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Original Article

Endoscopic submucosal dissection for superficial ultra-low rectal tumors: outcomes and predictive factors for procedure difficulty

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Abstract: Background: Ultra-low rectal endoscopic submucosal dissection (ESD) presents technical challenges due to anatomical features. The objective of this research was to determine the risk factors linked to unsuccessful curative resections and to create a nomogram predictive model to assess the likelihood of encountering technical challenges. Methods: Patients with ultra-low rectal tumors received ESD form June 2017 to December 2022 were retrospectively enrolled. An ESD procedure exceeding 30 min was deemed difficult. A logistic regression analysis was performed to pinpoint important factors and predictors. The effectiveness of the nomogram, which incorporated the identified predictors, was evaluated by employing receiver operating characteristic (ROC) curves, calibration plots, and decision curve analysis (DCA). Results: A total of 300 patients with ultra-low rectal tumors were enrolled, with a curative resection rate of 82.0%. Multivariate logistic regression revealed that poor lifting sign (OR = 3.282, P = 0.026), non-granular type laterally spreading tumors (LST-NG, OR = 2.230, P = 0.042) and procedure time ≥ 60 min (OR = 6.976, P = 0.010) contributed to non-curative resection. Predictors for ESD difficulty included tumor diameter ≥ 30 mm (compared with < 30 mm, 30-50 mm, OR = 2.450, P = 0.044; ≥ 50 mm, OR = 5.047, P = 0.009), ≥ 1/2 circumference involvement (OR = 3.183, P = 0.038); dentate line invasion (OR = 3.881, P = 0.026) and less colorectal ESD experience (OR = 3.415, P = 0.032). The nomogram performed well in both train and validation sets (area under the curve (AUC) = 0.873 and 0.810, respectively). Calibration plots exhibited satisfactory agreement between predicted and observed outcomes, and DCA showed superior clinical benefit of the model than individual predictors. Conclusions: Poor lifting sign, LST-NG and procedure time ≥ 60 min were associated with non-curative resection for ultra-low rectal ESD. By including factors such as tumor size, location, and the operator's experience with ESD, the nomogram can predict the complexity of the procedure before surgery.

Keywords: Ultra-low rectal tumor, endoscopic submucosal dissection, non-curative resection, technical difficulty, nomogram

Introduction

Colorectal cancer ranks as the third most prevalent malignancy globally, accounting for approximately 10% of deaths related to cancer [1]. In the past, treatment primarily involved extensive surgical removal with lymph node dissection and sometimes colostomy creation, procedures that frequently led to significant complications and reduced quality of life [2]. However, advancements in endoscopic methods have now enhanced the detection of superficial neoplasms, including ultra-low rectal tumors, prompting a substantial evolution in therapeutic strategies [3].

Endoscopic submucosal dissection (ESD) has emerged as a minimally invasive technique for the en bloc resection of superficial gastrointestinal neoplasms, including those in the rectum. According to current guidelines, ESD is now commonly utilized in the treatment of superficial gastrointestinal cancers and precancerous lesions [4, 5]. Compared to traditional endoscopic mucosal resection (EMR), ESD offers several advantages, such as higher rates of en

bloc resection and lower local recurrence rates [6]. Despite these advantages, ESD in the ultra-low rectum presents unique challenges. The confined space, sphincter contraction, and abundant submucosal vessels can make the procedure more technically demanding, potentially increasing the risk of non-curative resection and prolonging the procedure duration [7, 8]. Therefore, assessing curability and predicting procedural difficulty are crucial for optimizing the scheduling and outcomes of ESD procedures.

Several studies have investigated the factors contributing to the technical difficulty and outcomes of ESD. Tumor size is a critical factor; lesions larger than 50 mm in diameter are associated with longer procedure times and a higher rate of complications. Additionally, tumor morphology plays a significant role, with non-granular laterally spreading tumors (LST-NGs) presenting more challenging resections compared to granular LSTs (LST-Gs) due to less defined margins. Lesions involving the dentate line pose increased technical difficulties due to the complex anatomy of this region. Furthermore, the experience level of the endoscopist is a well-documented determinant of ESD success, with less experienced operators facing greater challenges in achieving complete resection and managing unexpected complications [9, 10]. Despite the existing research, there is a need for robust predictive models. A preoperative nomogram that can accurately predict the technical challenges and potential for non-curative resection would be valuable for clinical decision-making. Such a tool could help select appropriate candidates for ESD, plan the procedure, and prepare for potential complications [11, 12].

This study aims to determine the factors contributing to non-curative resections and to develop a preoperative nomogram for predicting technical challenges. Our goal is to furnish credible evidence that can inform and guide future clinical practices, thereby improving patient outcomes and the efficiency of ESD procedures.

Materials and methods

Research design and inclusion/exclusion criteria

We retrospectively evaluated all patients with superficial rectal tumors who underwent ESD at the Department of Digestive Endoscopy, Fujian Provincial Hospital, from January 2017 to December 2022 (**Figure 1**). Inclusion criteria: patients with solid tumor located within 3 cm above the dentate line or 5 cm above the anal verge [13]; patients who demonstrated high-grade intraepithelial neoplasia or pT1-stage adenocarcinoma histopathologically; patients without regional lymph node or distant metastasis demonstrated by endoscopic ultrasound (EUS) or CT/MRI. Exclusion criteria: presence of familial adenomatous polyps or inflammatory bowel disease; patients with chemoradiotherapy (CRT) or surgery prior to ESD; patients with incomplete data. The ethics committee of Fujian Provincial Hospital granted approval for this study, which adheres to the ethical standards set by the 1975 Declaration of Helsinki.

Preoperative assessment

The criteria for performing ESD on colorectal tumors adhered to the guidelines set by the Japan Gastroenterological Endoscopy Society [5]. The tumors were macroscopically categorized into protruding tumors (0-I, as per the Paris endoscopic classification) and LSTs [14]. LSTs are identified by their lateral expansion along the colorectal wall and have a diameter of at least 10 mm. They are further classified into LST-Gs and LST-NGs. LST-G exhibits a nodular surface similar with the protruding tumor, whereas the latter has a smooth or depressed surface [15].

A standard single-channel colonoscope (GIF-Q260J, Olympus, Japan) equipped with a transparent hood (Olympus, Japan) on its tip was employed. Chromoendoscopy using 0.4% indigo-carmine dye and narrow band imaging (NBI) with high magnification was utilized to outline the lesion margins and assess the pit patterns. Lesions observed using NBI were classified based on the NBI International Colorectal Endoscopic (NICE) criteria [16]. Additionally, EUS was conducted to more accurately assess the depth of tumor infiltration and the involvement of peripheral lymph nodes.

ESD procedures

All procedures were carried out under general anesthesia or deep sedation. The standard steps for performing ESD included: (1) identifying the lesion, (2) marking mucosal spots, (3)

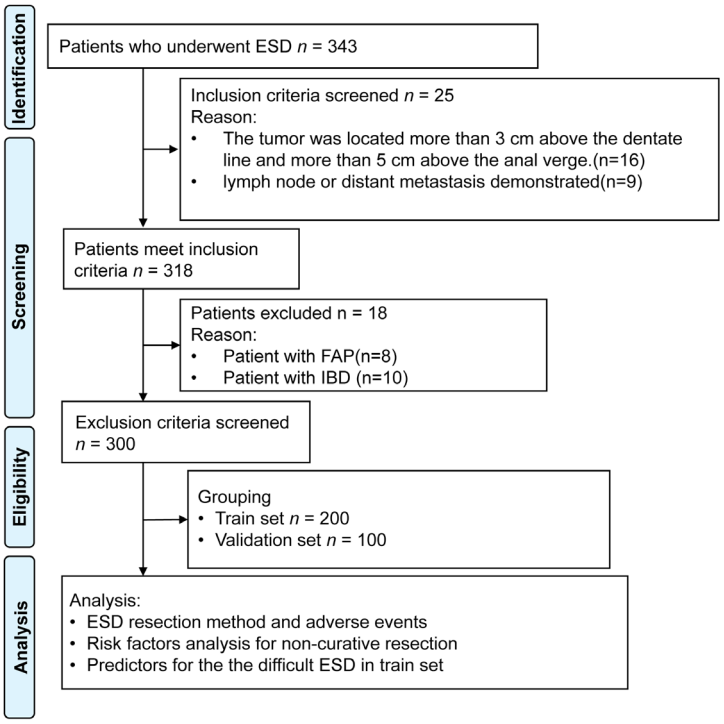

Figure 1. Study flow chart.

injecting the submucosal layer, (4) making a mucosal incision and performing submucosal dissection, and (5) achieving hemostasis and closing all perforations (**Figure 2A-F**). In cases where difficulties arose during the ESD procedure, piecemeal resection was used as an alternative. The procedure time, recorded as the total duration in minutes from the initial mucosal marking to the complete removal of the lesion, was documented in the operation record.

Record of complications

Bleeding and perforation were common ESD related complications [17]. Intraoperative bleeding is defined as moderate to severe bleeding that requires control by hemostatic forceps or clip, and may even result in the suspension of the resection procedure. Postoperative bleeding was characterized by the presence of hematochezia within 14 days following the procedure, necessitating endoscopic hemostasis. Perforation during an ESD was identified as an intraoperative event involving a full-thickness defect [17-19].

Pathological diagnosis and follow-up

ESD specimens, with standard formalin fixation and hematoxylin/eosin staining, were examined by experienced gastrointestinal pathologists. Lesions were categorized based on the most recent WHO classifications [20]. Complete resection (R0) was defined as the one-piece removal of the lesion with both vertical and horizontal margins being free of disease. A resection was considered curative when an R0 resection was achieved, and the tumor exhibited less than 1000 μm (SM1) submucosal invasion from the muscularis mucosae, with no evidence of lymphatic invasion, vascular involvement, tumor budding, or poorly differentiated components [4, 21]. All patients were followed up for 3 months.

The outcome indicators for the development of the predictive model for non-curative resection were diameter, circumference, lifting sign, LST-NG morphology, and procedure time. The factors used to analyze the risk for non-curative resection included patient-related ones (age and gender), tumor-related ones (size, location, morphology, lifting sign, NICE classification), and endoscopist experience.

Statistical analysis

Statistical analyses were performed using SPSS software (Version 26.0; Chicago, IL, USA) and R software (Version 4.0.1; http://www.R-project.org). The minimum sample size was calculated using G * Power. Using a significance level (α) of 0.05 and a power (1 - β) of 0.95, the minimum required sample size was determined to be 88 patients. The sample size calculation was performed using the following formula:

$$N = [(Z1\text{-}\alpha/2 + Z1\text{-}\beta)/d]^2 \times [p_1 (1\text{-}p_1) + p_2 (1\text{-}p_2)]$$

Where $Z_{1-\alpha/2}$ is the standard normal deviate corresponding to the desired significance level (1.96 for α = 0.05); $Z_{1-\beta}$ is the standard normal deviate corresponding to the desired power (1.645 for power = 0.95); *d* is the effect size (difference in proportions between two groups); p_1 and p_2 are the expected proportions in the two groups.

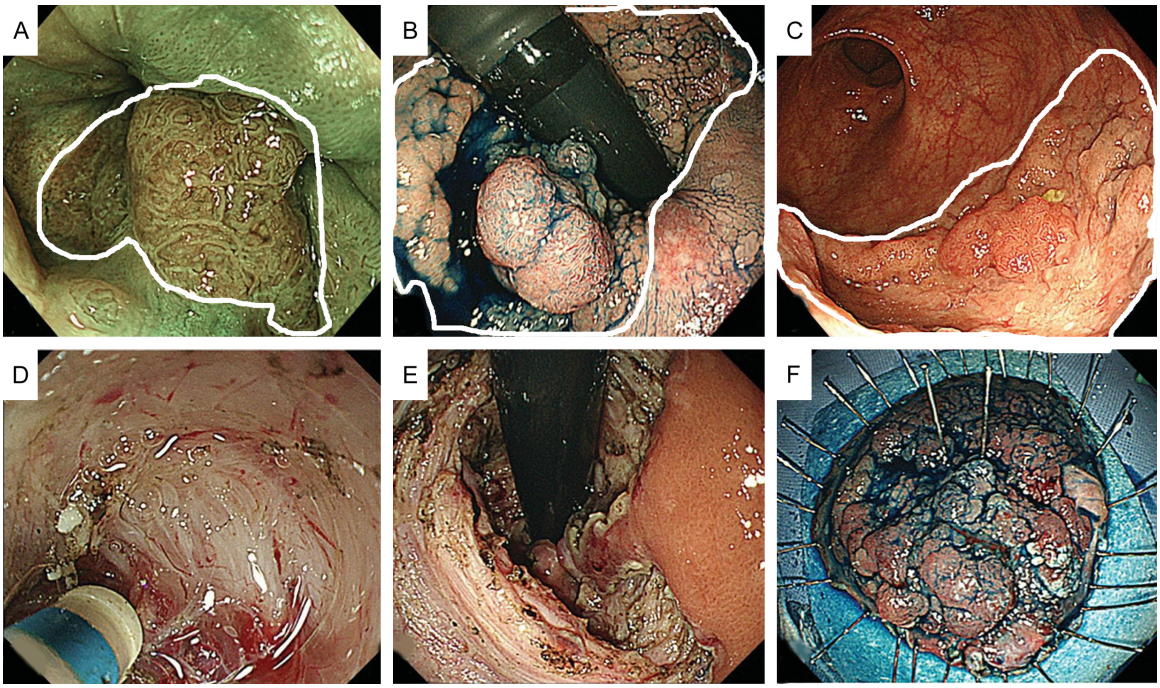

Figure 2. Endoscopic and histological findings of LST-G and ESD procedure. A. The tumor margin at the anal side extends to the dentate line; B and C. Retroflexed and forward view of LST-G, respectively; D. The submucosal dissection was performed just above the muscularis propria layer; E. Retroflexed view after completion of ESD; F. Resection specimen. LST-G, granular-type laterally spreading tumor; ESD, endoscopic submucosal dissection.

To ensure robustness, all 300 patients met the criteria were included in the study and were divided into a train set (n = 200) and a validation set (n = 100). The Shapiro-Wilk test was applied to assess the normality of the distribution for continuous variables. For continuous variables that did not follow a normal distribution, data were reported using the median and interquartile range (IQR), and compared using the nonparametric Mann-Whitney test. Categorical variables were presented as frequencies and percentages, with comparisons conducted using the Chi-squared test or Fisher's exact test where appropriate. Factors associated with non-curative resection and difficult ESD procedures were explored through logistic regression analysis. The identified independent factors were considered as predictors to develop the nomogram model (rms package). The effectiveness of the nomogram was evaluated in both the training and validation sets through receiver operating characteristic (ROC) analyses and calibration curves. Clinical utility in the validation dataset was assessed using decision curve analysis (DCA). All reported *P* values were two-sided, with statistical significance defined as 0.05. The construction of the predictive model for the "risk factors analysis for non-curative resection" was performed using the xgbTree method, which is a well-established gradient boosting tree technique. This method employs classification and regression trees to evaluate the risk factors for non-curative resection.

Results

Characteristics of the population and lesions

Three hundred patients with superficial ultra-low rectal tumors treated by ESD were included in the study. The median patient age was 65 years (IQR, 53-71 years), and the median tumor diameter was 30 mm (IQR, 15-52.5 mm). A detailed summary of the study population and lesion characteristics is provided in **Table 1**. There were no significant differences in patient characteristics between the train set (n = 200) and the validation set (n = 100). At our center, endoscopists are required to perform over 200 colorectal polypectomies before progressing to colorectal ESD procedures. The operator's experience was determined based on the num-

Table 1. Baseline characteristics of patients and tumors

Characteristics	All	Train set	Validation set	*P* value
Age, year, median (IQR)	65 (53-71)	66.5 (57-73)	65 (52-70)	0.533
Gender, n (%)				0.368
Male	158 (52.7)	109 (54.5)	49 (49.0)	
Female	142 (47.3)	91 (45.5)	51 (51.0)	
Family history of CRC, n (%)				0.606
No	282 (94.0)	189 (94.5)	93 (93.0)	
Yes	18 (6.0)	11 (5.5)	7 (7.0)	
ASA classification, n (%)				0.823
1	189 (63.0)	127 (63.5)	62 (62.0)	
2	72 (24.0)	46 (23.0)	26 (26.0)	
3	39 (13.0)	27 (13.5)	12 (12.0)	
Procedure time, min, median (IQR)	55.5 (20-95)	57 (20-103)	50 (15-88)	0.612
Diameter[1], mm, median (IQR)	30 (15-52.5)	32 (20-55)	30 (17.5-50)	0.575
Circumference, n (%)				0.494
< 1/2	232 (77.3)	157 (78.5)	75 (75.0)	
≥ 1/2	68 (22.7)	43 (21.5)	25 (25.0)	
Dentate line invasion, n (%)				0.682
No	163 (54.3)	107 (53.5)	56 (56.0)	
Yes	137 (45.7)	93 (46.5)	44 (44.0)	
Morphology, n (%)				0.389
Protruding tumor/LST-G	228 (76.0)	149 (74.5)	79 (79.0)	
LST-NG	72 (24.0)	51 (25.5)	21 (21.0)	
NICE classification				0.754
Type 1/2	278 (92.7)	186 (93.0)	92 (92.0)	
Type 3	22 (7.3)	14 (7.0)	8 (8.0)	
Surface depression, n (%)				0.342
No	259 (86.3)	170 (85.0)	89 (89.0)	
Yes	41 (13.7)	30 (15.0)	11 (11.0)	
Lifting sign, n (%)				0.532
Good	243 (81.0)	164 (82.0)	79 (79.0)	
Poor	57 (19.0)	36 (18.0)	21 (21.0)	
Histopathology, n (%)				0.077
HGIN	92 (30.7)	68 (34.0)	24 (24.0)	
Cancer	208 (69.3)	132 (66.0)	76 (76.0)	0.560
Intramucosal cancer	142 (47.3)	92 (46.0)	50 (50.0)	
Submucosal cancer	66 (22.0)	40 (20.0)	26 (26.0)	
Infiltration, n (%)				0.237
Mucosa	234 (78.0)	160 (80.0)	74 (74.0)	
Submucosa	66 (22.0)	40 (20.0)	26 (26.0)	

[1]Tumor diameter was the longitudinal length of the lesion. CRC, colorectal carcinoma; ASA classification, American Society of Anesthesiologists Physical Status Classification; LST-G, granular-type laterally spreading tumor; LST-NG, non-granular-type laterally spreading tumors; HGIN, high-grade intraepithelial neoplasia.

ber of colorectal ESD cases completed prior to the current procedure. Using an ROC curve, we established the cutoff value for defining experienced endoscopists at 200 cases.

Table 2. The ESD resection outcomes and adverse events

Outcomes	All	Train set	Validation set	*P* value
Complete resection, n (%)	266 (88.7)	176 (88.0)	90 (90.0)	0.607
Curative resection, n (%)	246 (82.0)	167 (83.5)	79 (79.0)	0.339
Adverse events, n (%)				0.840
Pain	56 (18.7)	38 (19.0)	18 (18.0)	
Bleeding	47 (15.7)	32 (16.0)	15 (15.0)	
Perforation	7 (2.3)	4 (2.0)	3 (3.0)	

ESD, endoscopic submucosal dissection.

ESD related outcomes

The procedural outcomes are presented in **Table 2**. Histologically, the rate of complete and curative resection was 88.7% and 82%, respectively. The common complications were perianal pain and bleeding, occurring in 18.7% and 15.6% of patients, respectively. Perforation only occurred in 7 patients, all of whom received emergency treatment and had an uneventful postoperative course. No significant differences in outcomes were found between the train and validation sets.

For non-curative cases, univariate logistic analysis revealed the association with large lesion diameter, wide circumferential involvement, poor lifting sign, LST-NG, prolonged time, and less colorectal ESD experience. Multivariate logistic analysis showed that the poor lifting sign (OR = 3.282, 95% CI: 1.842-4.305, *P* = 0.026), LST-NG (OR = 2.230, 95% CI: 1.052-4.305, *P* = 0.042), and procedure time ≥ 60 min (OR = 6.976, 95% CI: 2.831-9.445, *P* = 0.010) were the independent risk factors. Additionally, a trend for non-curative resection was also noted in the group of endoscopists with less ESD experience (*P* = 0.052) (**Table 3**). In the development of the predictive model for non-curative resection, we included the significant factors identified through univariate and multivariate analyses. The final model incorporated the following predictors: diameter, circumference, lifting sign, LST-NG morphology and procedure time. The AUC of the predictive model for "Risk factors analysis for non-curative resection" was 0.936 (**Figure 3**).

Predictors associated with technical difficulty

A prolonged duration of ESD is significantly associated with a non-curative resection and has been used as the end point for defining technical difficulty in several studies. Accordingly, we define the ESD time exceeding 60 min as a difficult procedure. The cutoff value was approximately based on the median time [22, 23]. We included patient-related (age and gender), tumor-related (size, location, morphology, lifting sign, NICE classification), and endoscopist experience to identify factors associated with technical difficulty in ESD procedures. All these factors can be assessed before performing ESD. First, we conducted univariate logistic regression analyses for each potential predictor. Variables with a *p*-value < 0.2 in the univariate analysis were then included in the multivariate logistic regression model to adjust for confounding factors. Univariate logistic regression analysis revealed that age (P = 0.047), tumor diameter (P = 0.043, P = 0.003), circumference involvement (P = 0.033), dentate line invasion (P = 0.034), LST-NG morphology, and experience of the endoscopist (P = 0.022) were significantly associated with technical difficulty (**Table 4**). Multivariate logistic regression analysis indicated that larger tumor size (both diameter and circumference), involvement of the dentate line, and limited colorectal ESD experience were significant predictors of procedure difficulty. The odds ratios (ORs) for tumor size between 30-50 mm and ≥ 50 mm were 2.450 (95% CI: 1.621-3.404, *P* = 0.044) and 5.047 (95% CI: 1.593-11.501, *P* = 0.009), respectively. Lesions that exceeding half the circumference (OR = 3.183, 95% CI: 2.126-4.603, *P* = 0.038) and those involving the dentate line (OR = 3.881, 95% CI: 1.713-4.325, *P* = 0.026) were more likely to result in technical difficulty. Additionally, less experience in ESD of the endoscopist was also associated with increased procedural difficulty (OR = 3.415, 95% CI: 1.063-4.107, *P* = 0.032).

Table 3. Risk factors analysis for non-curative resection

Characteristics	Non-curative resection rate	*P* value	Multivariate analysis	
			OR (95% CI)	*P* value
Age[1]				
< 65 years	16.4% (22/134)	0.522	NA	
≥ 65 years	19.3% (32/166)			
Gender				
Male	15.8% (25/158)	0.301	NA	
Female	20.4% (29/142)			
Family history of CRC				
No	27.5% (50/182)	0.632	NA	
Yes	22.2% (4/18)			
ASA classification				
1	15.9% (30/189)	0.189	NA	
2	18.1% (13/72)			
3	28.2% (11/39)			
Diameter[2]				
< 30 mm	13.0% (21/161)	0.009*	Reference	
30-50 mm	19.6% (20/102)		1.882 (0.830-2.732)	0.361
≥ 50 mm	35.1% (13/37)		4.014 (0.967-8.323)	0.221
Circumference				
< 1/2	15.5% (36/232)	0.038*	2.813 (0.621-4.404)	0.261
≥ 1/2	26.5% (18/68)			
Lifting sign				
Good	15.6% (38/243)	0.028	3.282 (1.842-4.305)	0.026*
Poor	28.1% (16/57)			
Dentate line invasion				
No	16.0% (26/163)	0.314	NA	
Yes	20.4% (28/137)			
Surface depression				
No	16.6% (43/259)	0.113	NA	
Yes	26.8% (11/41)			
Morphology				
Protruding/LST-G	15.4% (35/228)	0.033	2.230 (1.052-4.305)	0.042*
LST-NG	26.4% (19/72)			
NICE classification				
Type 1/2	16.9% (47/278)	0.080	NA	
Type 3	31.8% (7/22)			
Procedure time[1]				
< 60 min	13.6% (23/169)	0.025	6.976 (2.831-9.445)	0.010*
≥ 60 min	23.7% (31/131)			
Experience of endoscopist				
< 200 cases	13.2% (22/167)	0.015	2.862 (0.975-4.012)	0.052
≥ 200 cases	24.0% (32/133)			

[1]The cutoff value was defined according to the median. [2]Tumor diameter was the longitudinal length of the lesion. CRC, colorectal carcinoma; OR, odds ratio; 95% CI, 95% confidence interval; LST-G, granular-type laterally spreading tumor; LST-NG, non-granular-type laterally spreading tumors. *P < 0.05.

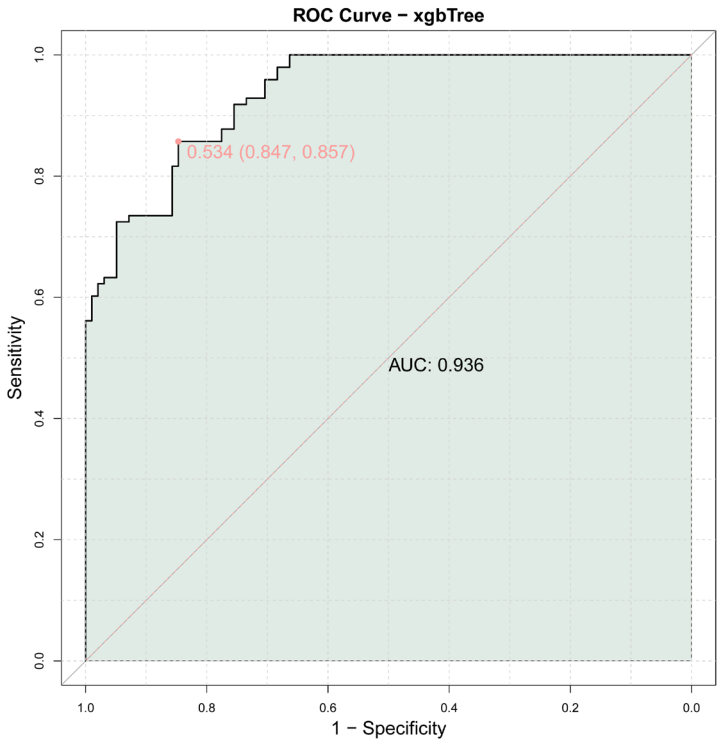

Figure 3. Predictive model for "Risk factors analysis for non-curative resection".

Development and validation of the prediction nomogram

Model development: The model was developed using above predictors and presented as a nomogram (**Figure 4**). Each predictor was assigned points, weighted based on the calculated OR, with the sum placed on a total point scale. The probability of difficult procedures was then correlated with the probability scale vertically.

Model fit and discrimination: The Hosmer-Lemeshow test produced a nonsignificant result (P = 0.193), suggesting good model fit. ROC analysis demonstrated an area under the curve (AUC) of 0.873 (95% CI: 0.830-0.916, P < 0.01) for the train set and 0.810 (95% CI: 0.719-0.900, P < 0.01) for the validation set (**Figure 5A** and **5C**). These results indicate that the model possesses strong discriminatory power. The model's performance was further validated using calibration plots with bootstrap resampling. In these plots, the X-axis represents the predicted probability of difficult ESD for ultra-low rectal tumors, while the Y-axis shows the actual probability. The scatter line labeled "Ideal" represents perfect alignment between predicted and actual probabilities. The dashed line labeled "Apparent" indicates consistency between the calculated one-time predicted probability and the actual probability derived from the model. The "Bias-corrected (solid line)" reflects the average of modeled data after 1000 iterations of self-weighting (bootstrap 1000 repetitions), providing a better and more stable measure of the model. **Figure 5B** and **5D** demonstrate that the bias-corrected lines are closely aligned with the ideal lines, indicating strong agreement between the predicted outcomes and actual observations in both the train and validation sets.

Calibration and clinical applicability: DCA was employed to evaluate the potential clinical applicability. It is a method provides insight into the clinical net benefit based on threshold probability [24]. **Figure 6** showed the DCA for both the predictive nomogram and a model with a single predictor. The nomogram outperformed individual predictors in estimating the risk of difficult procedures across most of the threshold probability range (10-70%).

Discussion

ESD has been widely used for early colorectal tumors and precancerous lesions. Nonetheless, reports focusing on ultra-low rectal ESD remain scarce, showing a significant gap in the literature. Additionally, existing research indicates that anorectal ESD presents greater technical difficulty compared to conventional ESD, often resulting in increased rates of non-curative resections [10, 25]. Non-curative resections can lead to disease recurrence or progression, necessitating additional treatment and adversely affecting prognosis [26].

In this study, we identified that an operation time exceeding 60 min was the most significant risk factor for non-curative resection. This often reflects the meticulous attention and precision

Table 4. Predictors for difficult ESD in the train set

Characteristics	Non-difficult procedure N = 117	Difficult procedure N = 83	Univariate analysis		Multivariate analysis	
			OR (95% CI)	*P* value	OR (95% CI)	*P* value
Age[1], n (%)						
< 65 years	50 (42.7)	24 (28.9)	1.835 (1.007-3.341)	0.047	1.643 (0.878-4.531)	0.342
≥ 65 years	67 (57.3)	59 (71.1)				
Gender, n (%)						
Male	67 (57.3)	42 (50.6)	1.308 (0.743-2.302)	0.352	NA	
Female	50 (42.7)	41 (49.4)				
Diameter[2], n (%)						
< 30 mm	75 (64.1)	36 (43.4)	Reference		Reference	
30-50 mm	35 (30.0)	32 (38.5)	1.905 (1.022-3.550)	0.043	2.450 (1.621-3.404)	0.044*
≥ 50 mm	7 (5.9)	15 (18.1)	4.464 (1.673-11.909)	0.003	5.047 (1.593-11.501)	0.009*
Family history of CRC, n (%)						
No	110 (94.0)	79 (95.2)	0.796 (0.225-2.811)	0.723	NA	
Yes	7 (6.0)	4 (4.8)				
ASA, n (%)						
1	70 (59.8)	57 (68.7)	Reference		NA	
2	30 (25.6)	16 (19.3)	0.655 (0.325-1.319)	0.236		
3	17 (14.6)	10 (12.0)	0.722 (0.307-1.700)	0.456		
Circumference, n (%)						
< 1/2	98 (83.8)	59 (71.1)	2.098 (1.060-4.154)	0.033	3.183 (2.126-4.603)	0.038*
≥ 1/2	19 (16.2)	24 (28.9)				
Dentate line invasion, n (%)						
No	70 (59.8)	37 (44.6)	1.852 (1.048-3.271)	0.034	3.881 (1.713-4.325)	0.026*
Yes	47 (40.2)	46 (55.4)				
Surface depression, n (%)						
No	100 (85.5)	70 (84.3)	1.092 (0.499-2.393)	0.825	NA	
Yes	17 (14.5)	13 (15.7)				
Morphology, n (%)						
Protruding/LST-G	94 (80.3)	55 (66.3)	2.081 (1.093-3.962)	0.026	1.147 (0.927-2.362)	0.480
LST-NG	23 (19.7)	28 (33.7)				
NICE classification, n (%)						
Type 1/Type 2	111 (94.9)	75 (90.4)	1.973 (0.658-5.918)	0.225	NA	
Type 3	6 (5.1)	8 (9.6)				
Experience of endoscopist, n (%)						
< 200 cases	70 (59.8)	36 (43.4)	1.944 (1.099-3.439)	0.022	3.415 (1.063-4.107)	0.032*
≥ 200 cases	47 (40.2)	47 (56.6)				

[1]The cutoff value was defined according to the median. [2]Tumor diameter was the longitudinal length of the lesion. ESD, endoscopic submucosal dissection; CRC, colorectal carcinoma; OR, odds ratio; 95% CI, 95% confidence interval; LST-G, granular-type laterally spreading tumor; LST-NG, non-granular-type laterally spreading tumors. *P < 0.05.

required during marking, dissection steps, and devices exchanges, all of which are closely related to the procedural complexity [27]. The complexity of ESD, especially when dealing with challenging cases, requires sustained concentration and fine motor skills. Exceeding the 60-minute mark often indicates a need for more intricate maneuvers such as precise marking, dissection through fibrotic tissue, and frequent instrument exchanges, which can lead to fatigue and decreased concentration, thereby increasing the probability of incomplete resection and the occurrence of complications [28, 29]. Taken together, it is evident that the therapeutic outcome is influenced by the ESD duration. Therefore, evaluating the anticipated difficulty level preoperatively is imperative to improve both the safety and efficacy of the pro-

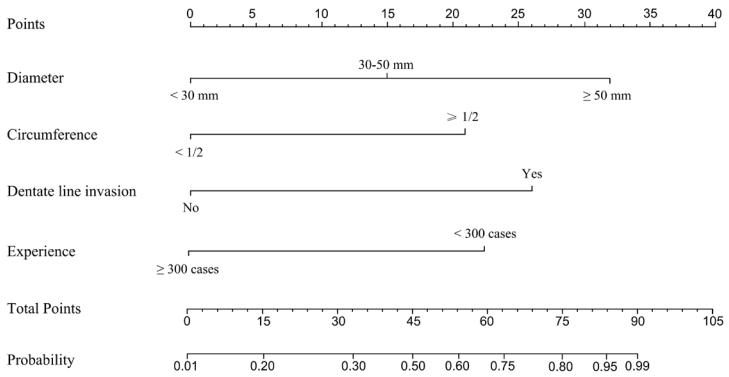

Figure 4. Nomogram model for predicting technical difficulty in ultra-low rectal ESD. ESD, endoscopic submucosal dissection; LST-G, granular-type laterally spreading tumor; LST-NG, non-granular-type laterally spreading tumors.

cedure. Predicting whether the procedure will exceed this 60-minute threshold allows for better planning of the surgical sequence, enhancing time efficiency.

The malignancy of a lesion is a significant factor influencing the difficulty of performing ESD. Our observations suggest a trend towards higher rates of non-curative resections in Type 3 lesions, which are characterized by advanced histopathological features such as deep submucosal invasion, unclear margins, vascular invasion, and extensive fibrosis [30, 31]. These characteristics not only increase the technical challenge but also elevate the risk of complications and incomplete resection. Although our analysis did not reveal a statistically significant correlation, possibly due to the limited number of Type 3 lesions, it highlights the importance of preoperative assessment and planning for complex cases.

The current study observed an increased ESD technical difficulty with larger tumor diameters. This finding aligns with other research, which consistently identifies diameter as a key factor impacting procedural complexity [32-35]. For instance, one study highlighted that tumors with a diameter ≥ 50 mm were a significant independent risk factor for extended procedure time [36]. Similarly, Sato et al. [32] and Mikhail [34] confirmed that larger tumor diameters independently contribute to the difficulty of colorectal ESD. Our results revealed that tumors measuring 30 to 50 mm and those ≥ 50 mm had ORs of 2.450 and 5.047, respectively, for not completing ESD within 60 minutes. Furthermore, larger lesions are associated with higher rates of incomplete endoscopic resection and increased intra- and postoperative adverse events, underscoring the impact of tumor diameter on procedure difficulty [37, 38]. In cases of extensive circumferential involvement, operators must continuously and carefully adjust the dissection direction to ensure complete removal. Li et al. identified lesions with a circumference ≥ 2/3 as the strongest independent factor contributing to the difficulty of colorectal ESD [35]. Another study also indicated that tumors involving more than half of the esophageal circumference predicted greater challenges during esophageal ESD [39]. Collectively, these findings and those of our study demonstrate that larger and more extensive lesions require more time and are more challenging to remove via ESD.

Tumor location is another predictor for difficult colorectal ESD. Previous studies have found that lesions located near Bauhin's valve and in curved areas are more technic demanding [40]. Current study observed the lesions extending into the dentate line in the distal rectum posed greater technical challenges. This finding is supported by Hihara et al. [41] and Andrisani et al. [7], who also reported prolonged procedure durations for tumors located at the dentate line compared to other rectal sites. The challenges are mainly associated with anatomical features: (1) Dentate line serves as the transition area between the squamous epithelium and the skin, with indistinct margins, posing challenges in identifying the lesion [42]; (2) The area is rich in sensory nerves and blood vessels, so accidental damage during procedures may lead to pain and bleeding; (3) The rectum's tortuosity at the anus, combined with the constriction caused by the sphincter muscle, limits the maneuverability of endoscope, thereby impacting the observation and effective procedure [8].

The technical difficulty of ESD was also found to be independently influenced by the relative inexperience of endoscopists. Less experi-

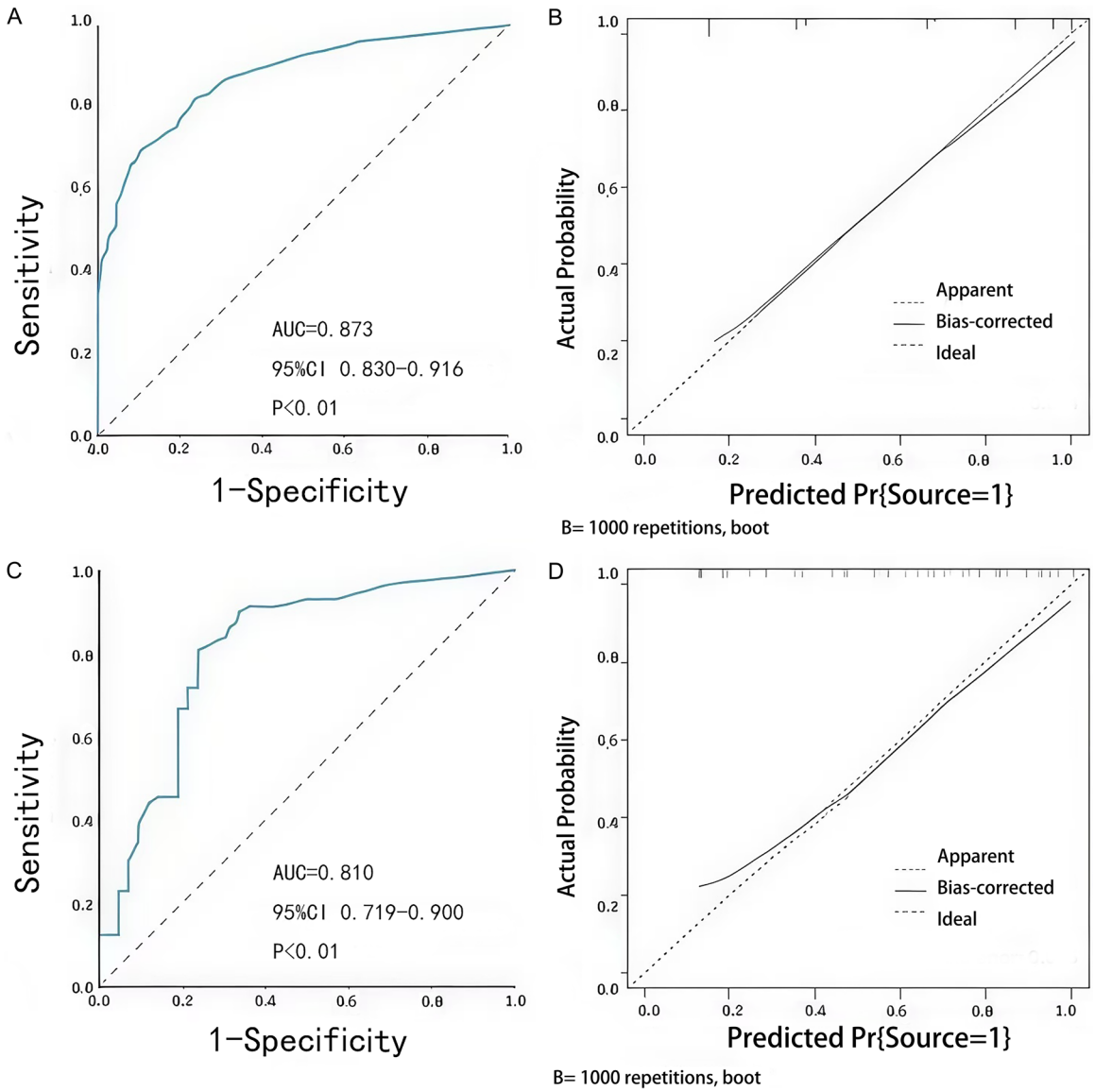

Figure 5. Nomogram validation for predicting technical difficulty. The receiver operating characteristic (ROC) curves based on the nomogram for the probability of difficult ultra-low rectal ESD in the train (A) and validation (C) sets. Calibration curves of the nomogram in the train (B) and validation (D) sets (bootstrap 1000 repetitions). Nomogram-predicted probability of difficult case is plotted on the x-axis, and actual probability is plotted on the y-axis. The dashed line represents a perfect prediction by an ideal model, and the solid line represents the performance of our nomogram, which lays closer to the dashed line, meaning a good performance. 95% CI, 95% confidence interval; AUC, area under the curve.

enced operators may struggle with identifying precise resection margins, handling unexpected complications, and employing advanced techniques efficiently. This lack of proficiency can lead to longer procedural time and poorer outcomes [43]. Therefore, implementing targeted training programs and fostering collaboration among endoscopists with varying levels of experience can help to enhance the overall quality and effectiveness of ESD procedures.

However, this study's retrospective design introduces certain limitations. Firstly, the sample size is relatively small. While it was sufficient for the primary objectives of this study, larger samples from multiple centers could provide additional insights and lead to more robust conclusions. Secondly, characteristics such as morphology and NICE classification were assessed based on the operators' expertise, introducing potential subjectivity and bias.

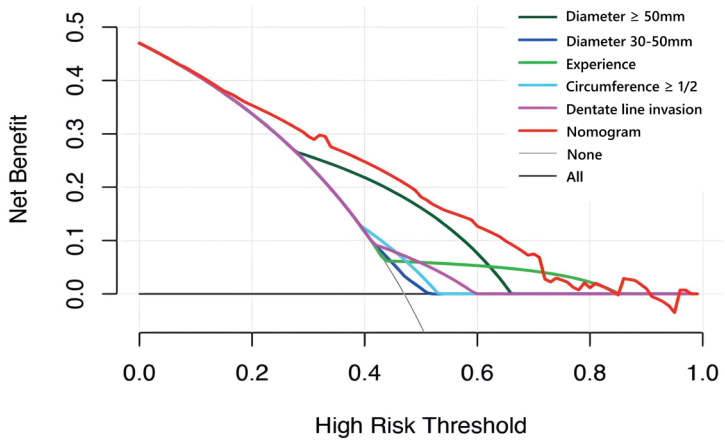

Figure 6. The decision curve analysis (DCA) for the nomogram and that for models with single predictor. The red dashed line represents the nomogram, and other colored lines represent different individual predictors. The curves showed that if the threshold probability is set between 10%-70%, using the nomogram to predict difficulty of colorectal ESD adds more net benefit than any other predictors alone.

Lastly, the study was conducted by the team that developed the model, so external validation by other research teams is recommended.

Conclusions

Poor lifting sign, LST-NG and procedure duration of ≥ 60 min were the risk factors of non-curative resection for ultra-low rectal ESD. The nomogram model, which includes lesion diameter, circumferential involvement, dentate line involvement, and limited colorectal ESD experience as predictors can quantitatively predict the likelihood of a colorectal ESD procedure being difficult.

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Disclosure of conflict of interest

None.

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