Original Paper

Factors associated with endoscopic treatment decisions for T1b or more deeply invading colorectal cancers

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Abstract

Surgical resection for colorectal cancer (CRC) that deeply invades the submucosa (≥1,000 μm) (T1b) has been recommended to reduce the potential risk of lymph node metastasis. In clinical settings, cases of pathological T1b exist, and these cases are treated with endoscopic resection (ER) for various reasons. However, factors that influence the choice of ER to treat T1b CRC remain unknown. Therefore, in this study, we investigated the factors associated with the choice of endoscopic treatments in patients diagnosed with pathological T1b or a more deeply invading CRC. To achieve this aim, we conducted a case series investigation of the previously conducted endoscopic diagnoses, after which we selected treatments for colorectal lesions. The case series comprised 83 lesions endoscopically diagnosed as early CRC, which was subsequently reviewed by eight endoscopists with various levels of experience in magnifying colonoscopy at Showa University Hospital. Then, pathological T1b or T2 lesions were extracted from the case series. We also assessed factors related to ER selection for these lesions using multiple logistic regression and analyzed their contributions using decision tree analysis. Eighteen cases with pathological T1b or more deeply invading lesions were extracted, and the analyses were conducted using 144 data obtained from these 18 lesions as interpreted by the eight reviewers. With multivariate logistic regression, a low estimation level for T1b and high confidence to perform ER were identified as independent factors affecting the selection of ER for T1b. The decision tree analysis further indicated that confidence levels to perform ER influenced treatment selection, especially in lesions diagnosed as probable T1b. Our study therefore demonstrated that factors affecting the selection of ER to treat T1b CRCs were low estimations during endoscopic diagnosis and high confidence to conduct the ER procedure.

Key words : T1b colorectal cancer, endoscopic resection, endoscopic diagnosis, therapeutic method selection

Introduction

Submucosal invasion depth correlates with the risk of lymph node metastasis in colorectal cancers (CRCs). However, cancers limited to the mucosa, slightly invading the submucosa (<1,000 μm) (Tis / T1a) without lymphovascular invasion[1], or those with poor differentiation have a low risk of lymph node metastasis[2, 3]. Therefore, Tis / T1a lesions are treated with endoscopic resection (ER) procedures such as endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD) without surgical resection (SR). Alternatively, because early CRCs deeply invading the submucosa (≥1,000 μm) (T1b)[1] have higher risks of lymph node metastasis, SR with lymph node dissection is recommended for these lesions[2, 3].

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As a result, the diagnostic accuracy of colonoscopy to predict the depth of invasion is essential in determining an appropriate therapeutic approach. Chromoendoscopy or image-enhanced endoscopy with magnification can be used to distinguish Tis / T1a from T1b[4-7]. Moreover, a previous study by Matsuda *et al*. reported that the sensitivity and specificity of chromoendoscopy with magnification for diagnosing T1b were approximately 70% and 90%, respectively[4]. Hisabe *et al*. also reported that the T1b diagnostic ability of the "nonextension sign" by nonmagnifying chromoendoscopy has 66% sensitivity and 95.8% specificity[8]. Thus, endoscopic prediction of early CRC invasion depth has relatively high reliability, and even some cases remain incorrectly diagnosed. Hence, it is difficult to clearly distinguish Tis / T1a from T1b by endoscopic diagnosis. It is also considered that the certainty of the diagnosis would affect treatment selection methods for detecting early CRC.

Furthermore, the development of ESD has enabled safe and cost effective en bloc resection of large Tis / T1a CRCs, which previously required SR[9-12]. Thus, advances in endoscopic treatment have led to more aggressive endoscopic treatments for early CRC, including suspected T1b cancers[13]. Nevertheless, the difficulty in performing ESD in the presence of some conditions, such as the location, morphology, and submucosal fibrosis of the lesion, has been demonstrated[14-16]. The increased indications of endoscopic treatments due to the development of ESD and an endoscopist's awareness of these difficult ESD conditions are also proposed to influence treatment choices.

Under such circumstances, multiple factors, such as the patient, lesion, and examiner, would influence treatment choices for early CRC. However, it is unclear which factor majorly influences these uncertainties. Therefore, this study examined the factors influencing the treatment decision for T1b. This study is the first to examine these factors.

Methods

Endoscopic procedure

All examinations were conducted using available colonoscopes (CF-HQ290ZI or PCF-H290ZI; Olympus Medical Systems, Tokyo, Japan) and a video endoscopy system (EVIS LUCERA ELITE; Olympus Medical Systems, Tokyo, Japan).

Selection of cases

We investigated 83 patients who were endo-scopically diagnosed with T1CRC and treated with ER or SR from April 2018 to September 2019 at Showa University Hospital. Targeted lesions were then extracted from the patients' electronic medical records, and cases with insufficient images for diagnosis or those with lacking conventional, narrow-band imaging and chromoendoscopy with magnification details were excluded. Subsequently, an expert colonoscopist (A.K.) who was not involved in this study reviewed all images and evaluated the appropriateness of this study, after which lesions judged as insufficient for endoscopic diagnosis were excluded. The selected lesions included 23 adenomas, 42 Tis / T1a lesions, 16 T1b lesions, and 2 T2 lesions (more detailed case series data are presented in Supplement 1).

Then, a PowerPoint presentation of cases containing patient and lesion information (age, sex, underlying disease, morphology, location of the lesion, and lesion size) in addition to still images of the lesions, including those with more than one image of each modality, was made by A.K. (Figure 1). After that, morphological findings were determined according to the Paris classification[17].

Supplement 1. Patient and lesion characteristics of the whole case series

	Index	No (%)
No. of patients / lesions		83 / 83
Age (mean)	Years	69.9 (33-91)
Sex	Male	57 (68.7)
	Female	26 (31.3)
Underlying disease	Absent	41 (49.3)
	Present	42 (50.7)
Morphology	Protruded	29 (35.0)
	Flat	44 (53.0)
	Depressed	10 (12.0)
Lesion size (median)	mm (range)	20 (5-60)
Location	Right side	36 (43.4)
	Left side	47 (56.6)
Histological type	W / D	48 (57.8)
	M / D	12 (14.5)
	Adenoma	23 (27.7)
Invasion depth	M	57 (68.7)
	T1a	8 (9.7)
	T1b	16 (19.2)
	T2	2 (2.4)

W / D: well-differentiated adenocarcinoma, M / D: moderately differentiated adenocarcinoma, M: limited to the mucosal layer

Patient And Lesion Information

Age: 60

Sex: Male

Underlying disease: None
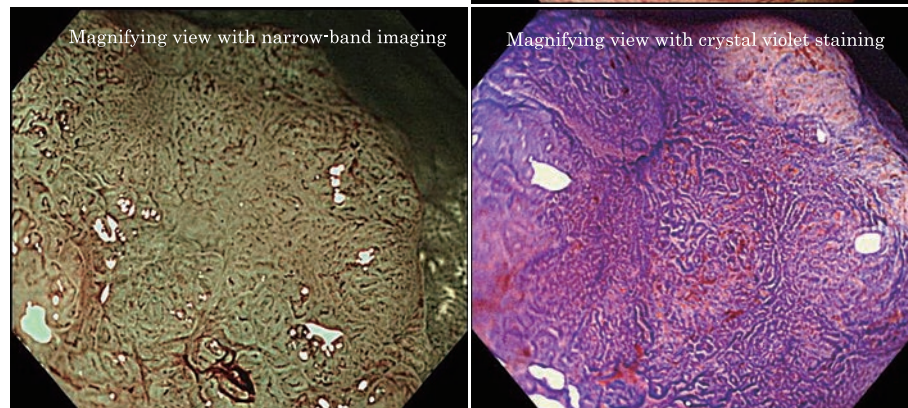
Location: Rb

Size: 18 mm

Morphology: 0-IIa+IIc

Fig. 1. An example of text and still images in the case series

Estimation by reviewers

Eight endoscopists who were blinded to the lesions' pathological findings reviewed the case series. These reviewers were then classified into three groups according to the following definitions: experts (gastroenterology specialists who have experienced more than 5,000 colonoscopy cases), middle-experienced colonoscopists (those who have experienced approximately 3,000 colonoscopy cases), and trainees (those undergoing specialty training and those who have completed 1–3 years of gastroenterology training).

The reviewers were blinded to the purpose of this validation to avoid bias in the treatment choices, after which the case series were distributed to each reviewer as digital data. For each lesion, the participating reviewers addressed the following items:

a) Comprehensive endoscopic estimation of cancer invasion depth and its confidence using a six-point scale according to the scale defined by Sakamoto T *et al*.[18]: (1) definite Tis / T1a, (2) probable Tis / T1a, (3) maybe Tis / T1a, (4) maybe T1b, (5) probable T1b, and (6) definite T1b;

b) The recommended therapy (ER or SR);

c) A motivation for the treatment choice selected (appropriate therapy, total excisional biopsy (TEB), and palliation); and

d) The confidence level to perform ER even in cases diagnosed as T1b. Here the lesion with low confidence was completed with low-ER, whereas the lesion with high confidence was completed with high-ER.

To avoid reviewer bias by limiting the case series to T1b cases, we also included lesions endoscopically suspected as being categorized from high-grade dysplasia to T1b. After the exercise, we finally extracted 18 lesions comprising T1b and T2 from the case series for further analyses. Subsequently, we analyzed 144 data obtained from the interpretation results by the eight endoscopists for these 18 cases (Figure 2). A six-point scale of the confidence level that endoscopically distinguishes Tis/T1a from T1b was then subdivided into three groups as follows: (1–4) lesions diagnosed as unlikely to be T1b (indefinite-T1b), (5) lesions diagnosed as probably T1b (med-T1b), and (6) lesions definitely diagnosed as T1b (definite-T1b) for the analyses.

Outcomes

We hypothesized that the following two factors would influence treatment choices for early CRC: 1) patient-related factors (patient's age and current medical history of systemic disease) and 2) examiner-
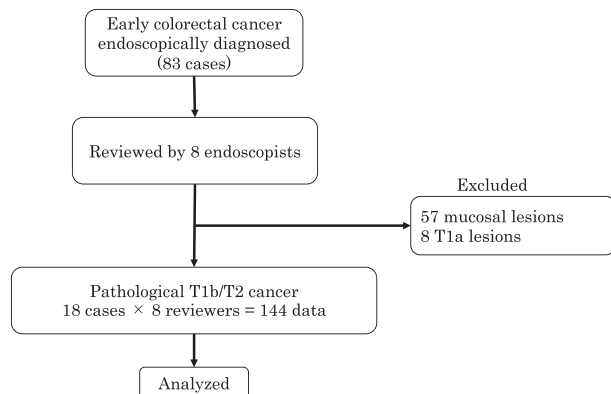
Fig. 2.　The study flowchart

Table 1.　Patient's and clinicopathological characteristics of the analyzed lesions

	Indices	No（%）
No. of patients / lesions		18 / 18
Sex	Male / Female	4 / 14
Age（median）	Year（range）	73.5（45–89）
Underlying disease	Absent	12（66.7）
	Present	6（33.3）
Morphology	Protruded	7（38.9）
	Flat	5（27.8）
	Depressed	6（33.3）
Lesion size（median）	mm,（range）	17.5（7–40）
Location	Right side	4（22.2）
	Left side	14（77.8）
Histological type	W / D	13（72.2）
	M / D	5（27.8）
Invasion depth	T1b	16（88.9）
	T2	2（11.1）

W / D：well-differentiated adenocarcinoma
M / D：moderately differentiated adenocarcinoma

related factors（diagnostic estimation level for T1b and confidence level to perform ER as judged by the examiner, including examiner's experience in colonoscopy）.

In subanalysis, we also investigated factors proposed to affect the estimation level for T1b, as well as factors influencing the confidence level to perform ER.

As detected from this study, the primary outcome was to clarify factors associated with the choice of ER for T1b.　However, the secondary outcome was to investigate the contribution of these extracted factors.

Statistical analysis

Multivariate logistic regression analyses were conducted to assess the factors for selecting ER treatment options for T1b.　Additionally, odds ratios （ORs） and 95% confidence intervals（95% CIs） were also calculated to evaluate the influencing factors in selecting ER treatment options for T1b. Statistical significance was set at $p < 0.05$.　A decision tree analysis was also conducted to analyze the contribution of the factors in selecting these ER treatment options.

All analyses were performed using JMP® 15 （SAS Institute Inc., Cary, NC, USA）.

Ethics

This study was conducted in accordance with the Declaration of Helsinki and was approved by the Showa University Review Board（study No. 2774）.

Results

Diagnostic accuracy for distinguishing T1b cancers from Tis / T1a lesions in the case series

In interpreting the entire case series, the partici-

pating reviewers' accuracy rates in distinguishing T1b from Tis / T1a were in the range of 78.1%–83.1% （Supplement 2）.　Furthermore, the breakdown of indefinite-T1b（n＝77） by the six-point score was 1 point, 10（13.0%）; 2 points, 38（49.3%）; 3 points, 14 （18.2%）; and 4 points, 15（19.5%）.

Patients and lesion characteristics

The age and sex of the patients included in this study, including the clinicopathological characteristics of the analyzed lesions, are shown in Table 1.

Factors associated with the choice of endoscopic treatment for T1b

From the 144 data obtained, ER and SR were selected in 93（64.6%） and 51（35.4%） of the preferred treatment options, respectively.　For each subgroup of the endoscopic estimation level for T1b, the percentage of ER selected as the optimal treatment option was 22.5%（9 / 40） for definite-T1b, 55.6%（15 / 27） for med-T1b, and 89.6%（69/77） for indefinite-T1b.　Alternatively, in terms of the confidence level to perform ER, the percentage of ER selected as the optimal treatment was 78.9% （71 / 90） for high-ER and 40.7%（22 / 54） for low-ER （Figure 3）.

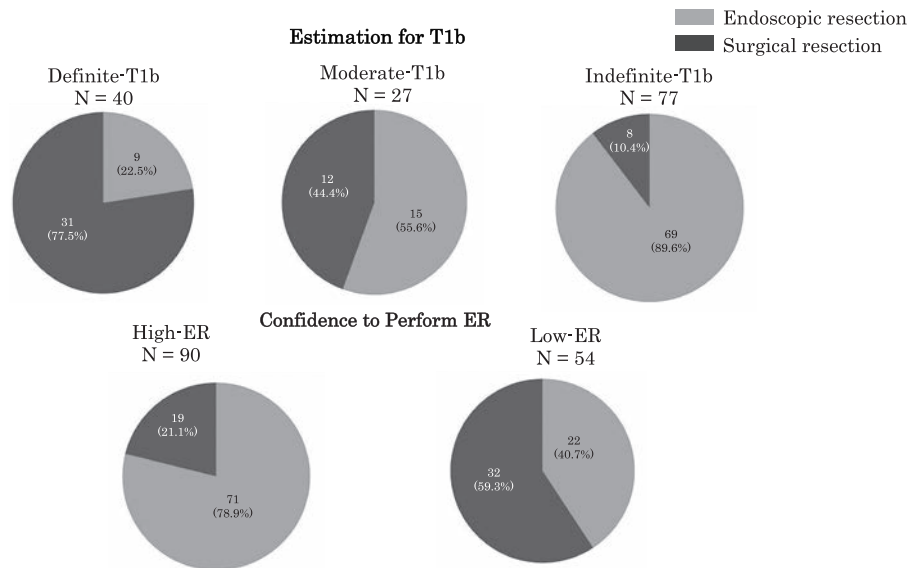Additionally, from the multivariate logistic regression

Fig. 3. Percentage of selected treatments by diagnostic estimation levels for T1b and the confidence level required to perform ER

results, a lower endoscopic estimation level for T1b and a high confidence level to perform ER were identified as independent factors affecting ER selection. Furthermore, according to the endoscopic estimation level for T1b, a tendency for ER to be more frequently selected was observed in cases of med-T1b and indefinite-T1b (OR＝6.20 and 34.1; 95% CI＝1.798–21.246 and 9.937–117.07; p＜0.01 for both) than in cases of definite-T1b. Moreover, ER was more frequently selected in cases judged as high-ER (OR＝10.2; 95% CI＝2.860–36.713; p＜0.01) than in those judged as low-ER (Table 2).

To investigate these factors' contributions to treatment selection using a decision tree analysis, the following four items were selected as candidates: diagnostic estimation level, confidence level to perform ER, age, and the presence or absence of underlying diseases. Subsequently, the decision tree was first branched because of the differences in diagnostic estimation levels. From the results, in indefinite-T1b, ER was selected in 89.3% of cases. By contrast, in definite-T1b and med-T1b, ER was selected in 22.5% and 55.8% of cases, respectively. However, in the second branch, med-T1b was divided into two groups according to the confidence level to perform ER. High-ER (83.3%) was selected more frequently than low-ER (33.3%). Moreover, patient' age, patient's underlying disease, and the reviewer's experience level were not detected as significant independent factors (Figure 4).

The factors associated with a low estimation level for

T1b and high confidence levels to perform ER

To extract factors related to indefinite-T1b, the macroscopic type of the lesion, size, and the examiner's experience level were examined as factors that can influence endoscopic diagnosis. From the multivariate logistic regression results, the macroscopic type of the lesion and size were identified as independent factors affecting endoscopic diagnosis, which were judged as indefinite-T1b. Additionally, the lesions with flat and protruded features were significantly less estimated as T1b (OR＝7.6 and 9.4; 95% CI＝2.653–21.548 and 3.641–24.064; p＜0.01 for both) than lesions with depressed features. Furthermore, similar results were found in lesions with larger sizes (≥30 mm) (OR＝3.3; 95% CI＝1.031–10.60; p＜0.044) than those with a size of ＜30 mm (Table 3).

Additionally, we investigated factors associated with a high confidence level to perform ER. The macroscopic type of the lesion, size, location of the lesion, and the examiner's experience level were also examined. From the multiple logistics regression results, the size and location of the lesion, including the examiner's experience level, were identified as independent factors affecting the confidence level to perform ER. Results also showed that the lesions located on the left-side colon had a significantly higher confidence to perform ER (OR＝10.1; 95% CI＝3.680–31.9930; p＜0.01) than those on the right-side colon. Similar results were found in lesions with a smaller size (＜30 mm) (OR＝3.1; 95% CI ＝1.109–9.127; p＜0.03) than in those with a size of

Table 2. Multivariate logistic analysis of ER ratings selected for T1b diagnosis and treatment

Factor	Multivariate, OR	95% CI	*P*-value
Estimation for T1b			
Definite-T1b	1		
Med-T1b	6.2	1.798–21.246	0.0038*
Indefinite-T1b	34.1	9.937–117.07	<0.0001*
Confidence to perform ER			
Low-ER	1		
High-ER	10.2	2.860–36.713	0.0004*
Reviewer experience			
Expert	1		
Middle	1.2	0.3494–4.1251	0.7716
Trainee	2.4	0.6312–9.2085	0.1981
Age			
<75	1		
≥75	1.43	0.4818–4.2302	0.5207
Underlying disease			
Present	1		
Absent	1.02	0.35045–2.9987	0.9639

OR：odds ratio, CI：confidence interval, ER：endoscopic resection
Definite-T1b：lesions definitely diagnosed as T1b
Med-T1b：lesions diagnosed as probably T1b
Indefinite-T1b：lesions diagnosed as unlikely to be T1b
Low-ER：ER is expected to be difficult
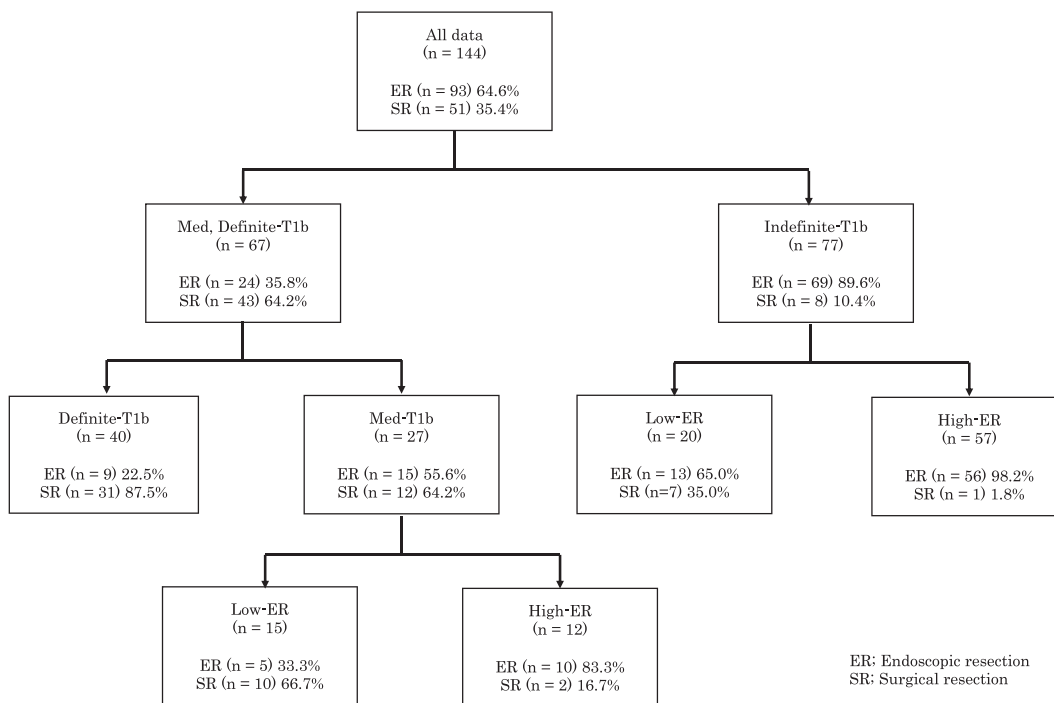High-ER：ER is expected not to be difficult

Fig. 4. Decision tree analysis to investigate the factor's contribution to treatment selection for T1b

Table 3. Multiple logistic regression of factors associated with a low estimation for T1b

Factor	Multivariate, OR	95% CI	*P*-value
Morphology			
Depressed	1		
Flat	5.6	2.1800−15.3304	<0.01*
Protruded	9.2	3.7561−24.6854	<0.01*
Size of lesion			
<30 mm	1		
≥30 mm	4.3	1.4689−14.2827	<0.01*
Reviewer's experience			
Expert	1		
Middle	2.0	0.7830−5.4751	0.14
Trainee	2.1	0.9077−5.1835	0.08

*Statistically significant
OR : odds ratio, CI : confidence interval

≥30 mm. Regarding the examiner's experience level, expert endoscopists judged ER more confidently than nonexperts (trainees and middle-experienced colonoscopist) (OR＝6.0 ; 95% CI＝2.4768-16.2639 ; p <0.01) (Table 4).

The motive for selecting ER to treat T1b

ER was selected as an appropriate therapy in 91 cases. The reviewer's motives of selecting ER were as follows : TEB, 50 cases (54.9%); an appropriate therapy for Tis / T1a (due to misdiagnosis), 33 cases (36.3%); and palliative local disease control (palliative ER), eight cases (8.8%).

Discussion

This study is the first to investigate factors that influence the use of ER to treat T1b CRCs. In this study, a low estimation level of endoscopic diagnosis for T1b and high confidence to conduct ER for treating lesions were recognized as factors influencing ER selection.

As observed, the most influential factor in ER selection for T1b treatment was the estimation level of endoscopic diagnosis. However, after analysis, a lower estimation level was selected for T1b. It was also the most frequently selected ER type.

Additionally, in this study, the sensitivity and specificity distinguishing Tis / T1a from T1b during the whole case series were 38.9%−77.8% and 71.5%− 95.4%, respectively. However, some reviewers reported lower sensitivity than previously reported (Supplement 2). It has also been reported that flat and protruded lesions have low sensitivity to

be diagnosed as T1b than depressed lesions[4, 8]. Nevertheless, in this study, the proportion of flat lesions was relatively high (87.9%) compared with that in previous reports. Hence, we propose that such differences in the targeted lesions affected low sensitivity in our study. Furthermore, although a difference was observed in their diagnostic abilities, we examined relationships the reliability of the endoscopic diagnosis chosen in relation to their treatment selections, not the accuracy of endoscopic diagnosis itself, to remove bias as much as possible. Moreover, in the six-point scale evaluation of the estimation level for T1b, the indefinite-T1b subgroup included T1b lesions misdiagnosed as Tis / T1a (1 to 3 points ; 80.5%) in addition to lesions with low diagnostic certainties even if T1b was correctly suspected (4 points ; 19.5%). Therefore, it is natural that ER, which is a minimally invasive treatment for early CRC, is selected for lesions diagnosed as Tis / T1a or lesions less likely to be T1b.

Additionally, in our study, the subanalysis of the relationships between a low estimation level for T1b and factors related to lesions indicated flat and protruded macroscopic lesion types as independent factors. However, it is proposed that the diagnostic difficulty for detecting flat and protruded lesions would affect the examiner's estimation level for T1b.

To avoid this inappropriate treatment choice of ER due to underestimation, the diagnostic ability to distinguish Tis / T1a from T1b should be improved. Recently, various approaches for diagnosing submucosal invading depths, such as endoscopic ultrasound sonography (EUS) and artificial intelligence (AI), have been attempted. Yamada *et al*. reported

Table 4. Multiple logistic regression of factors associated with high confidence to perform ER

Factor	Multivariate, OR	95% CI	*P*-value
Morphology			
Depressed	1		
Flat	1.7	0.6341–5.0076	0.28
Protruded	2.4	0.9551–6.2968	0.06
Size of lesion			
≥30 mm	1		
<30 mm	3.1	1.10519–9.0276	0.03*
Location			
Right side	1		
Left side	10.1	3.6506–31.5534	<0.01*
Reviewer's experience			
Trainee and Middle	1		
Expert	6.0	2.4768–16.2639	<0.01*

*Statistically significant
OR：odds ratio, CI：confidence interval, ER：endoscopic resection

Supplement 2. The diagnostic accuracy of distinguishing T1b from Tis/T1a as decided by each reviewer

Reviewer	Experience	Sensitivity	Specificity	PPV	NPV	Accuracy
1	Expert	38.9	95.4	70.0	84.9	83.1
2	Expert	72.2	83.1	54.1	91.5	80.7
3	Expert	66.7	93.9	75.0	91.0	88.0
4	Middle	66.7	87.7	60.0	90.5	83.1
5	Middle	77.8	71.5	53.9	93.0	80.7
6	Trainee	44.4	90.8	57.1	85.5	80.7
7	Trainee	50.0	89.2	56.3	87.9	80.7
8	Trainee	38.9	89.2	50.0	84.1	78.1

PPV：positive predictive value, NPV：negative predictive value   (%)

that magnifying chromoendoscopy and EUS showed similar diagnostic powers for predicting invasion depth of early CRC. However, neither approach was accurate enough[19]. Ito *et al*. also reported that T1b's sensitivity, specificity, and accuracy using an automatic computer-aided diagnosis system were 67.5%, 89.0%, and 81.2%, respectively[20]. Likewise, Nakajima *et al*. reported that T1b specificity was 87% for an automatic computer-aided diagnosis system, and they concluded that its specificity was superior to that of the trainees but slightly inferior to that of the experts[21]. Therefore, although the diagnosis using AI is still under development, it is expected that the AI's diagnostic performance will exceed that

of using magnifying chromoendoscopy as the current gold standard in the future. However, to perform an appropriate therapy for early CRC, a novel diagnostic method should be developed in the future[22].

A second influential factor was extracted at high confidence to perform ER, and multivariate analysis indicated that smaller lesions (<30 mm in size), lesions at the left side, and expert examiners were detected as significant factors influencing it. From this result, it is considered that inappropriate ER would be performed for the T1b lesions with small sizes or those diagnosed by colonoscopic experts.

Therefore, in our decision tree analysis, the first branch was divided according to the estimation level

for T1b endoscopic diagnosis. As observed, SR was frequently selected in definite-T1b, whereas ER was frequently selected in indefinite-T1b regardless of the low-ER level. Alternatively, in med-T1b, the confidence level to perform ER contributed to treatment selection. However, the ER selection rate was higher for the high-ER than for the low-ER. Furthermore, the confidence to perform ER affected treatment choices, especially in the case of med-T1b. Thus, this result suggested that the confidence to perform ER should not be emphasized in treatment selection for med-T1b (probably diagnosed as T1b).

Studies have shown that ESD for early CRC has become widespread in Japan, and it has become possible to reliably excise tumors, including those in the submucosa[10-12]. Additionally, the difficulty of performing ESD in the presence of some conditions has been demonstrated[14-16], and it is considered that the correct judgment of its feasibility among Japanese colonoscopists would have been improved. Further, the short- and long-term safety of additional SR for T1b patients who have undergone ESD as an initial treatment has been reported[23-25]. Therefore, ESD as TEB becoming a reliable leading ER option is considered feasible. Furthermore, these situations in which ESD can be performed actively are proposed to be the reason that ER was selected in some cases as a treatment in cases of T1b.

Moreover, we expected that SR would be avoided to some extent in cases involving older adults or those having underlying diseases, which are considered as having a low tolerance for invasive treatments, such as SR. However, these were not extracted as significant factors for ER selection to treat T1b. It is also currently recommended that treatment for T1CRC in elderly patients should be chosen considering various patient conditions[26]. Nevertheless, in this study, we used a case series mainly composed of lesion images that excluded information on surgical tolerance other than details regarding the patient's age and underlying diseases. Hence, it is expected that information regarding the patient's appearance or physical activity will affect treatment choices. This lack of information is proposed to be the reason for the difference between our assumptions and the results.

Additionally, in this study, we also investigated the motivation for endoscopists' choice of ER to treat T1b, and ER as a palliative treatment was selected in 8.8% of total cases. Palliative ER as local control for high-risk patients is a promising option. However, the efficacy and safety of palliative ER for CRC, especially lesions strongly suspected to be invading deeper into the submucosa, are yet to be clarified. Japan has an increasing aging population, and it is expected that the number of CRC patients with poor surgical tolerance will increase. Thus, its effectiveness, especially as a minimally invasive local disease control for patients strongly suspected to have T1b should be evaluated in the future.

This study had several limitations. First, this research was a retrospective case series study conducted at a single center. Second, this study included a small number of T1b lesions. Third, only one expert endoscopist who did not participate in reviewing the findings selected the still images of all cases. Fourth, the case series in this study contained few still images of the lesion. This condition is considered different from the actual clinical setting. Fifth, information on surgical tolerance was limited to the patient's age and underlying disease.

Conclusively, our study demonstrated that the factors affecting the ER selection for treating T1b were low diagnostic estimation levels for T1b and low confidence to perform ER for a lesion. However, for patients with a lesion probably diagnosed as T1b, treatment should be selected by considering the influence of confidence to perform ER.

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