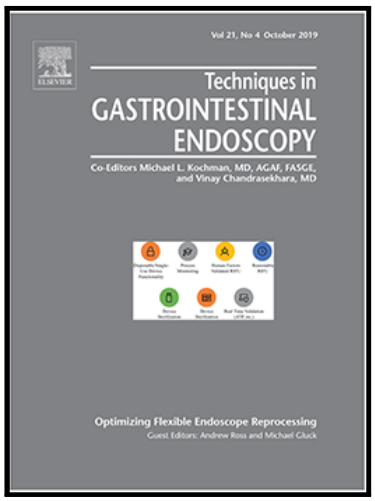

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PII: S2590-0307(21)00086-6
DOI: https://doi.org/10.1016/j.tige.2021.11.005
Reference: TIGE 150751

To appear in: *Techniques and Innovations in Gastrointestinal Endoscopy*

Received date: 4 October 2021
Revised date: 9 November 2021
Accepted date: 13 November 2021

Please cite this article as: Akinori Sasaki , Ryoko Shimizuguchi , Akinari Takao , Satomi Shibata , Souichiro Natsume , Shin-ichiro Horiguchi , Daisuke Nakano , Tatsuro Yamaguchi , Koichi Koizumi , Endoscopic Scoring System for T2 Invasion in Colorectal Cancer, *Techniques and Innovations in Gastrointestinal Endoscopy* (2021), doi: https://doi.org/10.1016/j.tige.2021.11.005

Endoscopic Scoring System for T2 Invasion in Colorectal Cancer

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Conflicts of Interest: All authors have no conflicts of interests or financial disclosures relevant to the manuscript.

Funding: No source of funding

Running title: Endoscopic findings in tumor invasion of CRC

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Ethical Statement: The corresponding author, on behalf of all authors, jointly and severally, certifies that their institution has approved the protocol for any investigation involving humans or animals and that all experimentation was conducted in conformity with ethical and humane principles of research.

Abstract

Background and Aims

The depth of tumor invasion in colorectal cancer (CRC), especially T1b or T2, is crucial in treatment decision-making. However, their differences are not well-characterized. Thus, this study aimed to investigate the predictive endoscopic findings in tumor invasion of CRC.

Findings

T2 invasion was predicted by 6 characteristics. The risk scoring system was developed using the regression coefficient values of the above variables. The area under the ROC curve was 0.894. Cases with a score ≥4 had a high risk of T2.

Implications for patient care

our scoring system is a valid tool for predicting tumor invasion and distinguishing between T1b and T2. The indications for ESD may be expanded especially in elderly people by these findings.

Methods

Data from patients with T1b or T2 CRCs resected endoscopically or surgically were reviewed retrospectively. The patients were divided into two groups: T1b (n=298) and T2 (n=267) tumor invasion. A scoring system was established based on the endoscopic findings in each group, and the accuracy of the system was assessed using a receiver-operating-characteristic (ROC) curve analysis.

Results

T2 invasion was predicted by tumor size, irregular bottom of depression, existence of depression, expansion appearance, convergency of folds, and erosion or white coat. The risk scoring system was developed using the regression coefficient values of the above variables. The area under the ROC curve was 0.894 (95% confidence interval, 0.868–0921). Cases with a score ≥4 had a high risk of T2 (sensitivity, 84.5%; specificity, 78.9%).

Conclusion

Our scoring system was useful for the diagnosis of T1b and T2, and a score ≥4 could predict T2 invasion. Additional studies are warranted to confirm these results before our scoring system can be applied clinically.

Keywords: colorectal cancer; endoscopic findings; T1b; T2; scoring system

Introduction

Colorectal cancer (CRC) is the third most common cancer globally, accounting for more than 1.8 million new cases and almost 900,000 deaths each year.[1] Endoscopic resection (ER) for early-stage CRC is recommended, and it is a widely accepted type of treatment.[2, 3] The curability of the tumor can be estimated using pathological factors according to the Japanese Society for Cancer of the Colon and Rectum Guidelines.[4] If the lesion is invasive, negative vertical and horizontal margins and the following four factors are required for resection to be considered curative: depth of submucosal invasion <1000 μm, well and/or moderately differentiated adenocarcinoma, negative lymphovascular invasion, and a budding grade of 1.

In contrast, T1b, depth of submucosal invasion ≥1000, colorectal cancer is not included as an indication for ER because of the possibility of lymph node metastasis.[5] Therefore, an additional surgical procedure is required when the resected lesion reveals submucosal invasion histologically, since submucosal invasion suggests the presence of lymph node metastasis.[5, 6] However, several patients with T1b CRC, especially elderly patients, are considered for ER even when they do not wish to undergo surgery or there is no indication for surgery. In fact, ER for T1b CRC is occasionally selected as one of the treatments.

T2 CRC is defined when there is invasion into the muscularis propria. It is generally considered that T2 CRC cannot be resected completely by ER. It is recommended that patients with T2 CRC undergo complete tumor resection.

Thus, it is critical for patients with T2 CRC to be distinguished from patients with T1b so that complete tumor resection is performed. Previous studies have indicated that T1a can be distinguished from T1b using endoscopic findings.[7, 8] However, the endoscopic difference between T1b and T2 invasion remains unclear. Therefore, in this study, we assessed the characteristic factors of T2 invasion and aimed to create a scoring system for the diagnosis of T2 invasion.

Methods

Patients

A retrospective study was performed to examine the predictive factor of tumor invasion in patients with CRC (T1b or T2). We conducted an image evaluation study of digital files containing endoscopic images of localized neoplastic lesions in patients who had been treated with ER, including endoscopic mucosal resection, endoscopic submucosal dissection (ESD), or surgical operation between April 2008 and April 2020. The exclusion criteria were pedunculated lesions, neoplastic lesions associated with inflammatory bowel disease and familial adenomatous polyposis, neoplastic lesions for which patients had undergone previous chemotherapy or chemoradiotherapy, and recurrence of lesions after treatment procedures. The clinical and clinicopathological information was collected from the hospital records and was reviewed retrospectively.

This study protocol was approved by the Institutional Review Board at the Tokyo Metropolitan Cancer and Infectious Diseases Center at Komagome Hospital and followed the principles outlined in the Declaration of Helsinki.

Endoscopic assessment

The primary objective of our study was to develop a scoring system that differentiates T1b from T2 CRC. Initially, experienced colonoscopists (AS and KK) interpreted the images obtained from 653 cases. Histological diagnoses were reviewed by a pathologist (SH) with expertise in the field of colorectal tumors. Histopathology was defined according to the World Health Organization classification system.[9]

Tumors from the cecum to the transverse colon were defined as right-sided cancers. Tumors located in the rectosigmoid junction or within the rectum were considered rectal cancers. Tumors were classified into several types: 0 (including I p, I sp, I s, II a, II b, IIc, I s + II c, II a + II sp, II a + II c, and II c + II a), 1, 2, 3, and 4, according to the Japanese Classification of Colorectal, Appendiceal, and Anal Carcinoma.[4] The pathological types of tumors are defined as follows: tub1, well-differentiated adenocarcinoma; tub2, moderately differentiated adenocarcinoma; and por, poorly differentiated adenocarcinoma. In addition, mucinous carcinoma and signet-ring cell carcinoma were classified into other types of carcinomas.

Endoscopic findings were assessed as follows: tumor size, unclear lobulation, deep depression surface, irregular bottom of depression, existence of depression, expansion appearance, convergency of folds, and erosion or white coat with reference to a previous study.[10]

Endoscopic characteristics are shown in Figure 1. Tumor size was recorded as the maximum horizontal tumor diameter, as measured from formalin-fixed tumor samples. Unclear lobulation was defined as loss of normal lobulation in the tumor surface. Deep depression surface was defined as deep depressed areas on the surface of tumor, 3 mm or deeper from the edge of the tumor. Irregular bottom of depression was defined as bumpy surface in the depressed area of the tumor. Existence of depression was described as a depressed demarcation within the lesion that was evident without indigocarmine spray. Expansion appearance was determined as a firm, hardly deformable appearance，filled to bursting. Fold convergence was defined as the convergence of at least four mucosal folds toward a central lesion and erosion or white coat as larger than the quarter of area covered with an apparent surface bleeding or white coat.

The evaluation of these endoscopic characteristics was independently performed by two colonoscopists. The third reviewer further evaluated the endoscopic characteristics when the opinion of the two colonoscopists were divided.

Statistical analysis

Statistical comparisons of baseline characteristics between T1b and T2 invasion cases were performed using the χ^2 test or Fisher's exact test for categorical data and the Student's *t* test or Mann–Whitney's test for continuous data. All statistical analyses were performed with 5% alpha risk or 95% confidence intervals using SPSS version 25 (IBM, Chicago, IL). Multivariate analysis was conducted to adjust the odds ratio using endoscopic findings which showed difference between T1b and T2 invasion.

ROC curves and the area under the curve (AUC) were analyzed to determine the accuracy of the scoring system. An AUC of 1.0 was an error-free prediction of cancer in patients, whereas an AUC of 0.50 represents a half likelihood of an accurate prediction of cancer invasion. The higher the AUC-ROC, the bigger the discriminatory power of the scoring system.

Results

Patient characteristics

Among 639 patients with CRC and 653 lesions treated with endoscopy and surgery between April 2008 and April 2020, 88 cases were excluded because of the above criteria. Thus, in total, 552 patients with 565 lesions were eligible for inclusion in this study (Fig. 2).

Table 1 shows the patient characteristics. The median patient age was 69.0 (range, 61.0–76.0) years, and 326 patients (57.7%) were males. Tumor location was not significantly different between the two groups. Regarding histology, the frequency of tub2 (moderately differentiated adenocarcinoma) was higher in the T2 group than in the T1b group (59.6% vs. 30.9%, P<0.001). Vascular invasion was significantly higher in the T2 group than in the T1b group (63.1% vs. 39.6%, P<0.001). Conversely, there were no significant differences in lymphatic invasion and lymph node metastases between the two groups.

Risk factors for T2 invasion

The univariate and multivariate predictive powers of T2 risk factors are shown in Table 2. Univariate comparison of the endoscopic characteristics revealed that tumor size, unclear lobulation, deep depression surface, irregular bottom of depression, expansion appearance, convergency of folds, and erosion or white coat were significantly different in the T1b and T2 groups. In addition, multiple logistic regression analysis demonstrated six independent variables that were significantly associated with T2 CRC: tumor size, irregular bottom of depression, existence of depression, expansion appearance, convergency of folds, and erosion or white coat.

Based on the method used to evaluate the six independent factors, the following formula was obtained:

Risk Score of T2 invasion = (2 × tumor size) + (2 × existence of depression) + (2 × Convergency of folds) + (1 × irregular bottom of depression) + (1 × expansion appearance) + (1 × erosion or white coat)

This formula uses the coefficients of the regression analysis reported in Table 2. A tumor size ≥ median, existence of depression, convergency of folds, irregular bottom of depression, expansion appearance, and erosion or white coat were attributed with scores of 2, 2, 2, 1, 1, and 1, respectively. According to the above formula, the risk score for a single patient can be within the range of 0–9. The discriminate validity for the risk score was assessed ($P<0.001$) and ROC curve analysis was used for the evaluation of sensitivity and specificity of the scores for all T1b and T2 groups. It revealed that cases with a score ≥4 had a high risk of T2 (sensitivity, 84.5%; specificity, 78.9%; and AUC, 0.894) (Fig. 3).

Discussion

In this study, we evaluated the efficacy of a scoring system based on endoscopic findings in patients with CRC. To our knowledge, this is the first report of the accuracy of such a scoring system for the prediction of T2 CRC. The strong efficacy of this tool for the prediction of T2 revealed by this study may be due to the cumulative effect of several endoscopic characteristics (such as tumor size, existence of depression, convergency of folds, irregular bottom of depression, expansion appearance, and erosion or white coat). The sensitivity and specificity of this scoring system based on a cut-off score of 4 points have been estimated to be 84.5% and 78.9%, respectively. A previous study reported that experienced endoscopists can accurately estimate the depth of invasion of about 80% of lesions on conventional endoscopy alone.[11] Our study demonstrated that the accuracy of our scoring system was higher than conventional endoscopy assessed by experienced endoscopists. Additionally, the ROC curve for risk score revealed an AUC of 0.894 for distinguishing T2 invasion from T1b, which provides evidence that our scoring system is a useful indicator for differentiating tumor invasion.

According to the guidelines, additional surgery is recommended for all patients after ESD when the current curative criteria, including a depth of submucosal invasion <1000 μm for colorectal cancer, are not met. However, sometimes patients, especially elderly patients, do not wish to

undergo additional surgery. Moreover, the physicians decide not to perform a surgical procedure in consideration of the patient's characteristics, such as age, performance status, and comorbidities. In fact, there is only a 10%–15% risk of lymph node metastasis when colorectal cancer involves submucosal invasion of 1000 μm or deeper.[5] In addition, the postoperative mortality rates are reported to be 1.4% and 1.3% for right and left hemicolectomy, respectively.[12] Therefore, it is not a contraindication for patients with CRC to undergo ER if the tumor shows submucosal invasion of 1000 μm or deeper. However, ER for T2 CRC is commonly a contraindication because the tumor grows into the muscularis propria. In this study, 81.3% of cases achieved pathological complete resection by ER in the T1b group, whereas no case achieved pathological complete resection by ER in the T2. The results show that it is crucial to distinguish T1b from T2.

Endoscopic ultrasonography (EUS) has been considered a useful technique for the diagnosis of invasion depth in patients with colorectal cancer. In a previous study, the sensitivity of EUS was 90% and the specificity was 87%.[13] However, EUS-based diagnosis requires high-cost equipment and can be challenging even for experienced endoscopists. In this context, our scoring system can be useful in estimating the depth of tumor invasion as it simply divides cases into T1b and T2.

It is critical to note the limitations of our study. First, this was a retrospective study of endoscopic data from a single institution with a limited sample size, which has a potential for bias. Second, each endoscopic characteristic was assessed by only two physicians. Therefore, it is possible that there was bias in the assessment of endoscopic findings. Third, there were several types of lesions, such as 0-I p, 0-I s, 0-II a, etc., assessed by endoscopic examination in this study. Tumor invasions may be different depending on endoscopic findings. Given these limitations, the current study only generates a hypothesis, and a more detailed system needs to be further evaluated.

In conclusion, our scoring system is a valid tool for predicting tumor invasion and distinguishing between T1b and T2. These findings deserve further investigation in a larger cohort to validate the efficacy of this scoring system.

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Table 1. Patient characteristics in the both group

features	T1b (n = 298)	T2 (n = 267)	P value
Age, median	69.0	68.50	0.78
Male, n (%)	169 (56.7)	157 (58.8)	0.67
Location			
Cecum	17 (5.7)	14 (5.2)	0.03
Ascending colon	39 (13.1)	26 (9.7)	
Transverse colon	30 (10.1)	20 (7.5)	
Descending colon	19 (6.4)	3 (1.1)	

Sigmoid colon	86 (28.9)	74 (27.7)	
Rectum	107 (35.9)	130 (48.7)	
Location			
Right side	86 (28.9)	60 (22.5)	0.102
Left side	212 (71.1)	207 (77.5)	
Histology			
Tub1	202 (67.8)	102 (38.2)	<0.001
Tub2	92 (30.9)	159 (59.6)	
por	2 (0.7)	1 (0.4)	
other	2 (0.7)	5 (1.9)	
Morphology			
0-Ⅰp	29 (9.7)	1 (0.4)	<0.001
0-Ⅰsp	64 (21.5)	15 (5.7)	
0-Ⅰs	108 (36.2)	36 (13.7)	
0-Ⅱa	39 (13.1)	3 (1.1)	
0-Ⅱb	0 (0)	0 (0)	
0-Ⅱc	2 (0.7)	0 (0)	
0-Ⅰs+Ⅱc	19 (6.4)	6 (2.3)	
0-Ⅱa+Ⅰsp	0 (0)	1 (0.4)	
0-Ⅱa+Ⅱc	24 (8.1)	11 (4.2)	

0-Ⅱc+Ⅱa	1 (0.3)	0 (0)	
1	2 (0.7)	55 (20.9)	
2	9 (3.0)	131 (49.8)	
3	1 (0.3)	3 (1.1)	
4	0 (0)	0 (0)	
Primary treatment			
Endoscopic resection	187 (62.8)	4 (1.5)	<0.001
Surgery	111 (37.2)	263 (98.5)	
Lymphatic invasion	86 (28.9)	69 (25.7)	0.450
Vascular invasion	118 (39.6)	169 (63.1)	<0.001
Lymph node metastases (503)	36 (15.3)	59 (22.1)	0.053

Table 2. endoscopic findings in the both group

features	T1b (n = 298)	T2 (n = 267)	Univariate analyses		Multivariate analyses	
			Odds Ratio (95% CI)	P value	Odds Ratio (95% CI)	P value
Tumor size, ≥ median, n (%)	102 (34.2)	183 (68.5)	4.19 (2.94, 5.95)	<0.001	4.85 (2.95, 8.00)	<0.001
Unclear	203	237	3.70 (2.35,	<0.001	1.78 (0.96,	0.069

lobulation	(68.1)	(88.8)	5.81)		3.30)	
Deep depression surface (≥ 3mm)	14 (4.7)	78 (29.2)	8.37 (4.60, 15.2)	<0.001	1.89 (0.85, 4.23)	0.12
Irregular bottom of depression	8 (2.7)	59 (22.1)	10.3 (4.81, 22.0)	<0.001	3.36 (1.35, 8.36)	0.009
Existence of depression	48 (16.1)	168 (63.2)	8.93 (6.00, 13.3)	<0.001	5.15 (2.94, 9.03)	<0.001
Expansion appearance	256 (85.9)	252 (94.4)	2.76 (1.49, 5.10)	0.001	2.32 (1.00, 5.37)	0.049
Convergency of folds	74 (24.8)	205 (76.8)	10.0 (6.80, 14.7)	<0.001	8.77 (5.39, 14.3)	<0.001
Erosion or white coat	111 (37.2)	164 (61.4)	2.68 (1.91, 3.77)	<0.001	1.97 (1.22, 3.19)	0.006

Figure legends

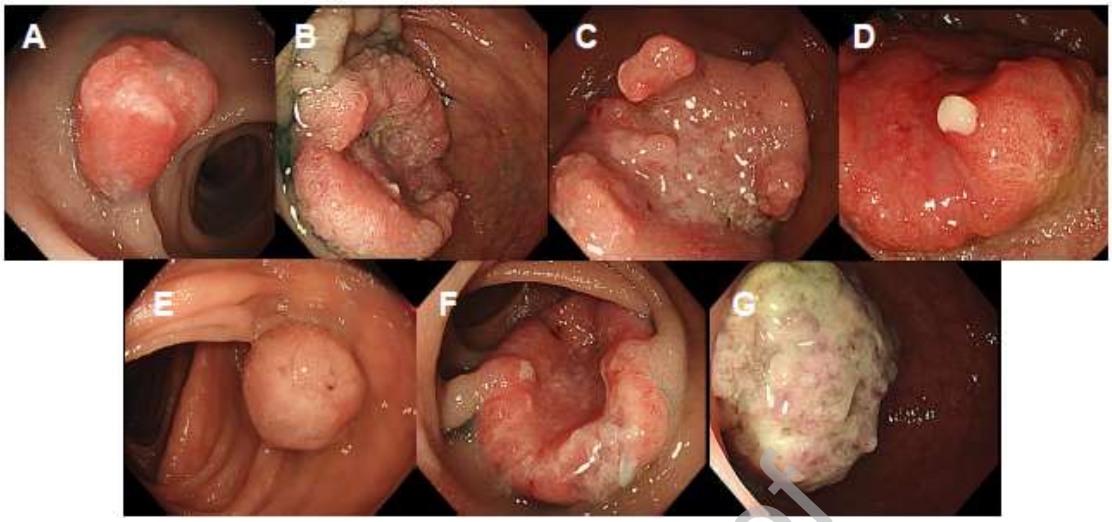

Figure 1. Examples of typical colonoscopic findings are shown. Unclear lobulation (A) was defined as loss of normal lobulation in the tumor surface. Deep depression surface (B) was defined as deep depressed areas on the surface of tumor, 3mm or deeper from the edge of the tumor. irregular bottom of depression (C) was defined as bumpy surface in the depressed area of the tumor. Existence of depression (D) was defined as a depressed demarcation within the lesion that was evident without indigocarmine spray. Expansion appearance (E) was defined as a firm, hardly deformable appearance, filled to bursting. Fold convergence (F) was defined as the convergence of at least four mucosal folds toward a central lesion. Erosion or white coat (G) was defined as an area covered with an apparent surface bleeding or white coat.

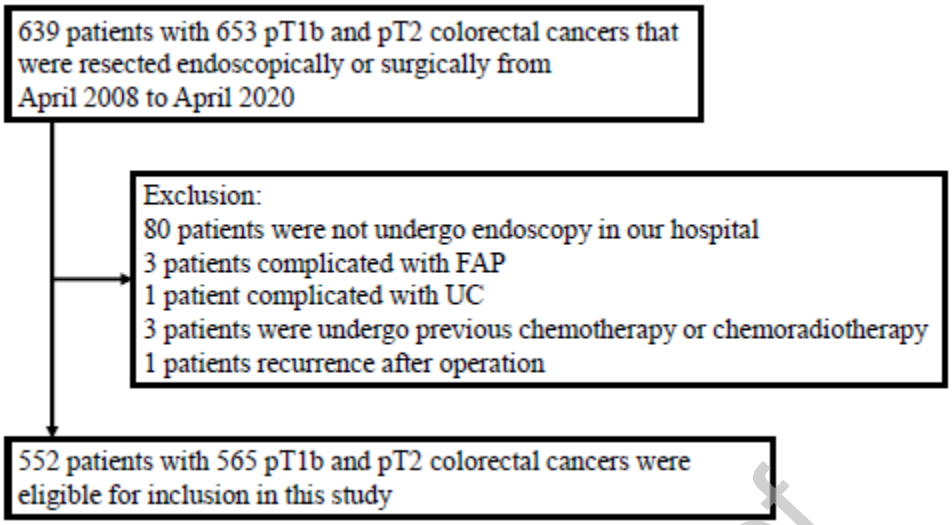

Figure 2. Consort flow diagram

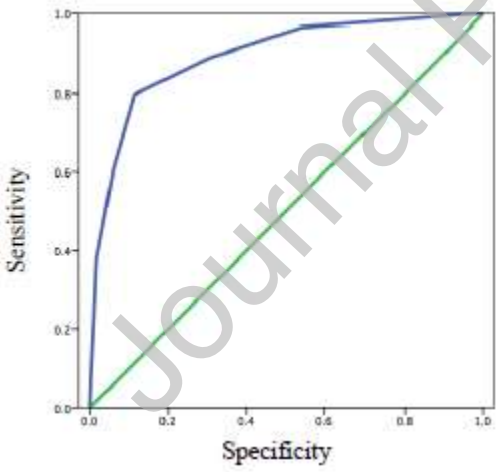

Figure 3. The ROC curve was constructed by SPSS. Area under curve was 0.894 (95% CI, 0.868-0.921). P<0.001.