Thieme

Diagnostic endoscopic submucosal dissection for colorectal lesions with suspected deep invasion

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ABSTRACT

Background Endoscopic submucosal dissection (ESD) is potentially a curative treatment for T1 colorectal cancer under certain conditions. The aim of this study was to evaluate the feasibility and effectiveness of ESD for lesions with a suspicion of focal deep invasion.

Methods In this retrospective multicenter study, consecutive patients with colorectal neoplasia displaying a focal (< 15 mm) deep invasive pattern (FDIP) that were treated by ESD were included. We excluded ulcerated lesions (Paris III), lesions with distant metastasis, and clearly advanced tumors (tumoral strictures).

Results 124 patients benefited from 126 diagnostic dissection attempts for FDIP lesions. Dissection was feasible in 120/126 attempts (95.2 %) and, where possible, the en bloc and R0 resection rates were 95.8 % (115/120) and 76.7 % (92/120), respectively. Thirty-three resections (26.2 %) were for very low risk tumors, so considered curative, and 38 (30.2 %) were for low risk lesions. Noncurative R0 resections were for lesions with lymphatic or vascular invasion (LVI; n = 8), or significant budding (n = 9), and LVI + budding combination (n = 4).

Conclusion ESD is feasible and safe for colorectal lesions with an FDIP ≤ 15 mm. It was curative in 26.6 % of patients and could be a valid option for a further 30.6 % of patients with low risk T1 cancers, especially for frail patients with co-morbidities.

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Introduction

Endoscopic submucosal dissection (ESD) is a safe and effective technique to obtain R0 resection of superficial colorectal neoplasia. The distinction between superficial colorectal neoplasia and deep invasive cancers is currently guided by Sano's [1] and Kudo's patterns [2]. Lesions classified as Sano IIIa and Kudo Vi, or CONECCT IIc [3, 4], are considered to be potentially invading the submucosa to a depth of < 1000 µm and are usually cured by ESD. In contrast, lesions that are Sano IIIb or Kudo Vn are considered to be invading the submucosa to a depth of > 1000 µm and are treated surgically.

The histopathological definition of curative ESD for superficial colorectal neoplasia includes R0 resected high grade dysplasia and very low risk submucosal adenocarcinomas [5–7]. Lesions treated by ESD that do not match this definition are referred for adjuvant surgical treatment. Recently, the 1000-µm depth of submucosal invasion (sm) has been debated. Some authors consider that this threshold does not constitute an independent risk factor for lymph node metastasis [5–7]. Expanded criteria for curative ESD are under investigation to include submucosal invasion > 1000 µm and minimal budding (grade 1), which is associated with a risk of lymph node metastasis of 3 % (low risk T1 cancer) [8]. T1 cancers displaying budding, lymphovascular invasion (LVI), or poor differentiation are considered at high risk of lymph node metastasis and should be referred for adjuvant surgical treatment.

Sano's and Kudo's patterns have proved their limits in differentiating superficial neoplasia from deep invasive cancers. Discrepancies between the endoscopic estimation of cancer risk and the definitive histopathological examination do exist, and lead to the surgical treatment of some lesions that could potentially be cured by ESD. Given the relative performance of endoscopy in predicting the real curability of T1 cancer, a diagnostic dissection strategy could be proposed to obtain a perfect pathological evaluation. The present study aimed to evaluate the feasibility and effectiveness of ESD for colorectal lesions presenting with a focal deep invasive pattern (FDIP).

Methods

This was a retrospective multicenter analysis of a prospectively collected database of colorectal diagnostic ESD cases from four university hospitals and one private hospital. We included all consecutive lesions displaying an FDIP described by the endoscopist performing the ESD. The 15-mm cutoff was arbitrarily retained in the inclusion criteria as we could find no threshold in the literature. We excluded ulcerated lesions (Paris III), lesions with distant metastasis, and clearly advanced tumors (tumoral strictures).

Procedures

Endoscopic management

Procedures were performed by eight expert endoscopists with the patient under general anesthesia and with the use of CO_2 insufflation. All procedures were performed using a dedicated colonoscope and an ESD knife. Optical evaluation was performed using high definition white-light endoscopy, magnifying endoscopy, and chromoendoscopy-assisted examination. Double clip and rubber-band traction-assisted ESD [8–10] was systematically used in the university hospitals. The procedure was interrupted if muscular invasion was noted or if submucosal fibrosis prevented en bloc resection being completed without perforation.

Histopathological evaluation

Histopathological examination was performed by expert digestive pathologists following the Vienna classification [11–13] and budding evaluation guidelines [14], with R0 corresponding to an absence of tumor at the resection margin (> 0 mm clearance) [14].

Data

Clinical data including sex, age at the time of ESD, and endoscopic description were collected. For each lesion, the location, size, classification according to the Paris, Sano, Kudo, and CONECCT classifications, and FDIP size (estimated during endoscopy or measured on the ESD specimen) were reported. Pictures of the lesions, when available, were collected. Follow-up data until the end of the study were recorded.

Definitions and outcomes

Definitions

The FDIP was defined as a focal zone of Sano IIIb, Kudo Vn, or CONECCT III pattern (≤ 15 mm) on the resected lesion.

Very low risk T1 cancers were defined as lesions resected with en bloc R0 resection displaying none of the following features: sm > 1000 µm, LVI, significant budding (> Bd1 [15]), or poor differentiation based on the worst area. Very low risk lesions were associated with strictly curative ESD.

Low risk T1 cancers were defined as lesions resected by an en bloc R0 resection with sm > 1000 µm displaying none of the following features: LVI, budding > Bd1, and poor differentiation. Low risk lesions were associated with expanded curative ESD.

Lesions were classified as high risk T1 cancers if one or more of the following criteria were met: muscular invasion, R1 resection, LVI, budding > Bd1, or poor differentiation. High risk lesions were associated with noncurative ESD.

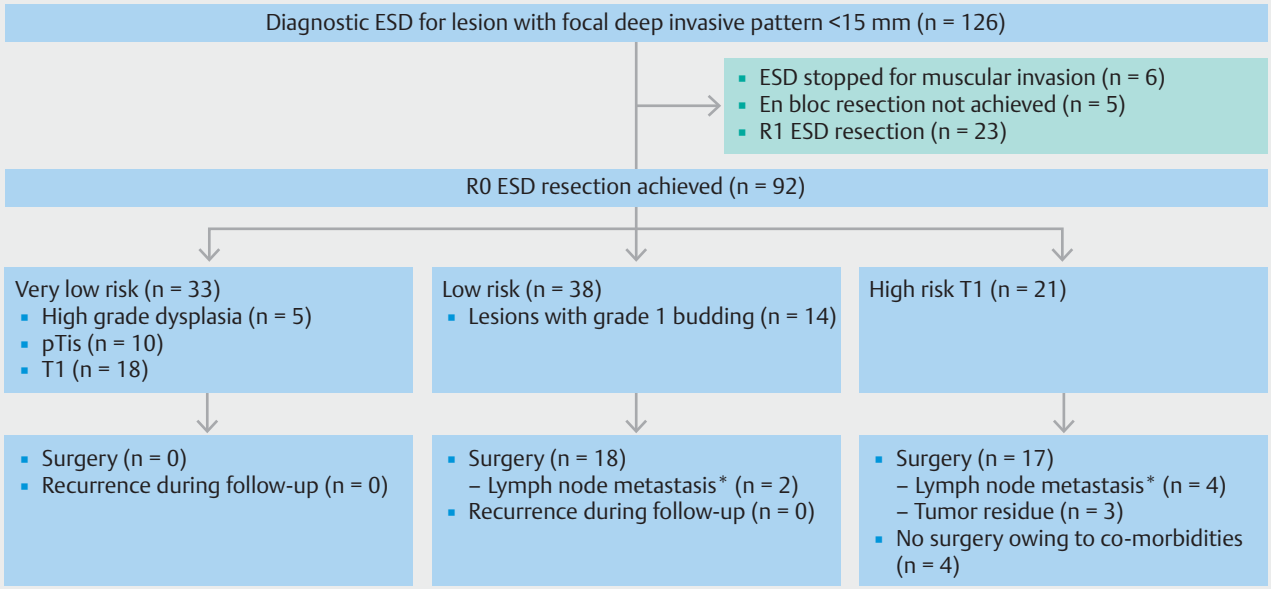
Primary outcome

We aimed to evaluate the rate of R0 resection for very low risk, low risk, and high risk lesions based on the histopathological evaluation. The factors associated with a curative (either very low risk or low risk) resection were analyzed according to the location of the lesion and the size of the FDIP.

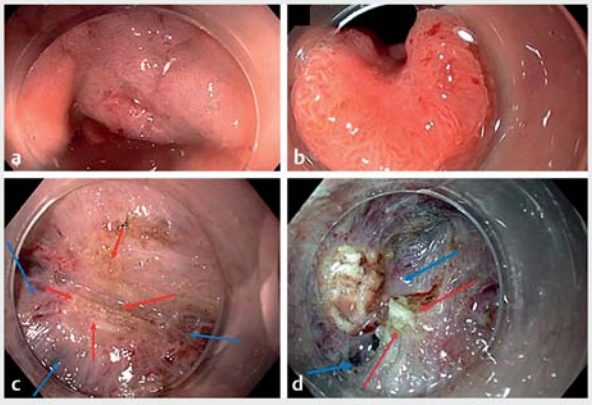
Secondary outcomes

Technical success was evaluated by the rate of en bloc resection.

The concordance between physicians in describing the FDIP was evaluated by reviewing the available pictures of the lesions while blinded to the histological results and from the previous endoscopic description.



▶ **Fig. 1** Flow chart of the study population. ESD, endoscopic submucosal dissection. * Nongranular laterally spreading tumors: 40 × 40 mm, pseudodepressed type in the descending colon, with FDIP of 3 mm and submucosal invasion to 2021 µm; and 22 × 12 mm, protruded type in the rectum, with FDIP of 6 mm, submucosal invasion to 2500 µm, and grade 1 budding.



▶ **Fig. 2** Example images showing the correlation between the endoscopic appearance (**a,c**) and submucosal invasion revealed during the submucosal dissection phase (**b, d**) for: **a, b** a T2 cancer; **c, d** a lesion with a 10-mm area of focal deep invasive pattern and a very small amount of muscular invasion.

Complications related to ESD were graded according to the Clavien–Dindo classification [13].

Statistical analysis

Quantitative variables were expressed as median (range); qualitative variables were expressed as frequency (percentage). Factors associated with a curative resection, either strict or meeting the expanded criteria, were analyzed by univariate and multivariable logistic regression. Factors included in the multivariable model were those for which the *P* value was < 0.05 on univariate analysis; a backward stepwise approach was used to simplify the multivariate model. *P* values ≤ 0.05 were considered significant.

Results

Population

A total of 124 patients (73 men; median age 68 years) underwent 126 diagnostic ESD attempts for lesions presenting an FDIP, which corresponded to 3.2 % of all the colorectal ESDs performed during the period. These lesions were mainly in the rectum (55.6 %) and the suspected invasive zone size was < 5 mm for 46.8 % of them (**Table 1s**, see online-only Supplementary material).

Outcomes

Diagnostic ESD was possible in 120/126 attempts (95.2 %) (▶ **Fig. 1**). ESD was interrupted in six cases because of visible muscular invasion during submucosal dissection (▶ **Fig. 2**). En bloc resection was achieved for 115/126 attempts (91.3 %), and R0 resection was achieved for 92/126 of ESD attempts (73.0 %). Among the 92 R0 resections, 33 (35.9 %), 38 (41.3 %), and 21 lesions (22.8 %) were classified as very low risk, low risk, and high risk, respectively (▶ **Table 1**).

Follow-up

Patients were systematically considered for complementary surgical treatment when en bloc resection failed (n = 11; 8.7 %), when R0 resection could not be obtained (n = 23; 18.3 %), and for high risk T1 lesions (▶ **Fig. 1**).

For R0 adenocarcinomas, multidisciplinary team meetings were held and their management was decided according to their risk factors for lymph node metastasis. Among the very low risk lesions, endoscopic follow-up outcomes were available for 28 patients; no recurrence occurred after a mean (interquartile range [IQR]) follow-up of 242 (0–288.5) days. Regarding the low risk lesions, 18 were treated with complementary surgery, with two cases of lymph node metastasis (11.1 %) noted. The other 20 low risk lesions were followed up by endoscopy and computed tomography (CT) scanning, and no recurrence occurred after a mean (IQR) follow-up of 127 (1–182) days. Surgical procedures for high risk lesions for which en bloc resection was obtained (n = 17) found three cases of tumoral residue and four cases of lymph node metastasis.

Factors associated with strictly or expanded curative resections

There was no significant association between the characteristics of the lesions and the occurrence of strictly curative resection (▶ **Table 2**). In the expanded curative resection lesions, a significantly higher proportion of successes were found for lesions with limited FDIP (< 5 mm) and a lower rate of success for lesions located in the rectum or the descending colon compared with other locations on both univariate and multivariable analyses (▶ **Table 2** and ▶ **Table 3**).

Safety

Complications related to diagnostic ESD occurred in 21/126 procedures (16.7 %) and included nine major complications (7.1 %): five bleeds requiring endoscopic treatment, three intraoperative perforations, and one delayed perforation (**Table 2 s**).

Evaluation of the tumor images

Images of the resected lesions were available for 96/126 ESD attempts (76.2 %), including eight T2 cancers, 49 T1 cancers with sm > 1000 µm, 27 T1 < 1000 µm, and 12 with high grade dysplasia (including 10 Vienna 4.4).

All of the 96 cases were reviewed by eight experts involved in the study. For 16 cases, the pictures were classified as being of insufficient quality for Sano's and Kudo's classifications to be used by more than half of the experts. Among the remaining 80 cases, 65 (81.3 %) were classified as Kudo Vn (all 65 Sano IIIb) by the majority of the experts. The rate of agreement among experts on the characterization of invasive patterns was significantly associated with the rate of high risk tumors with noncurative ESD ($P < 0.05$) (**Tables 3 s** and **4 s**; **Fig. 1 s**).

▶ **Table 1** Histological characteristics of the 126 diagnostic endoscopic submucosal dissection (ESD) attempts on colorectal lesions presenting with a focal deep invasive pattern (FDIP).

Diagnostic ESD outcome, n (%)	
▪ Completed	120/126 (95.2)
▪ Failed because of muscular invasion	6/126 (4.8)
En bloc resection, n (%)	115/120 (95.8)
Histology of the lesions resected en bloc, n (%)	
▪ High grade dysplastic adenoma (Vienna 4.1)	5/115 (4.3)
▪ Intramucosal adenocarcinoma (Vienna 4.4)	10/115 (8.7)
▪ Superficial submucosal adenocarcinoma (< 1000 µm)	35/115 (30.4)
▪ Deep submucosal adenocarcinoma (> 1000 µm)	63/115 (54.8)
▪ Intramuscular or deeper cancer	2/115 (1.7)
R0 resections, n (%)	92/115 (80.0)
R1 on deep resection margin, n (%)	22/115 (19.1)
R1 on lateral resection margin, n (%)	1/115 (0.9)
Curability of ESD, n (%)	
▪ Strictly curative	33/126 (26.2)
▪ Expanded curative	38/126 (30.2)
▪ Displaying grade 1 budding	14/126 (11.1)
▪ Strictly noncurative	55/126 (43.7)

Discussion

The present study showed that diagnostic ESD is feasible and safe for colorectal lesions with an FDIP of < 15 mm. It cured 26.6 % (95 %CI 18.8 %–34.8 %) of patients and could be a valid option for 30.6 % (95 %CI 22.0 %–38.9 %) of patients with low risk T1 cancers, especially for frail patients with co-morbidities. Moreover, it could cure 66.2 % of patients if the FDIP was < 5 mm.

Technically, diagnostic ESD is more difficult than the standard technique because of the reduced submucosal layer in T1 cancer, the fibrosis, and the increased risk of perforation. ESD with traction systems [16] seems to successfully expose the submucosa and allow resection of the lesion as close to the muscle as possible to obtain an adequate deep margin. Full-thickness resection with the full-thickness resection device (FTRD) system is an alternative to obtain a deeper resection when the overall size of the lesion is < 20 mm [17]; however, a size < 20 mm is rare for these relatively advanced lesions. A newer option, endoscopic intermuscular resection, allows the whole thickness of the submucosa to be reached, but data are needed to demonstrate its efficacy and safety [18].

Currently, there is a debate about the importance of the different histopathological criteria and their respective weight in assessing the risk of lymph node recurrence. While significant budding [5, 19–22], LVI [5, 22–24], and poorly differentiated components are clearly recognized as pejorative criteria, depth of invasion beyond 1000 µm is increasingly being questioned [5, 25]. In the present study, no focal or metastatic tumor recurrence was reported for very low risk lesions considered cured by ESD; however, we cannot exclude a significant risk of recurrence, particularly for low risk lesions. Two of the 18 patients with expanded criteria resections (but submucosal invasion > 2000 µm) who benefited from secondary surgery had lymph node involvement. Despite the small sample size of our study, the discussion about a new threshold of acceptable submucosal invasion is open because none of the patients with low

▶ **Table 2** Subgroup analysis of predictive factors: associations between lesion characteristics and the occurrence of strictly curative resection and expanded curative resection.

	Strictly curative ESD	Odds ratio (95 %CI)	*P* value	Expanded curative ESD	Odds ratio (95 %CI)	*P* value
FDIP size, mm			0.13			0.03
▪ <5	19/58 (32.8 %)	–		39/58 (67.2 %)	–	
▪ ≥5 and ≤10	10/43 (23.3 %)	0.62 (0.25–1.52)		22/43 (51.2 %)	0.51 (0.23–1.15)	
▪ >10	4/23 (17.4 %)	0.43 (0.13–1.45)		10/23 (43.5 %)	0.37 (0.14–1.01)	
Lesion largest diameter, mm[1]			0.66			0.04
▪ ≤20	10/33 (30.3 %)	–		21/33 (63.6 %)	–	
▪ >20 to ≤25	2/16 (12.5 %)	0.30 (0.06–1.48)		10/16 (62.5 %)	0.93 (0.29–2.96)	
▪ >25 to ≤40	6/36 (16.7 %)	0.42 (0.15–1.21)		17/36 (47.2 %)	0.50 (0.21–1.18)	
▪ >40	7/19 (36.8 %)	1.23 (0.41–3.70)		8/19 (42.1 %)	0.41 (0.14–1.18)	
Location			0.30			0.02
▪ Rectum	19/70 (27.1 %)	–		43/70 (61.4 %)	–	
▪ Descending colon	3/25 (12.0 %)	0.30 (0.06–1.48)		7/25 (28.0 %)	0.24 (0.09–0.66)	
▪ Transverse colon	1/4 (25.0 %)	0.89 (0.09–9.14)		3/4 (75.0 %)	1.88 (0.19–19.05)	
▪ Ascending colon	6/16 (37.5 %)	1.61 (0.51–5.04)		12/16 (75.0 %)	1.88 (0.55–6.44)	
▪ Cecum	4/11 (36.4 %)	1.53 (0.40–5.84)		6/11 (54.5 %)	0.75 (0.21–2.71)	
Kudo's and Sano's pattern association			0.79			0.49
▪ Kudo Vn and Sano IIIb	22/96 (22.9 %)	0.89 (0.31–2.52)		50/96 (52.1 %)	0.65 (0.26–1.63)	

ESD, endoscopic submucosal dissection; FDIP, focal deep invasive pattern.
[1] 1 value missing in the strictly curative resection group and 2 values missing in the expanded curative resection group.

▶ **Table 3** Multivariable analysis of factors associated with the occurrence of expanded curative resection.

	Odds ratio (95 %CI)	*P* value
FDIP, mm (reference <5)		0.02
▪ ≥5 and ≤10	0.321 (0.117–0.818)	
▪ >10	0.226 (0.068–0.701)	
Lesion size, mm (reference ≤20)		0.22
▪ >20 to ≤25	0.952 (0.279–3.434)	
▪ >25 to ≤40	0.884 (0.088–0.972)	
▪ >40	0.302 (0.088–0.972)	
Location (reference rectum)		<0.001
▪ Descending colon	0.116 (0.032–0.363)	
▪ Cecum, ascending, or transverse colon	0.834 (0.315–2.239)	

FDIP, focal deep invasive pattern.

risk T1 cancers with submucosal invasion between 1000 and 2000 µm experienced recurrence or lymph node involvement. This 2000-µm threshold has already been reported in a large Japanese study [23]. Systematically referring lesions with an FDIP to surgical treatment may not be adequate, particularly for elderly patients or those presenting with several co-morbidities.

If endoscopic resection becomes an alternative for the treatment of low risk T1 colorectal cancer, new diagnostic criteria will be required to predict the benefits of diagnostic ESD. Endoscopic characterization is associated with invasion under or over the threshold of 1000 µm. Kudo's Vn and Sano's IIIb patterns have shown their limits in identifying deep invasive can-

cers. In our study, even when only one expert described the pattern as invasive, only 80 % of resections were curative. Managing patients according to these fallible patterns could therefore lead to unnecessary invasive treatment. However, the size of the FDIP component could be associated with the resection success. ESD was particularly effective for lesions presenting an FDIP of < 5 mm as more than 65 % of these resections were curative according to the expanded criteria.

This study has some limitations. First, this strategy is relatively recent and the follow-up period is for now consequently short. Therefore, the follow-up duration was not long enough to ensure the absence of recurrence in the nonsurgical group. Secondly, the retrospective design of our study meant that we only included lesions with an FDIP for which ESD was attempted, particularly in patients with co-morbidities.

In conclusion, diagnostic ESD is feasible and safe for colorectal lesions with an FDIP ≤ 15 mm. It could be proposed as a way to obtain a precise pathological assessment in order to avoid systematic surgery.

Competing interests

The authors declare that they have no conflict of interest.

Clinical trial

Trial Registration: ClinicalTrials.gov | Registration number (trial ID): NCT04592003 | Type of study: Retrospective

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