Outcomes and Learning Curve in Endoscopic Submucosal Dissection of Rectal Neoplasms with Severe Fibrosis: Experience of a Western Center

Catarina Félix[a]   Pedro Barreiro[a, b]   Rui Mendo[a]   André Mascarenhas[a]
Cristina Chagas[a]

[a]Gastroenterology Department, Centro Hospitalar de Lisboa Ocidental EPE, Lisbon, Portugal; [b]Lisbon Advanced Endoscopic Center, Hospital Lusíadas, Lisbon, Portugal

Abstract

Introduction: Endoscopic submucosal dissection (ESD) of lesions with severe submucosal fibrosis has been associated with worse outcomes, such as lower curative resection rate and higher incidence of adverse events. This study aims to investigate its true impact on rectal ESD performed in the West and to assess predictive factors of severe fibrosis. *Methods:* We conducted a retrospective study including all rectal ESDs performed at our tertiary center from January 2013 to January 2021. Lesions were grouped as nonsevere fibrosis or severe fibrosis. ESD outcomes, predictors of severe fibrosis, and the learning curve were evaluated. *Results:* ESD was performed in 195 lesions, 45 with severe fibrosis. Three resections were interrupted (one due to severe fibrosis). The presence of severe fibrosis was related to a significantly lower resection speed (16.93 mm^2/min vs. 24.66 mm^2/min, p = 0.007), en bloc (86.4% vs. 96.6%, p = 0.019), R0 (61.4% vs. 79.7%, p = 0.013), and curative (54.5% vs. 78.4%, p = 0.003) resection rates and a higher rate of hybrid ESD required to complete resection (13.6% vs. 2.0%, p = 0.005). No significant difference was noted regarding adverse events rate (18.2% vs. 8.1%, p = 0.09). Male sex, ulcerative colitis, pelvic radiotherapy, a lesion on the anastomotic site, previous manipulation, and deep submucosal invasion were independent predictors for severe fibrosis. En bloc resection rate improved during time (60.0% vs. 94.1%, p = 0.018). *Conclusions:* Severe submucosal fibrosis is an important factor related to noncurative resections and challenging rectal ESD. Factors predicting its severity are extremely important and could allow more experienced endoscopists to be assigned to more difficult cases, allowing safer procedures.

© 2022 Sociedade Portuguesa de Gastrenterologia.
Published by S. Karger AG, Basel

Resultados e curva de aprendizagem da disseção endoscópica da submucosa de lesões retais com fibrose severa: experiência de um centro ocidental

Correspondence to:
Catarina Félix, sfelixcatarina@gmail.com

Resumo

Introdução: A disseção endoscópica da submucosa (DES) de lesões com fibrose severa tem sido associada a piores resultados, nomeadamente uma menor taxa de ressecção curativa e maior taxa de complicações. Este estudo tem como objetivo investigar o impacto da fibrose severa na DES de lesões do reto realizada no ocidente e avaliar fatores preditivos de fibrose severa. *Métodos:* Foi realizado um estudo retrospetivo incluindo todas as DES de lesões do reto realizadas no nosso centro entre janeiro de 2013 e janeiro de 2021. As lesões foram agrupadas em lesões sem fibrose severa ou com fibrose severa. Foram analisados os resultados da DES, preditores de fibrose severa e a curva de aprendizagem. *Resultados:* Foi realizada DES em 195 lesões: 45 com fibrose severa. Três resseções foram interrompidas (uma devido a fibrose severa). A presença de fibrose severa associou-se a uma significativa menor velocidade de resseção (16.93 mm²/min vs. 24.66 mm²/min, $p = 0.007$) e significativas menores taxas de excisão em bloco (86.4% vs. 96.6%, $p = 0.019$), R0 (61.4% vs. 79.7%, $p = 0.013$) e curativa (54.5% vs. 78.4%, $p = 0.003$), bem como uma maior taxa de resseção híbrida necessária para completar a excisão (13.6% vs. 2.0%, $p = 0.005$). Não se verificou uma diferença estatisticamente significativa em relação aos efeitos adversos nos dois grupos (18.2% vs. 8.1%, $p = 0.09$). O sexo masculino, a presença de colite ulcerosa, radioterapia pélvica prévia, localização em anastomose, manipulação prévia ou invasão profunda da submucosa foram identificados como fatores preditores de fibrose severa. A taxa de excisão em bloco aumentou ao longo do tempo (60.0% vs. 94.1%, $p = 0.018$). *Conclusão:* A fibrose severa é um importante fator relacionado com excisões não curativas e mais complexas. A identificação de fatores proditores da sua gravidade é de extrema importância e pode permitir a alocação de endoscopistas mais experientes para casos mais difíceis, permitindo procedimentos mais seguros.

© 2022 Sociedade Portuguesa de Gastrenterologia.
Published by S. Karger AG, Basel

Introduction

Endoscopic submucosal dissection (ESD) is a well-established treatment for colorectal lesions, enabling en bloc resection regardless of a lesion's size and morphology and allowing precise assessment of histological curability [1, 2]. However, its implementation in Western countries has been slow and challenging, mainly due to the long learning curve required, higher risk of associated adverse events, lack of structured training programs, few suitable starting cases in the stomach, and lack of experts [3, 4]. As a result, only a handful of centers in Europe have established comprehensive and proficient ESD programs.

When compared to the stomach, colorectal ESD remains technically challenging due to anatomical features of the colon, including thin walls, narrow lumen, and the presence of peristalsis, which are associated with difficulties on the endoscopic maneuverability.

Besides these anatomical features, several studies have shown that submucosal fibrosis, tumor size and location, and paradoxical movements of the endoscope were also related to procedure difficulty during colorectal ESD [5–7]. Severe submucosal fibrosis can complicate the identification of the appropriate submucosal layer and its separation from the muscular layer and has been linked to incomplete resection, lengthy procedure time, and higher rate of perforation [7–12]. It has been related to prior biopsy or tattooing, residual or recurrent lesions, chronic inflammation (such as ulcerative colitis), and tumor invasion of the submucosal layer [12–19]. Simultaneously, large tumor size, lesions across the fold, protruding morphology, nodular-mixed granular lateral spreading tumors (LST G-M), and non-granular pseudo-depressed type LST (LST NG-PD) have inconsistently been identified as preoperative predictors of severe fibrosis [8, 14, 19, 20].

These observations have been obtained from expert centers in Asia, and data on the effect of severe fibrosis on the results of rectal ESD performed in the West, where endoscopic mucosal resection (EMR) is widely performed (predictably resulting in lesions with profound submucosa fibrosis), are lacking.

Therefore, we conducted a retrospective study to compare outcomes of rectal ESD between lesions with severe fibrosis and lesions without severe fibrosis in a European center and examined the learning curve in lesions with severe fibrosis.

Patients and Methods

Patients and Lesions
We reviewed the records of 195 lesions in 192 consecutive patients with rectal neoplasms referred to ESD at our tertiary center at Centro Hospitalar de Lisboa Ocidental between January 2013 and January 2021. All patients had been informed about the risks and benefits of ESD and provided written informed consent.

All ESDs were performed by the same expert endoscopist (P.B.), and lesions were investigated by white light and narrowband imaging to detect signs of invasive cancer and to assess the most optimal endoscopic resection technique.

Fig. 1. Degree of fibrosis of the submucosal layers according to appearance of the layers during submucosa injection. **a** F0. **b** F1. **c** F2.

The endoscopic appearance of the lesions was classified according to the Paris endoscopic classification, and tumors were macroscopically classified as protruding tumors (0-Is) or 1 of the 4 subtypes of LST: LST granular homogeneous (LST G-H), LST G-M, LST non-granular flat-elevated (LST NG-F), and LST NG-PD [21, 22].

Indications for rectal ESD were described in a previous study of our center and were adapted from those proposed by the Colorectal ESD Standardization Implementation Working Group and in accordance with the European Society of Gastrointestinal Endoscopy (ESGE) [23–25]. Those included LST NG ≥20 mm, LST G (mixed type) ≥40 mm, depressed tumors ≥20 mm, lesions with type 2B classification of the Japan Narrow Band Imaging Expert Team (JNET) Classification, and lesions that otherwise cannot be optimally and radically removed by snare-based techniques (i.e., lesions located near or at the dentate line, those with non-lifting sign, prior failed EMR, sporadic localized tumors in chronic inflammation) [26]. Neuroendocrine tumors and subepithelial lesions were excluded.

ESD Procedure
According to the expected procedure time and difficulty, procedures were performed by using conscious sedation (with midazolam and fentanyl), deep sedation, or general anesthesia with endotracheal intubation, at the discretion of the endoscopist and anesthesiologist (if involved). Patients were monitored with continuous electrocardiographic registration, pulse oximetry, and noninvasive blood pressure measurement.

With slight variations, rectal ESD was performed in accordance with our previous report [23]. A single-channel gastroscope (GIF-HQ190; Olympus America, Inc., Center Valley, PA, USA) with a disposable distal attachment (D-201; Olympus, Tokyo, Japan) on the tip and carbon dioxide insufflation were used. DualKnife (KD-650L; Olympus) was routinely used in combination with ITknife nano (KD-612L; Olympus) until the end of June 2017, while from July 2017, the endoscopist mostly used a FlushKnife BT (1.5 mm) (Fujinon-Toshiba ES System Co., Omiya, Japan). The electrosurgical ERBE ICC 200 generator unit (ERBE Elektromedizin, Tubingen, Germany) was set at "Endocut" (effect 3, 60 W) for mucosal incision, "Forced Coag" (45–55 W) for submucosal dissection, and "Soft Coagulation" for hemostasis (45–55 W). During submucosal dissection of areas with severe fibrosis, "Endocut" was used at the discretion of the endoscopist. Submucosal injection was per-

formed using a mixture of 4% gelatin solution (Gelofundin 4%, B. Braun Melsungen AG, Germany), indigo carmine and adrenaline (1:250,000). Hemostatic forceps (Coagrasper, FD-411UR, Olympus) were used if hemostasis by the knife in use was ineffective.

When the presence of severe submucosal fibrosis was predicted, the tunneling technique was performed ad initium. Whenever submucosal fibrosis was not predicted and was encountered during the procedure, different strategies were used, including tunneling technique, pocket-creation method, or rarely clip with line to assist traction, which have been described elsewhere [27–29]. In cases where ESD had to be abandoned, a conversion to EMR (Hybrid ESD) was considered.

Classification of Fibrosis
Submucosal fibrosis was evaluated based on findings obtained at the time of submucosal injection and dissection. The degree of submucosal fibrosis was classified into 3 types (F0–2): F0 – no fibrosis, which is demonstrated as a blue transparent layer; F1 – mild fibrosis, which appeared as a white web-like structure in the blue submucosal layer; and F2 – severe fibrosis, which appeared as a white muscular-like structure without a blue transparent layer in the submucosal layer (Fig. 1) [8].

Patients were divided into F0/F1 (nonsevere fibrosis) and F2 (severe fibrosis) groups.

Histopathology Assessment
The resected tissue specimens were pinned on cork after removal and fixed using 4% neutral buffered formalin, before being sent to the pathology department. In cases of piecemeal resections, if possible, the specimen was reconstructed by appropriate fixation onto cork. Histological evaluation was performed in accordance with ESGE guidelines [25, 30].

Outcome Measures and Definitions
Procedure time was defined as the time from mucosal incision to complete removal of the lesion. Resection speed was defined as square millimeter resected per minute (mm^2/min), calculated from the surface area (specimen diameter in long axis × specimen diameter in short axis × π × 0.25) divided by the procedure time [3].

En bloc resection was considered when the tumor was resected as a single piece with macroscopic evidence of complete lesion removal. Resection was considered complete (defined as R0) when

the tumor was removed en bloc with horizontal (at least 1 mm tumor free) and vertical margins tumor free. Resection was considered incomplete when tumors were removed in fragments (piecemeal), horizontal margins were positive (less than 1 mm tumor free), or margins could not be evaluated due to artificial burn effect (RX). When the vertical margin was positive for carcinoma, resection was defined as R1 [25].

Resection was considered curative when an en bloc R0 resection of a superficial lesion with histology no more advanced than a well-differentiated adenocarcinoma (G1/G2), <1 mm submucosal invasion, and with no lymphovascular invasion was achieved [25].

Learning Curve

For an analysis of the learning curve in lesions with severe fibrosis, the study time was divided into 2 periods: first period with resections 1–10 and second period with resections 11–44.

Adverse Events and Post-ESD Management

Perforation was diagnosed either when the muscle layer was injured, and the peritoneal cavity was observed endoscopically, or when free air was found on a plain abdominal radiograph or computed tomography image. Intraoperative bleeding was considered a *major* adverse event when it required special measures, such as emergency surgery, intraoperative blood transfusion, or vasopressor therapy, or when it led to the premature termination of the procedure. Intraoperative bleeding was considered a *minor* adverse event when it changed the procedure plan (e.g., use of hemoclips) or took ≥5 min to be controlled by endoscopy (without meeting criteria for *major* bleeding). Delayed bleeding was defined when clinical bleeding signs were observed (rectal bleeding or hemoglobin drop >2 g/L) until 30 days after ESD.

Noncurative resections were discussed in a multidisciplinary team and decision regarding subsequent management was made on a case-by-case basis and according to the patient's preferences. In curative resections, initially, all patients underwent surveillance endoscopy at 3–6 months after the index treatment, and 12 months after that surveillance if no recurrence was found [25]. However, as new evidence appeared, when a curative resection was observed, patients underwent surveillance endoscopy at 12 months after the index treatment [31]. After piecemeal resection or with presence of positive lateral margins without indication for surgery, colonoscopy was performed at 3–6 months [25]. In endoscopic surveillance, a residual disease was defined as the presence of a lesion at the same place where ESD was performed following a non-R0 resection, found in the first or second endoscopic control; after this period or if resection was R0, it was considered local recurrence.

Statistical Analysis

Categorical variables are presented as frequencies and percentages, and continuous variables as means and standard deviations, or median and interquartile ranges for skewed distributions. Continuous parameters were analyzed using Student's t test or the Mann-Whitney U test, whereas categorical variables were compared using the χ^2 test and Fisher's exact test, as appropriate. Multivariable logistic regression analysis was performed to assess factors predicting severe fibrosis. Odds ratios (OR) and 95% confidence intervals (95% CI) were calculated for each variable. Variables were included on the multivariable model and retained in the final model if the p value was <0.1 on univariate analysis.

All reported p values are two-tailed, with a p value of 0.05 indicating statistical significance. Analyses were performed with the use of SPSS software, version 23 (IBM Corp.; Armonk, NY, USA).

Results

Patients and Lesion Characteristics

A total of 195 lesions from 192 patients were evaluated (mean age 68.0 ± 11.0 years; 63.6% male). Median tumor size was 40 mm(IQR 27), and lesions were mainly located on the distal rectum (n = 99, 50.8%). Granular-type LST was the most common macroscopic type (n = 140, 71.8%; nodular mixed granular type n = 103, homogeneous granular type n = 37), followed by protruding type (n = 34, 17.4%) and nongranular type (n = 21, 10.8%; flat type n = 13, pseudodepressed n = 8). Three patients had 2 lesions that were simultaneously resected by ESD and 1 patient with noncurative ESD resection had a recurrence treated by ESD. Among the 195 lesions, 150 (76.9%) had no fibrosis or mild fibrosis (F0/F1 group), and 45 (23.1%) had severe fibrosis (F2 group). Resection could not be completed in 3 patients, 2 due to deep submucosal invasion diagnosed during ESD, and 1 due to severe fibrosis, and these were not included in the outcomes analysis. Baseline characteristics are shown in Table 1.

Table 2 shows ESD outcomes of the 192 lesions included (148 in the F0/F1 group and 44 in the F2 group). The median procedure time was 75 min (IQR 85). The overall en bloc, R0, and curative resection rates were 94.3%, 75.5%, and 72.9%, respectively. For tumors considered to have noncurative resections (n = 52), most comprised adenomatous lesions with a positive or no evaluable horizontal margin (n = 34) and 18 had deep submucosal invasion, 5 of which had a positive vertical margin. Hybrid ESD was necessary in 9 (4.7%) resections. Adverse events were observed in 20 patients (10.4%) and included intraoperative *minor* bleeding in 9 procedures (4.6%), delayed bleeding in 7 procedures (3.6%), and perforation in 3 procedures (1.6%); 1 patient had the procedure complicated by both intraoperative *minor* bleeding and perforation (0.5%). No adverse event required surgery or discontinuation of the ESD procedure. Additional surgery with lymphadenectomy was performed in 3 patients who underwent noncurative resections; none of these patients had lymph node metastasis.

Félix/Barreiro/Mendo/Mascarenhas/
Chagas

Table 1. Baseline characteristics of included patients and lesions and multivariable analysis of predictive factors for severe submucosal fibrosis

Baseline	All (n = 195)	F0/F1 (n = 150)	F2 (n = 45)	p value	Adjusted OR (95% CI)*
Age, mean (SD), years	68.0 (11.0)	67.6 (11.1)	69.5 (10.6)	0.308	
Male sex, n (%)	124 (63.6)	87 (58.0)	37 (82.2)	0.003	12.275 (1.410–106.829)
Conditions (ulcerative colitis, pelvic radiotherapy, lesion on anastomotic site), n (%)	11 (5.6)	4 (2.7)	7 (15.6)	0.004	13.357 (2.215–80.568)
Size, median (IQR), mm	40.0 (27)	44.5 (30)	36.0 (26)	0.044	0.993 (0.973–1.013)
Diameter >40 mm, n (%)	103 (52.8)	83 (55.3)	20 (44.4)	0.199	
Location, n (%)				0.557	
Distal rectum	99 (50.8)	73 (48.7)	26 (57.8)		
Medium rectum	52 (26.7)	42 (28.0)	10 (22.2)		
Proximal rectum	44 (22.6)	35 (23.3)	9 (20.0)		
Paris classification, n (%)				0.301	
Is	33 (16.9)	22 (14.7)	11 (24.4)		
IIa	83 (42.6)	62 (41.3)	21 (46.7)		
Is + IIa	23 (11.8)	18 (12.0)	5 (11.1)		
IIa + Is	46 (23.6)	40 (26.7)	6 (13.3)		
IIa + IIc	10 (5.1)	8 (5.3)	2 (4.4)		
Morphology, n (%)				0.039	
LST G-M	103 (52.8)	86 (57.3)	17 (37.8)		1
LST G-H	37 (19.0)	25 (16.7)	12 (26.7)		0.340 (0.057–2.009)
LST NG-F	13 (6.7)	8 (5.3)	5 (11.1)		0.781 (0.080–7.616)
LST NG-PD	8 (4.1)	8 (5.3)	0 (0)		0
Protruded	34 (17.4)	23 (15.3)	11 (24.4)		0.713 (0.149–3.405)
Previous manipulation (EMR attempt/residual or recurrent lesion), n (%)	30 (15.4)	2 (1.3)	28 (62.2)	<0.001	663.320 (57.162–7,697.335)
Previous tattoo, n (%)	5 (2.6)	2 (1.3)	3 (6.7)	0.082	0.772 (0.003–189.494)
Previous biopsies, n (%)	45 (23.1)	35 (23.3)	10 (22.2)	0.877	
Histology, n (%)				–	
Adenoma	171 (87.7)	136 (90.7)	35 (77.8)		
Superficial SM carcinoma	4 (2.0)	4 (2.6)	0 (0)		
Deep SM carcinoma	20 (10.3)	10 (6.7)	10 (22.2)		
Deep SM invasion, n (%)	20 (10.3)	10 (6.7)	10 (22.2)	0.003	11.558 (2.865–46.627)
Interrupted, n (%)	3 (1.5)	2 (1.3)	1 (2.2)	0.547	

SD, standard deviation; IQR, interquartile range; LST G-M, lateral spreading tumor granular nodular-mixed; LST G-H, LST granular homogeneous; LST NG-F, LST non-granular flat-elevated; LST NG-PD, LST non-granular pseudodepressed; EMR, endoscopic mucosal resection; SM, submucosal. * Variables with p value <0.1 on univariable analysis were included in the model.

Severity of Submucosal Fibrosis, Lesion Characteristics, and Procedure Results

Compared to lesions with nonsevere fibrosis, lesions with severe fibrosis were significantly smaller (F2 group: mean size 36 mm, IQR 26; F0/F1 group: mean size 44.5 mm, IQR 30; $p = 0.044$) and were more frequently associated with deep submucosal invasion (22.2% vs. 6.7%, $p = 0.003$) (Table 1). There was a significant difference between groups concerning a predisposition for severe fibrosis in the presence of previous conditions (ulcerative colitis, pelvic radiotherapy, or a lesion on an anastomotic site) (15.6% vs. 2.7%, $p = 0.004$) and previous manipulation, such as a previous EMR attempt or a residual or recurrent lesion (62.2% vs. 1.3%, $p < 0.001$). Regarding morphology, most lesions in the F2 group were LST G-M

(37.8%), followed by LST G-H (26.7%) and protruded lesions (24.4%). No significant difference was found between the two groups regarding patient age, tumor location, previous tattooing, or pretreatment biopsies. The discontinuation rate was 2.2% in the F2 group and 1.3% in the F0/F1 group ($p = 0.547$).

No difference was observed regarding total procedure time between the F0/F1 and F2 groups (75 vs. 75 min, $p = 0.474$); however, for lesions in the F2 group, resection speed was lower (16.93 mm^2/min vs. 24.66 mm^2/min, $p = 0.007$) (Table 2). Severe fibrosis was associated with significantly lower rates of en bloc (86.4% vs. 96.6%, $p = 0.019$), R0 (61.4% vs. 79.7%, $p = 0.013$), and curative (54.5% vs. 78.4%, $p = 0.003$) resection. A significantly higher rate of hybrid ESD was required to complete resec-

Table 2. Outcome of rectal ESD according to degree of fibrosis

Baseline	All (n = 192)	F0/F1 (n = 148)	F2 (n = 44)	p value
Procedure time, median (IQR), min	75 (85)	75 (85)	75 (85)	0.474
Resection speed, median (IQR), mm^2/min	23.25 (26.63)	24.66 (28.17)	16.93 (21.21)	0.007
En bloc resection, n (%)	181 (94.3)	143 (96.6)	38 (86.4)	0.019
R0 resection, n (%)	145 (75.5)	118 (79.7)	27 (61.4)	0.013
R1 resection, n (%)	5 (2.6)	2 (1.4)	3 (6.8)	0.081
RX resection, n (%)	42 (21.9)	28 (18.9)	14 (31.8)	0.069
Curative resection, n (%)	140 (72.9)	116 (78.4)	24 (54.5)	0.003
Hybrid method, n (%)	9 (4.7)	3 (2.0)	6 (13.6)	0.005
Adverse events, n (%)	20 (10.4)	12 (8.1)	8 (18.2)	0.087
Perforation	4 (2.1)	3 (2.0)	1 (2.3)	1

IQR, interquartile range.

Table 3. Learning curve of lesions with severe fibrosis

Baseline	First period (1–10)	Second period (11–44)	p value
Procedure time, median (IQR), min	117.5 (69)	70 (83)	0.11
Resection speed, median (IQR), mm^2/min	5.94 (5.64)	21.99 (20.31)	0.007
En bloc resection rate, n (%)	6 (60.0)	32 (94.1)	0.018
R0 resection rate, n (%)	7 (70.0)	20 (58.8)	0.716
Curative resection rate, n (%)	6 (60.0)	18 (52.9)	0.734
Hybrid method, n (%)	5 (50.0)	1 (2.9)	0.001
Adverse events, n (%)	2 (20)	6 (17.6)	1
Perforation	0 (0)	1 (2.9)	1

IQR, interquartile range.

tion in the F2 group (13.6% vs. 2.0%, p = 0.005). Adverse events were more commonly observed in the F2 group (18.2% vs. 8.1%, p = 0.087), but this did not reach statistical significance.

Predictive Factors of Severe Fibrosis

Multiple logistic regression analysis was performed to identify independent factors predictive of severe fibrosis. Male sex (OR 12.275; 95% CI 1.410–106.829), the presence of previous conditions (ulcerative colitis, pelvic radiotherapy, or a lesion on the anastomotic site) (OR 13.357; 95% CI 2.215–80.568), previous EMR attempt or residual/recurrent lesions (OR 663.320; 95% CI 57.162–7,697.335), and deep submucosal invasion (OR 11.558; 95% CI 2.865–46.627) were identified as independent predictors of severe fibrosis (Table 1).

Learning Curve of Lesions with Severe Fibrosis

Based on the analysis according to earlier and later periods (10 and 34 lesions, respectively), procedure time improved (earlier period, median 117.5 min; later period, median 70 min; p = 0.11) and resection speed improved significantly (earlier period, median 5.94 mm^2/min; later period, median 21.99 mm^2/min; p = 0.007). En bloc resection rate was significantly higher in the later period (earlier vs. later, 60.0% vs. 94.1%, p = 0.018), and R0 and curative resection rates were nonsignificantly lower in the later period (earlier vs. later, 70.0% vs. 58.8%, p = 0.716, and 60.0% vs. 52.9%, p = 0.734, respectively). A significantly lower rate of hybrid ESD was required to complete resection in the later period (earlier vs. later, 50.0% vs. 2.9%, p = 0.001). Adverse events were reduced nonsignificantly over time (earlier vs. later, 20.0% vs. 17.6%, p = 1) (Table 3).

Long-Term Prognosis after Noncurative ESD

No residual disease nor local recurrence was found in patients with curative resections. Among the 52 patients with noncurative resections, 34 comprised adenomatous lesions with a positive or no evaluable horizontal margin,

and during a mean follow-up of 27.3 months, 2 local recurrences were observed and treated endoscopically. The remaining 18 patients had lesions with deep submucosal invasion, and 3 were submitted to salvage surgery with lymphadenopathy (specimen analysis revealed no residual tumor and no lymph node metastasis), 6 were submitted to adjuvant therapy with radiotherapy (with or without chemotherapy), and 9 patients were kept on surveillance; during a mean follow-up of 20.8 months, 1 recurrence was diagnosed and endoscopically treated.

Discussion

In this retrospective study, we aimed to determine whether the presence of severe fibrosis would interfere with the clinical outcomes of rectal ESD. Results of our study demonstrated that the presence of severe fibrosis in submucosa is associated with a lower resection speed (16.93 mm²/min vs. 24.66 mm²/min), lower rates of en bloc (86.4% vs. 96.6%), R0 (61.4% vs. 79.7%), and curative resections (54.5% vs. 78.4%), and higher rate of hybrid ESD required to complete resection (13.6% vs. 2.0%). In our study, no difference was observed in procedure time (75 min), probably because lesions with severe fibrosis were smaller than those without severe fibrosis. Overall, our R0 and curative resection rates were low (75.5% and 72.9%, respectively), especially when compared to our high en bloc resection rate (94.3%). This may be explained by our conservative definition of R0 resection, in which we only considered R0 in the presence of a horizontal margin of at least 1 mm tumor free, contrarily to definitions presented in other studies where only a lateral margin free of tumor was needed to be considered a complete resection [2]. Consequently, despite our low R0 and curative resection rates in lesions with severe fibrosis, only 1 patient developed local recurrence in the nonmalignant group, which was manageable endoscopically; simultaneously, in the noncurative group, due to deep submucosal invasion, only 1 patient presented with local recurrence, which was once again treated endoscopically. We observed a higher rate of adverse events in the excision of lesions with severe fibrosis (18.2% vs. 8.1%); however, all adverse events were *minor* and were solved conservatively or endoscopically.

Our results reinforce the necessity of accurately predicting fibrosis prior to rectal ESD, as this would allow a more experienced endoscopist to be assigned to more difficult cases, allowing safer procedures. Simultaneously, it would allow some considerations to be taken during the procedure, such as the performance of the initial mucosal incision further away from the lesion than usual, the exposure in advance of the fibrotic areas by thoroughly dissecting the surrounding nonfibrotic submucosa, the utilization of different settings on the electrosurgical generator unit, and the use of traction methods or alternative strategies to assist the dissection. In a retrospective study, Yoshida et al. [32] described the utilization of the pocket-creation method as an aid for lesions with severe fibrosis, allowing a safer and accurate dissection of the fibrosis and resulting in higher en bloc resection rates, shortened procedure time, and reduced discontinuation rate. Several studies have tried to preoperatively predict fibrosis, mainly based on the morphology of the lesion; however, their results are inconsistent. Matsumoto et al. [8] reported an incidence of F2 fibrosis in LST G-M that was significantly higher than that in LST G-H, Chiba et al. [14] found LST NG-PD to be an independent predictor of fibrosis, and Kaosombatwattana et al. [20] observed that tumors with protruding morphology carried a higher possibility of severe fibrosis. In our study, no morphological aspects were associated with the presence of severe fibrosis, possibly related to the small number of cases. Some studies have reported the influence of preoperative biopsy for rectal lesions on ESD. Fukunaga et al. [13] reported that preoperative biopsies tended to cause F2 fibrosis in the submucosal layer. In our study, no difference was found between the two groups (F0/F1 and F2) regarding preoperative biopsies. However, it should be mentioned that most lesions were referred from other institutions to ESD in our center, hampering the correct assessment of previous biopsies. Makino et al. [33] tried to propose endoscopic ultrasonography as a means to preoperatively assess submucosal fibrosis; however, endoscopic ultrasonography in LST showed only moderate sensitivity and low specificity (77.8% and 57.1%, respectively) for the prediction of fibrosis; as a result, its relevance is still undefined. In our study, severe submucosal fibrosis was independently associated with male sex, the presence of previous conditions, such as ulcerative colitis, pelvic radiotherapy, or a lesion located on an anastomotic site, previous manipulation (EMR attempt and residual or recurrent lesion), and deep submucosal invasion. Nevertheless, our confidence interval was large, due to the small sample size of our study, and caution should be taken when interpreting the results.

We analyzed our learning curve during ESD performed in lesions with severe fibrosis. As expected, procedure time and hybrid ESD decreased, and procedure speed and en bloc resection rate increased over time.

Contrary to our predictions, a nonsignificant reduction in R0 and curative resection rates over time was noted. This may be explained by an increase in the complexity of lesions removed by ESD in our center over time. As our experience increased, more complex cases were referred. As an example, we performed ESD for coalescent polyps located in the anal transitional zone after restorative proctocolectomy and ileal-pouch anal anastomosis in a patient with familiar adenomatous polyposis [34].

Our study has several limitations. First, it is a single-center retrospective study and is limited by a small sample size, especially for subgroup analysis. Second, we evaluated the degree of fibrosis based on endoscopic findings during the procedure. Histopathological assessment may be more objective than clinical assessment, which depends on the judgment of the operator; however, many studies reported clinical evaluation of the degree of fibrosis by the endoscopist during the procedure [8, 10–13, 19]. Histological assessment may be influenced by the dissection procedure, the depth of the dissection, or thermal injury by electrocoagulation [13]. Therefore, histologic severity of fibrosis does not necessarily reflect endoscopic severity, and subsequently its clinical relevance. Third, we have a mean follow-up of about 2 years, which might limit the evaluation of recurrence, particularly metastatic disease. A main strength of our study was the performance of all the procedures by the same endoscopist, circumventing performance variation between different endoscopists. However, caution should be taken when extrapolating the results.

In conclusion, ESD is a safe and effective treatment for complete resection of lesions with severe fibrosis, despite being associated with lower en bloc, R0, and curative resection rates, even with expert endoscopists. The presence of ulcerative colitis, pelvic radiotherapy, a lesion located on an anastomotic site, or previous manipulation can preoperatively help to predict cases with severe fibrosis. To the best of our knowledge, this is the first European study to assess the relevance of severe fibrosis on the ESD outcomes and the learning curve of lesions with severe fibrosis.

Statement of Ethics

The study was conducted in accordance with the Declaration of Helsinki for Medical Research Involving Human Subjects, and all patients provided written informed consent. Due to the retrospective design, it was waived by the ethical committee.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

There is no funding source to report.

Author Contributions

Catarina Félix and Pedro Barreiro were involved in the conception and design of the study, analysis and interpretation of the data; Catarina Félix wrote the article; all authors critically revised the article and approved its final version.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further enquiries can be directed to the corresponding author.

References

1 Fujishiro M, Yahagi N, Kakushima N, Kodashima S, Muraki Y, Ono S, et al. Outcomes of endoscopic submucosal dissection for colorectal epithelial neoplasms in 200 consecutive cases. Clin Gastroenterol Hepatol. 2007 Jun;5(6):678–83.

2 Lee EJ, Lee JB, Lee SH, Kim DS, Lee DH, Lee DS, et al. Endoscopic submucosal dissection for colorectal tumors: 1,000 colorectal ESD cases – one specialized institute's experiences. Surg Endosc. 2013 Jan;27(1):31–9.

3 Rönnow CF, Uedo N, Toth E, Thorlacius H. Endoscopic submucosal dissection of 301 large colorectal neoplasias: outcome and learning curve from a specialized center in Europe. Endosc Int Open. 2018 Nov;6(11):C5.

4 Probst A, Golger D, Anthuber M, Märkl B, Messmann H. Endoscopic submucosal dissection in large sessile lesions of the rectosigmoid: learning curve in a European center. Endoscopy. 2012 Jul;44(7):660–7.

5 Imai K, Hotta K, Yamaguchi Y, Kakushima N, Tanaka M, Takizawa K, et al. Preoperative indicators of failure of en bloc resection or perforation in colorectal endoscopic submucosal dissection: implications for lesion stratification by technical difficulties during stepwise training. Gastrointest Endosc. 2016 May;83(5):954–62.

6 Sato K, Ito S, Kitagawa T, Kato M, Tominaga K, Suzuki T, et al. Factors affecting the technical difficulty and clinical outcome of endoscopic submucosal dissection for colorectal tumors. Surg Endosc. 2014 Oct;28(10):2959–65.

7 Isomoto H, Nishiyama H, Yamaguchi N, Fukuda E, Ishii H, Ikeda K, et al. Clinicopathological factors associated with clinical outcomes of endoscopic submucosal dissection for colorectal epithelial neoplasms. Endoscopy. 2009 Aug;41(8):679–83.

8 Matsumoto A, Tanaka S, Oba S, Kanao H, Oka S, Yoshihara M, et al. Outcome of endoscopic submucosal dissection for colorectal tumors accompanied by fibrosis. Scand J Gastroenterol. 2010 Nov;45(11):1329–37.

9 Kim ES, Cho KB, Park KS, Lee KI, Jang BK, Chung WJ, et al. Factors predictive of perforation during endoscopic submucosal dissection for the treatment of colorectal tumors. Endoscopy. 2011 Jul;43(7):573–8.

10 Hayashi N, Tanaka S, Nishiyama S, Terasaki M, Nakadoi K, Oka S, et al. Predictors of incomplete resection and perforation associated with endoscopic submucosal dissection for colorectal tumors. Gastrointest Endosc. 2014 Mar;79(3):427–35.

11 Kim EK, Han DS, Ro Y, Eun CS, Yoo KS, Oh YH. The submucosal fibrosis: what does it mean for colorectal endoscopic submucosal dissection? Intest Res. 2016;14(4):358–64.

12 Lee SP, Kim JH, Sung IK, Lee SY, Park HS, Shim CS, et al. Effect of submucosal fibrosis on endoscopic submucosal dissection of colorectal tumors: pathologic review of 173 cases. J Gastroenterol Hepatol. 2015 May;30(5):872–8.

13 Fukunaga S, Nagami Y, Shiba M, Sakai T, Maruyama H, Ominami M, et al. Impact of preoperative biopsy sampling on severe submucosal fibrosis on endoscopic submucosal dissection for colorectal laterally spreading tumors: a propensity score analysis. Gastrointest Endosc. 2019 Mar;89(3):470–8.

14 Chiba H, Tachikawa J, Arimoto J, Ashikari K, Kuwabara H, Nakaoka M, et al. Predictive factors of mild and severe fibrosis in colorectal endoscopic submucosal dissection. Dig Dis Sci. 2020 Jan;65(1):232–42.

15 Iacopini F, Saito Y, Yamada M, Grossi C, Rigato P, Costamagna G, et al. Curative endoscopic submucosal dissection of large nonpolypoid superficial neoplasms in ulcerative colitis (with videos). Gastrointest Endosc. 2015 Oct;82(4):734–8.

16 Chiba H, Tachikawa J, Kurihara D, Ashikari K, Takahashi A, Kuwabara H, et al. Successful endoscopic submucosal dissection of colon cancer with severe fibrosis after tattooing. Clin J Gastroenterol. 2017 Oct;10(5):426–30.

17 Kuroha M, Shiga H, Kanazawa Y, Nagai H, Handa T, Ichikawa R, et al. Factors associated with fibrosis during colorectal endoscopic submucosal dissection: does pretreatment biopsy potentially elicit submucosal fibrosis and affect endoscopic submucosal dissection outcomes? Digestion. 2021 Aug;102(4):590–8.

18 Tanaka H, Oka S, Tanaka S, Nagata S, Kunihiro M, Kuwai T, et al. Salvage endoscopic submucosal dissection for local residual/recurrent colorectal tumor after endoscopic resection: large multicenter 10-year study. Dig Endosc. 2021 May;33(4):608–15.

19 Inada Y, Yoshida N, Kugai M, Kamada K, Katada K, Uchiyama K, et al. Prediction and treatment of difficult cases in colorectal endoscopic submucosal dissection. Gastroenterol Res Pract. 2013;2013:523084.

20 Kaosombatwattana U, Yamamura T, Limsrivilai J, Nakamura M, Leelakusolvong S, Hirooka Y, et al. Preoperative endoscopic predictors of severe submucosal fibrosis in colorectal tumors undergoing endoscopic submucosal dissection. Endosc Int Open. 2019 Apr;7(4):E421–30.

21 Participants in the Paris Workshop. The Paris endoscopic classification of superficial neoplastic lesions: esophagus, stomach, and colon – November 30 to December 1, 2002. Gastrointest Endosc. 2003 Dec;58(6 Suppl):S3–43.

22 Kudoei S, Lambert R, Allen JI, Fujii H, Fujii T, Kashida H, et al. Nonpolypoid neoplastic lesions of the colorectal mucosa. Gastrointest Endosc. 2008 Oct;68(4 Suppl):S3–47.

23 Rodrigues J, Carmo J, Carvalho L, Barreiro P, Chagas C. Endoscopic submucosal dissection for gastrointestinal superficial lesions: initial experience in a single Portuguese center. GE Port J Gastroenterol. 2015 Sep;22(5):190–7.

24 Uraoka T, Parra-Blanco A, Yahagi N. Colorectal endoscopic submucosal dissection: is it suitable in western countries? J Gastroenterol Hepatol. 2013 Mar;28(3):406–14.

25 Pimentel-Nunes P, Dinis-Ribeiro M, Ponchon T, Repici A, Vieth M, de Ceglie A, et al. Endoscopic submucosal dissection: European Society of Gastrointestinal Endoscopy (ESGE) guideline. Endoscopy. 2015 Aug;47(9):829–54.

26 Sano Y, Tanaka S, Kudo SE, Saito S, Matsuda T, Wada Y, et al. Narrow-band imaging (NBI) magnifying endoscopic classification of colorectal tumors proposed by the Japan NBI expert team. Dig Endosc. 2016 Jul;28(5):526–33.

27 Imai K, Hotta K, Yamaguchi Y, Hirasawa K, Ito S, Kawata N, et al. Submucosal tunneling technique using insulated-tip knife in complete circumferential endoscopic submucosal dissection. Gastrointest Endosc. 2016 Oct;84(4):742.

28 Hayashi Y, Sunada K, Takahashi H, Shinhata H, Lefor AT, Tanaka A, et al. Pocket-creation method of endoscopic submucosal dissection to achieve en bloc resection of giant colorectal subpedunculated neoplastic lesions. Endoscopy. 2014;46(Suppl 1 UCTN):E421–2.

29 Tsuji K, Yoshida N, Nakanishi H, Takemura K, Yamada S, Doyama H. Recent traction methods for endoscopic submucosal dissection. World J Gastroenterol. 2016;22(26):5917–26.

30 Ferlitsch M, Moss A, Hassan C, Bhandari P, Dumonceau JM, Paspatis G, et al. Colorectal polypectomy and endoscopic mucosal resection (EMR): European Society of Gastrointestinal Endoscopy (ESGE) clinical guideline. Endoscopy. 2017 Feb;49(3):270–97.

31 Hassan C, Wysocki PT, Fuccio L, Seufferlein T, Dinis-Ribeiro M, Brandão C, et al. Correction: Endoscopic surveillance after surgical or endoscopic resection for colorectal cancer: European Society of Gastrointestinal Endoscopy (ESGE) and European Society of Digestive Oncology (ESDO) guideline. Endoscopy. 2019 Mar;51(3):C1.

32 Yoshida N, Naito Y, Yasuda R, Murakami T, Hirose R, Ogiso K, et al. The efficacy of the pocket-creation method for cases with severe fibrosis in colorectal endoscopic submucosal dissection. Endosc Int Open. 2018 Aug;6(8):E975–83.

33 Makino T, Kanmura S, Sasaki F, Nasu Y, Funakawa K, Tanaka A, et al. Preoperative classification of submucosal fibrosis in colorectal laterally spreading tumors by endoscopic ultrasonography. Endosc Int Open. 2015 Apr;3(4):E363–7.

34 O'Neill C, Barreiro P, Mendo R, Félix C, Costa I, Chagas C. Endoscopic submucosal dissection for polyps in the anal transitional zone after ileoanal anastomosis in a patient with familial adenomatous polyposis. Endoscopy. 2022;54(1):E11–2.