.6)/39 (53.4)	270 (37.2)/455 (62.8)	0.13
Tumor budding (BD 2 or 3/BD 1)	21 (28.8)/52 (71.2)	193 (26.6)/532 (73.4)	0.68
Lymph node metastasis (±)	9 (12.3)/64 (87.7)	79 (10.9)/ 646 (89.1)	0.70

¹Por or Muc, poorly differentiated adenocarcinoma or mucinous carcinoma. Results are expressed as mean ± SD or number of patients (%), as appropriate.

DISCUSSION

LNM is present in approximately 10% of T1 CRC cases in which surgical resection with lymph node dissection is required to achieve a cure[15-18]. Therefore, we determine the need for additional surgical resection after endoscopic resection of T1 CRC according to the risk of LNM on the basis of the pathological factors. Although a consensus has been reached for several risk factors, including lymphovascular invasion, tumor differentiation, or tumor budding, no consensus has been reached for tumor size. Several reports investigated the relationship between tumor size and the rate of LNM in T1 CRC[19-21] with differing conclusions. Several claimed that tumor size is unrelated to LNM, while others reported that tumor size is related to LNM[22-27]. In this study, we concluded that tumor size alone not a risk factor for LNM.

Our findings revealed that the small group had higher rate of depressed type morphology. Kudo *et al*[28] recently reported the malignant potential of depressed type lesions. In their research, depressed type lesions showed a higher rate of LNM, followed by vascular invasion and lymphatic invasion, than other types of morphology (flat and protruded type). They speculated that the difference in the molecular phenotype by whole-exome sequencing and RNA sequencing was a potential reason for this observation. The small group showed a significantly higher rate of depressed type morphology in this study. This is a potential reason for why there were no significant differences in LNM between small and large T1 CRCs. Information on tumor morphology obtained by endoscopy is important and we should take care when performing resections, especially for such lesions even though they are small.

The "resect and discard" strategy using optical diagnosis is an attractive approach for endoscopists, pathologists, and patients, and enables a major reduction in the cost of screening and surveillance colonoscopy[29,30]. However, it has the potential risk to discard small, advanced neoplasia, which are lesions of less than 10 mm with advanced histology (high grade dysplasia, villous component, and adenocarcinoma). Notably, in T1 CRC, additional surgical resection after endoscopic resection is required according to the risk of LNM on the basis of the pathological findings of resected specimens to achieve a cure. More than 60% of T1 CRCs are misdiagnosed as adenoma by endoscopists according to a recent prospective study in the Netherlands[31]. In our study, small lesions occupied approximately 10.1% of total T1 CRCs, which had equal potential for metastasis to lymph nodes compared with large lesions. Therefore, careful observation by endoscopy should be undertaken when adopting the "resect

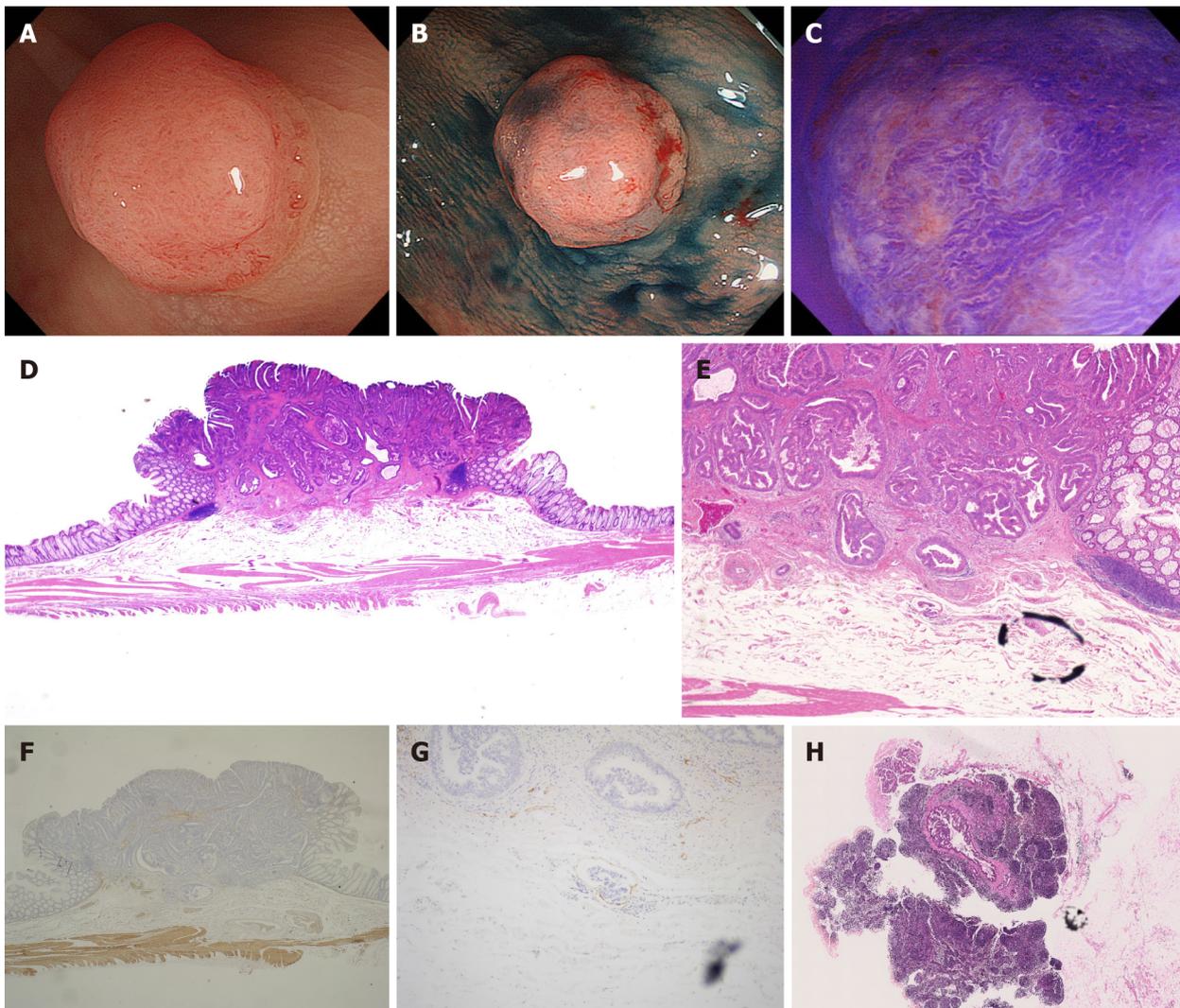


Figure 2 A typical case of small T1 colorectal cancer with lymph node metastasis positivity. A: An 8-mm-sized lesion of erythematous color located in the sigmoid colon was detected by white light observation; B: Indigo carmine spray observation showed elevation in the center and a depression line at the edge, and was diagnosed as Is + IIc by morphology; C: By magnification observation with crystal violet staining, a non-structured area was identified around severe irregular pits diagnosed as V_N type pit pattern; D: Hematoxylin and eosin (H&E) staining showing well to moderately differentiated adenocarcinoma; E: Victoria blue staining. Vascular invasion was positive; F: Desmin staining. Depth of invasion was 3750 μ m; G: D2-40 staining. Lymphatic invasion was positive; H: Dissected lymph nodes by H&E staining. Metastasis was positive.

and discard" strategy.

This study had several limitations. First, it was a retrospective analysis of patients treated at a single institution. Second, when evaluating the incidence of LNM, only patients who had undergone surgery were included. Patients treated by endoscopic resection alone were excluded because the incidence of LNM this group was not precisely assessed.

CONCLUSION

In conclusion, we investigated the clinicopathological features of small T1 CRCs and revealed that there was no significant difference in the rate of LNM, followed by the rate of vascular invasion, lymphatic invasion, or histological grade, between the small and large tumor groups. Therefore, requirements for additional surgical resection after endoscopic resection of T1 CRC should be determined on the basis of a careful pathological diagnosis, even if it is a small lesion.

ARTICLE HIGHLIGHTS

Research background

Additional surgical resection of T1 colorectal cancer after endoscopic resection is determined according to the risk of lymph node metastasis (LNM) on the basis of the histopathological findings of resected specimens.

Research motivation

Clinicopathological features including the rate of LNM in small (< 10 mm) T1 colorectal cancer were unknown.

Research objectives

The purpose of this study was to clarify the clinicopathological characteristics of small (< 10 mm) T1 colorectal cancer compared with large (\geq 10 mm) tumors.

Research methods

We retrospectively analyzed clinicopathological features, including the rate of LNM, of 1152 T1 colorectal cancers divided into two groups: small (< 10 mm) and large (\geq 10 mm) tumors.

Research results

Small T1 colorectal cancer had a similar rate of LNM, followed by a positive rate of histological grade and lymphovascular invasion, compared with large tumors.

Research conclusions

Because there were no significant differences in the rate of LNM between small and large T1 colorectal cancers, the decision on whether to undertake secondary surgical resection should be determined according to pathological findings, regardless of tumor size.

Research perspectives

Because this was a single-center retrospective study, prospective multicenter studies are required to validate these findings.

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