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Endoscopic submucosal dissection for proximal colonic lesions: An effective therapeutic option

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ABSTRACT

Background and study aims Due to the greater risks of adverse events (AEs) and the lower rate of submucosal invasive cancer (SMIC), large proximal colonic polyps are frequently treated by piecemeal endoscopic mucosal resection (EMR) in the West. However, this implies the risk of surgery to radicalize non-curative endoscopic resection in case of early colorectal cancer (CRC). We evaluated procedure outcomes in patients undergoing ESD for proximal colonic lesions at risk of SMIC.

Patients and methods All consecutive patients with lesions at risk of SMIC proximal to splenic flexure referred for ESD at a tertiary center were prospectively included from 2019 to 2021. En bloc, R0, and curative resection rates were primary outcomes, while length of hospitalization, AEs, need for surgery due to AEs, and recurrence rates were secondary outcomes.

Results A total of 116 patients (mean age: 68.4±10.91 years; men: 69.8%) were included. En bloc, R0, and curative resection rates were 84.5%, 78.4%, and 72.4%, respectively. T1 adenocarcinoma was reported in 25% of lesions (29/116). Eleven patients (9.5%) underwent secondary surgery due to non-curative resections; residual disease was found in one patient. Most frequent AE was intra-procedural perforation (9.9%); no AE required surgery. Median follow-up was 36 months; three of 97 recurrences (3.1%) at 6 months and one of 85 recurrence (1.2%) at 36 months were reported, which were all endoscopically treated.

Conclusions In expert hands, ESD is effective and safe for proximal colonic lesions at risk of SMIC for the favorable balance between risk of AEs and benefit of avoiding unnecessary surgery, even for early CRC.

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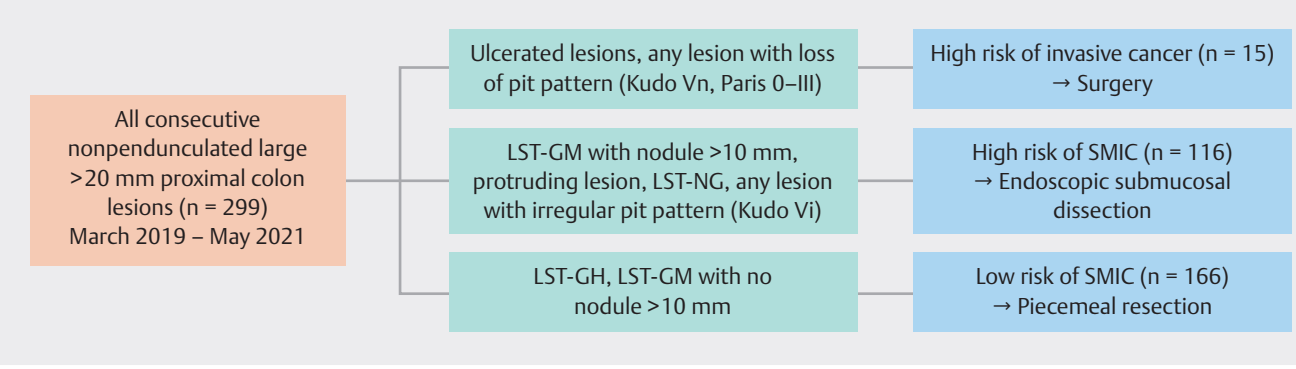


▶ **Fig. 1** Process for selecting the resection technique according to lesion features.

Introduction

Colorectal cancer (CRC) is the third most common cancer worldwide [1]. Although the overall prognosis has improved over the last decades, CRC still represents the second leading cause of cancer-related mortality [1, 2, 3]. Large nonpedunculated colorectal lesions require advanced resection techniques.

Among them, endoscopic submucosal dissection (ESD), originally developed in Japan, has been shown to provide great R0 and curative resection rates leading to noninvasive potentially curative treatment of early CRC with very low recurrence rates [4, 5]. Nevertheless, this technique is challenging, time-consuming, and risky [6], especially in the proximal colon due to its tortuous nature, presence of folds, the thin wall layer, and variable scope maneuverability. Taking into account these factors, together with the known relatively low risk of submucosal invasive cancer (SMIC), adoption of ESD in this tract is limited in favor of piecemeal endoscopic mucosal resection (EMR) in the Western world [6, 7, 8, 9, 10].

However, this can lead to surgery in case of piecemeal resection of early CRCs, which is affected by a not negligible rate of complications and mortality [11]. We performed a retrospective analysis of efficiency and safety outcomes in a tertiary center prospective cohort of ESD for proximal colon lesions with high-risk features of SMIC.

Patients and methods

Study design

The methods of our study were based upon the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) recommendations [12]. Institutional review board approval was obtained (ENDO-OPER-REGISTRO/01; n° 255/2019).

From March 2019 to May 2021, all consecutive patients referred for colorectal ESD of colonic lesions proximal to the splenic flexure were prospectively enrolled at an Italian tertiary center (Humanitas Research Hospital). The sample size of this study depended on the volume of ESD for this selected group of lesions during the study period. A retrospective analysis of efficiency and safety outcomes was performed. Patients provided written informed consent for the endoscopic procedure and data collection. All authors had access to the anonymized study data and approved the final manuscript.

Inclusion and exclusion criteria

All patients with nonpedunculated proximal colorectal lesions > 20 mm with high-risk features of SMIC (LST-GM with nodule > 10 mm, protruding lesion, LST-NG, any lesion with area with irregular pit pattern (Kudo Vi)) were included (▶ **Fig. 1**). Patients with nonpedunculated colonic lesions highly suspicious for deep submucosal cancer were referred for surgery as per standard guidelines [7]. On the other hand, lesions with no high-risk feature of superficial submucosal invasion were treated by EMR and, thus, excluded (▶ **Fig. 1**). Presence of other cancers, inflammatory bowel diseases, and familial adenomatous polyposis were considered as exclusion criteria. Patients unable to provide consent or who objected to use of their data were excluded, as were minors (< 18 years of age).

Procedure

All ESDs were performed by two endoscopists (A.R and R.M.) with the patient in deep sedation administered by a dedicated anesthesiologist. The two endoscopists were proficient in colorectal ESD, having performed more than 250 cases, The equipment included a standard colonoscope (EC-760R-V/I Fujifilm Endoscopy, Tokyo, Japan) with a distal cap fitted, a needle-type ESD knife (Clearcut FINEMEDIX Ltd., Daegu, Korea), a 23-gauge injection needle (Boston Scientific Corporation, Massachusetts, United States), and a microprocessor electrosurgical unit (VIO3 or VIO 300 D Erbe Elektromedizin, Tubingen, Germany). A pair of hemostatic forceps (Coagrasper, Olympus, Tokyo, Japan) was used for blood vessel cauterization and hemostasis. After submucosal injection with saline solution with dilute adrenaline mixed with methylene blue, circumferential or partial mucosal incision was performed. Then, submucosal dissection was carried out. The specific technique (e. g., conventional, tunnelling, pocket creation method) was left at operator preference, as was use of counter traction. At the end of the procedure, the choice of performing prophylactic coagulation of visible vessels was left to the discretion of the endoscopist, as was prophylactic closure of the post-resection mucosal defect. Spe-

cimens were finally collected, measured, pinned, and sent in formalin for histopathological examination.

Variables and outcomes

The following variables were recorded for each patient: age, gender, lesion location (cecum, ileocecal valve, ascending colon, right hepatic flexure, transverse colon) and endoscopic characteristics of the lesion, including morphology (according to Paris classification) and surface glandular pattern (according to Kudo classification). Sessile and/or bulky polyps (0-Is sec Paris) were reported as protruding lesions. For flat lesions, termed laterally spreading tumors, morphology was also reported as granular, granular mixed-type, and nongranular according to European Society of Gastrointestinal Endoscopy (ESGE) guidelines[13]. We also reported data on the size of the resected specimen (mm), total procedure time (minutes, defined as time from submucosal injection to complete lesion removal), and histopathological results (**Supplementary material; Appendix A)** [14, 15]**.**

The primary outcome of the study was efficacy assessed in terms of en bloc, R0, and curative resection rates. En bloc resection was defined as a resection of the target lesion in one piece. Resection was defined as R0 when the neoplastic/dysplastic tissue was removed en bloc with free lateral and vertical margins. For submucosal invasive cancers, the following variables were also collected: grade of tumor differentiation, lymphovascular invasion, depth of submucosal infiltration, and grade of tumor budding. R0 resection was diagnosed as curative for all benign lesions (low-grade dysplasia and high-grade dysplasia) and in all early CRCs without high-risk features on pathology (depth of submucosal invasion > 1000 µm, lymphovascular invasion, poor differentiation, high-grade budding). Patients with non-curative resections underwent subsequent surgical resection with regional lymph node dissection or strict follow-up according to multidisciplinary team decision weighted on each selective case. Moreover, histologic analysis of surgical specimens from patients undergoing surgery for non-curative resections was performed.

Secondary outcomes included recurrence rates, length of hospitalization, adverse event (AE) rates, and need for surgery due to AEs. AEs analyzed were bleeding, perforation, and post-electrocoagulation syndrome. Immediate bleeding was defined as persistent bleeding requiring a pause in resection to apply dedicated endoscopic hemostasis with a device other than the ESD knife. Delayed bleeding was defined as clinical evidence of bleeding (melena or hematochezia) with a drop in hemoglobin ≥ 2 g/dL up to 14 days after the procedure.

Intraprocedure perforation was defined as exposure of the peritoneal space as a result of a muscular defect occurring during ESD. Delayed perforation was defined as abdominal pain with evidence of free air or peritonitis, or wall-defect as seen on computed tomography after the end and within 30 days of the procedure or intraoperatively.

Post-electrocoagulation syndrome was defined as development of abdominal pain and fever in the absence of bowel perforation after the end and within 7 days of the procedure.

Secondary surgery due to AEs was defined as any surgery linked to early or delayed AEs. All patients were monitored for the next hours following the procedure to assess AEs. In addition, after discharge, all patients received phone calls at 3, 15, and 30 days to assess AEs.

Finally, we also aimed to identify significant predictors of R0 resection, AEs, and recurrence.

Follow-up

For patients who did not undergo secondary surgery, endoscopic follow-up examinations were scheduled at 6 and 12 months and then at subsequent intervals according to endoscopic findings to assess local recurrence. Suspected recurrent lesions on mucosal scars were examined with virtual chromoendoscopy. Visible neoplasia at the resection scar with the same histology as the original lesion during any follow-up examination was defined as a recurrence. If any follow-up endoscopy detected an adenoma/tumor recurrence, it was resected endoscopically and sent for histology; in the case of suspicious invasive neoplasia, biopsies were taken. In the absence of endoscopic visible recurrence, no biopsies of the scar were obtained for en bloc resections, while they were systematically performed for piecemeal resections.

Statistical analysis

Continuous variable distribution was assessed using the Shapiro-Wilk test of normality and reported as a mean with standard deviation (SD) or a median with interquartile range (IQR). Categorical variables were expressed as counts and percentages. Comparisons were made by the χ^2 test or Fisher's exact test for categorical data, Mann-Whitney U for non-normally distributed or independent *t* test for normally distributed continuous data. Predictive factors of R0 resection, AEs, and recurrence rates were investigated by univariate and multivariate analysis. For recurrence rate, time to events was defined as time from the ESD procedure to the event or censoring. Patients were censored if they were event-free through the end of the study observation. The log-rank test was applied to assess the association between each possible predictive variable and post-ESD recurrence. All statistical analyses were performed with STATA (ver. 18, Texas, United States).

Results

Clinicopathological characteristics of patients

From March 2019 to May 2021, 299 consecutive patients with large (> 20 mm) proximal colonic lesions were considered for inclusion at our center. Among them, 166 underwent piecemeal resection. Seventeen patients met the exclusion criteria. Therefore, a total of 116 ESDs were enrolled. Baseline patient and lesion characteristics are detailed in ▶ **Table 1**.

Primary outcomes

Of the lesions, 84.5% were resected en bloc, with a R0 resection rate of 78.4%. Curative resection was achieved in 72.4% of cases. Histopathological characteristics are reported in ▶ **Table 2**.

▶ **Table 1** Clinical and endoscopic characteristics of included patients.

Parameter	Value (n = 116)
Age, mean (SD), y	68.36 (± 10.91)
Sex, n (%)	
Male	81 (69.8)
Female	35 (30.2)
Diameter, mean (SD), mm	34.16 (±13.53)
Type of lesion, n (%)	
LST-GM	64 (55.2)
LST-NG	30 (25.9)
Protruding	22 (18.9)
Presence of nodule > 10 mm	30 (25.9)
Localization, n (%)	
Cecum	23 (19.8)
Ileocecal valve	2 (1.7)
Right colon	51 (44)
Hepatic flexure	20 (17.2)
Transverse colon	20 (17.2)
Pit pattern, n (%)	
IIIL + IIIS + IV	63 (54.3)
Vi	53 (45.7)

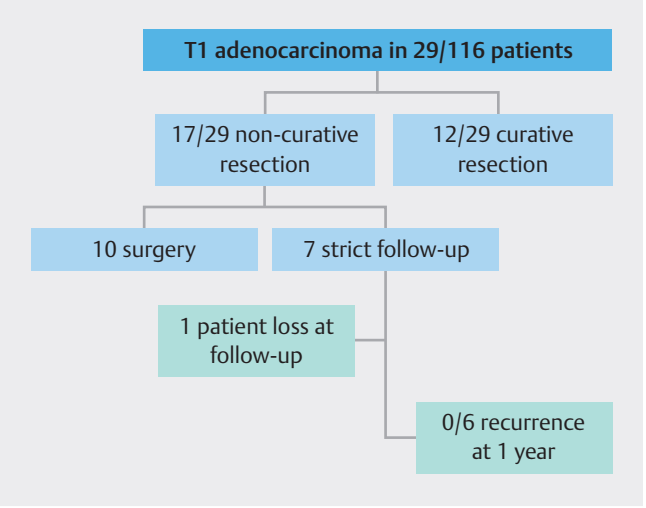
LST-GM, laterally spreading tumor granular-mixed; LST-NG, laterally spreading tumor non-granular; SD, standard deviation.

▶ **Table 2** Histopathological characteristics of included patients.

Parameter	Value (n = 116)
En bloc resection, n (%)	98 (84.5)
R0, n (%)	91 (78.4)
Curative resection, n (%)	82 (72.4)
Histological result, n (%)	
LGD	48(41.4)
HGD	39 (33.6)
ADK	29 (25)
ADK + HRF	14 (12.1)

ADK, adenocarcinoma; HGD, high-grade dysplasia; HRF, high-risk features; LGD, low-grade dysplasia.

Twenty-nine of 116 specimens (25%) resulted in T1 colorectal adenocarcinoma; among this subgroup, 14 of 29 were T1 adenocarcinoma with high-risk features such as poor differentiation, lymphovascular invasion, high-grade budding, or submucosal invasion > 1000 µm. Of the 29 adenocarcinomas treated, en bloc and R0 resection were achieved in 24 (82.8%) and 19 (65.5%), respectively, whereas curative resection was obtained in 12 cases (41.4%). Secondary surgery was performed due to non-curative resections of 10 T1 CRCs and one high-grade dysplasia; in this group, endoscopic R0 resection had been achieved in five of 11 cases. All the other patients with non-curative resections underwent strict follow-up according to multidisciplinary team decision weighted on each selective case (▶ **Fig. 2**).



▶ **Fig. 2** Flow chart of patients with T1 adenocarcinoma according to curativeness of endoscopic resection.

Histologic analysis of surgical specimens for patients undergoing surgery for oncological reasons found residual disease in only one patient (T2N0), whose resection was a piecemeal resection of a T1 adenocarcinoma with involvement of both lateral and deep margins. No positive lymph nodes were found in any surgical specimen (▶ **Table 3**).

Univariate analysis found no significant association between lesion characteristics and R0 resection rate (**Supplementary Table 1**).

Secondary outcomes

Mean procedure duration was 78.98 minutes (± 38.93). Mean length of hospitalization was 1.63 days (± 1.09); 68% of patients were discharged the day of the procedure.

Overall, 22 of 166 patients (19%) suffered from AEs. A total of 17 (13.8%) intraprocedure AEs occurred, including intraprocedure perforation (9.9%) and immediate bleeding (3.9). Globally, eight delayed AEs (7%) were reported, comprising delayed bleeding (1.8%), post-electrocoagulation syndrome (4.3%), and delayed perforation (0.9%). No AE required surgery (▶ **Table 4**). No significant association was found between lesion characteristics and AEs (**Supplementary Table 2**).

▶ **Table 3** Endoscopic histopathological features and surgery histology of patients undergoing secondary surgery due to non-curative resections.

En bloc resection	Histology	Grading	Lympho-vascular invasion	Lateral margin	Deep margin	R0 resection	Budding	Submucosal invasion depth	Surgery histology
Yes	ADK	G1-G2	No	Negative	Negative	Yes	High-grade	Sm1	T0N0
Yes	ADK	G1-G2	No	Positive	Negative	No	High-grade	Sm2–3	T0N0
Yes	ADK	G1-G2	Yes	Negative	Negative	Yes	High-grade	Sm1	T0N0
Yes	ADK	G1-G2	No	Negative	Positive	No	High-grade	Sm2–3	T0N0
No	ADK	G1-G2	No	Positive	Positive	No	Low-grade	Sm1	T2N0
Yes	ADK	G3	Yes	Negative	Negative	Yes	High-grade	Sm2–3	T0N0
Yes	ADK	G3	No	Negative	Negative	Yes	Low-grade	Sm1	T0N0
Yes	ADK	G1-G2	No	Negative	Negative	Yes	Low-grade	Sm2–3	T0N0
Yes	ADK	G1-G2	No	Negative	Positive	No	Low-grade	Sm2–3	T0N0
No	HGD			Positive	Positive	No			T0N0
Yes	ADK	G1-G2	No	Negative	Positive	No	High-grade	Sm2–3	T0N0

ADK, adenocarcinoma; HGD, high-grade dysplasia.

▶ **Table 4** Proximal colon endoscopic submucosal dissection-related adverse events.

Parameter	Value (n = 116)
Early adverse events, n (%)	17 (13.8)
Intraprocedure perforation	12 (9.9)
Immediate bleeding	5 (3.9)
Delayed adverse events, n (%)	8 (7)
Delayed bleeding	2 (1.8)
Delayed perforation	1 (0.9)
Post-electrocoagulation syndrome	5 (4.3)
Surgery due to AEs, n (%)	0 (0)

AE, adverse event; ESD, endoscopic submucosal dissection.

▶ **Table 5** Recurrence at follow-up endoscopy after proximal colon ESD.

Parameter	Value
Adenoma recurrence, n (%)	
6 months	3/97 (3.1)
12 months	0/95 (0)
36 months	1/85 (1.2)
Neoplastic recurrence, n (%)	
6 months	0/97 (0)
12 months	0/95 (0)
36 months	0/85 (0)

ESD, endoscopic submucosal dissection.

Follow-up and recurrence

Endoscopic follow-up analysis included 97 patients with a median follow-up of 3 years (range 0.5–5.0). No neoplastic recurrence was detected. Three of 97 patients (3.1%) had adenoma recurrence at 6-month follow-up endoscopy; two were R0 resections (high-grade dysplasia and low-grade dysplasia, respectively), the other was a R1 resection (high-grade dysplasia). One of 85 (1.2%) had adenoma recurrence at 36-month follow-up endoscopy (▶ **Table 5**); it was a curative resection of an early CRC with no evidence of recurrence at 6- and 12-month follow-up endoscopies. All recurrences detected were endoscopically treated with no evidence of recurrence at subsequent surveillance endoscopies.

According to our time-dependent analysis, neither lesion characteristic nor histology was significantly correlated with recurrence (**Supplementary Table 3**).

Discussion

Our study shows that, in expert hands, ESD is a feasible approach for large proximal colon non-pedunculated polyps at risk of SMIC due to a beneficial balance between risk of AEs and benefit of sparing unnecessary surgery, even for early CRCs.

Taking into account known risks and technical difficulties of endoscopic resection of proximal colon lesions, we applied a selective strategy to choose the more appropriate treatment for each lesion as recommended by European guidelines [7].

Our findings are clinically relevant for several reasons. First, our selective approach, reserving ESD for lesions with high-risk features of SMIC, led to a higher rate of adenocarcinoma (> 25%) in our cohort in comparison to what has been reported by other prospective colonic ESD cohorts, which included all large superficial colonic lesions [5, 16]. On the other hand, bearing in mind our selective strategy, this remarkable proportion of adenocarcinoma is consistent with what has been previously reported by Burgess et al. and by our group [9, 17]. Hence, our data underscore the value of optical diagnosis and the relevance of macroscopic and microscopic features to reliably predict risk of early CRC as reported by high-quality studies [9, 15]. As a matter of fact, when specific features are reported, the relevant risk of SMIC in our cohort justifies our aim of an en bloc resection.

In this regard, the fact that our efficacy data in terms of en bloc, R0, and curative resection rates appear comparable to most of the Western series [18] makes our findings even more relevant if considering both the high rate of early CRCs and the proximal location, which are considered as predictive factors for ESD difficulty[19].

Furthermore, follow-up data showed colorectal ESD as an effective therapy in the proximal colon with good outcomes in both the short and long term. Indeed, although several patients did not undergo surgery after non-curative ESD and poor maneuverability and submucosal invasion are known risk factors affecting both R0 resection and recurrence rates [17, 20], our study found low recurrence rates, which are significantly lower than those observed in piecemeal EMR cohorts[21]. Moreover, absence of residual disease in most surgical specimens with no positive lymph nodes detected strengthens the curative role of ESD.

Second, even if risk of AEs is the main reason why adoption of colonic ESD in the Western world has been challenging, we have described a promising safety profile in our series. Risk of immediate bleeding (3.9%) was indeed comparable to previously observed rates in both Eastern and Western cohorts [8, 10, 18, 22, 23]. On the other hand, the intraprocedure perforation rate (9.9%) was higher compared to most Western studies [18]. However, if considering the series including a relatively high amount of proximal colon lesions, similar rates of perforation were reported [24, 25]. As a matter of fact, this was not unexpected, considering the proximal colon variable scope maneuverability, which has been shown to be significantly associated with perforation risk [20]; Nevertheless, all the intraprocedure perforations were endoscopically managed in our cohort. Indeed, absence of surgery due to AEs meets the ESGE quality standard (< 1%) and is even better than that reported by Asian cohorts (N.B. not restricted to proximal lesions) [10, 22, 26]. In addition, the minimal impact of the procedures is underscored by the limited mean hospitalization time, with more than two-thirds of patients managed as outpatients.

Third, considering the abovementioned efficacy and safety profile, the risk in terms of oncological outcomes of a minimally invasive approach appears to be favorable when considering the opportunity to provide a potentially curative treatment that spares major surgery. In this regard, ESD can provide a real added benefit for lesions with high-risk features of SMIC, allowing a noninvasive, definitive, one-session treatment, avoiding morbidity, mortality, and costs related to surgery [4, 11]. Moreover, proximal colon ESD does not hinder any subsequent surgical approach when it fails in the curative intent, but it also may eradicate the disease even for lesions with histological high-risk features beyond the curative criteria [27]. This latter issue should be evaluated in future larger multicenter studies. In fact, if ESD could eliminate the disease even when not judged as curative, the subsequent surgical referral could be questioned, especially for older patients or subjects with multiple comorbidities[28].

The main strength of our study is the robust methodology implying a prospective enrollment with long-term follow-up. This design minimized the risk of biases, providing reliable long-term data aimed at finding the proper role for proximal colonic ESD in the real world. Finally, this cohort was assembled in a very short period of time, avoiding potential biases due to major advances in devices and techniques.

Despite the several strengths, our study has some flaws. Absence of a control arm prevents us from comparing ESD with other endoscopic techniques, such as piecemeal EMR, and surgery. However, the main aim of the study was not to merely compare the pure procedural outcomes of different techniques but to test how the benefit/risk balance of ESD may fit a selected subgroup of proximal lesions with high risk of SMIC. Furthermore, no available studies have assessed outcomes of piecemeal EMR for a group of such lesions. Nevertheless, a large multicenter retrospective study on endoscopic resection of early colorectal cancer has reported piecemeal resection as an independent risk factor for incomplete resection [29].

According to the available literature, we can speculate that piecemeal EMR for such lesions would have led to significantly lower curative resection rates, requiring higher secondary surgery rates to eradicate the disease. On the other hand, perforation rates likely would have been lower than the 9.9% reported by our study [16]. However, no surgery due to AEs was reported by our study and almost 70% of patients were discharged the same day of the procedure, thus minimizing the burden of a more dangerous and difficult procedure.

On the other hand, a meta-analysis on procedure outcomes of surgery for potentially benign polyps has underlined the high efficacy in terms of completeness of resection, but at the price of higher morbidity and mortality rates related to surgery and longer hospitalization even for right hemicolectomy, which has less impact on the patients in comparison to rectal surgery [11]. Thus, in light of our good results in terms of curativeness and low recurrence, we can speculate that a surgical approach for a group of such lesions would have led to significantly higher morbidity and mortality rates, without adding a significant advantage in terms of long-term outcomes. Furthermore, the monocentric setting, limited to a referral center, may undermine the reproducibility of our results. On the other hand, even if ESD is increasingly adopted in the Western world, the lesions treated in our cohort need to be considered as challenging cases, still requiring advanced expertise in third-space endoscopy. Finally, the small sample size most likely could

have prevented us from identifying risk factors significantly associated with both efficacy and safety outcomes in our analysis. However, the feasibility of the approach reported in our study may provide reassure regarding the design of future larger multicenter studies.

Conclusions

In summary, ESD appears to be a feasible option in a Western expert setting, even for proximal colonic lesions at high risk of superficial submucosal invasion, with good outcomes and an acceptable safety profile. The potential benefit of eradicating early CRC with a noninvasive approach, indeed, was not hindered by the risk of condemning the patients to unnecessary surgery due to risk of AEs.

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Conflict of Interest

RM is a consultant for ERBE, Fujifilm, 3DMatrix and Boston Scientific. CH is a consultant for Fujifilm, Medtronic, and Olympus. AC is a consultant for ERBE. AR is a consultant for Medtronic, ERBE, Fujifilm, and Olympus. The other authors have nothing to declare.

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