

Performance of novices in Endoscopic Submucosal Dissection starting directly in human patients under direct supervision of an expert endoscopist

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Abstract

Background and study aim: The ESGE curriculum guideline on training in ESD advises an extensive experience in animal models before commencing ESD training on humans. However, the evidence on which this recommendation is based, is rather limited. In this study we evaluate the performance of novices in ESD during their one-year training period; with continuous supervision of an endoscopist with extensive experience in ESD.

Patients and Methods: During a 6.5 years period, all ESD procedures performed by an expert endoscopist (eESD) or by one of the 3 novices (sESD), in a single non-academic center, were retrospectively collected.

Primary outcome parameters were rate of en-bloc resection and clinically relevant adverse events. The secondary outcome was R0 resection, recurrence rate and delayed adverse events.

Results: In total 210 ESD procedures were included. Of these 97 sESD (46.2%), were performed by a novice endoscopist under supervision and 113 eESD (53.8%) by an expert. En-bloc resection rate was 99.1% vs 99% ($p = ns$), R0 resection rate was 80.5 % vs 79.4 % ($p=ns$). Clinically relevant complications 14.2% vs 6.2 % ($p = 0.04$) and severe complications 4.4% vs 2.1 % ($p=ns$). Perforation was the most frequent reported serious complication. Three patients in the eESD group versus one in the other group needed additionally surgery due to a complication ($p=ns$). Recurrence rate was 2.2% for eESD and 1.3 % for sESD ($p=ns$).

Conclusion: This retrospective analysis demonstrates that learning ESD in humans without extensive prior animal model training is safe and feasible, on the condition that continuous supervision by an expert is provided. (*Acta gastroenterol. belg.*, 2024, 87, 478-483).

Keywords: Endoscopic submucosal dissection, complications, training, endoscopy, cancer.

Introduction

Endoscopic submucosal dissection (ESD) for en-bloc resection of superficial gastrointestinal neoplasms was first described more than 30 years ago in Japan and is now rapidly permeating throughout Europe and the United States (1-4).

The introduction of ESD has revolutionized endoscopic resection. En-bloc resection permits an optimal histopathological assessment of the resected specimen and reduces recurrence rate. Compared to other endoscopic mucosal resection techniques ESD is associated with a longer procedure time and a higher complication rate. The technique requires a high level of skill and expertise, and therefore a long learning curve and a set of prerequisites that have to be met before training can be commenced (5-12).

In 2019, the European Society of Gastrointestinal Endoscopy (ESGE) published the curriculum guideline on training in ESD. This guideline discourages initial training of ESD in humans. Instead, it is recommended to commence practice on live animals or ex vivo animal models to obtain the basic skills. The evidence on which this recommendation is based, is rather limited (13). Furthermore, there is a limited availability of ESD training courses that can offer live tissue training on such models in Europe, Japan and the United states. One might also raise ethical issues in the use of animals, especially in case of live tissue training (14).

Alternatively, ESD training in Korea and Japan is pursued in few expert centers through a designated master-apprentice training model.

In this retrospective study we evaluate such master-apprentice training program by comparing the performance of novices in ESD during their one-year training period compared to the performance of an expert in ESD.

The novices had none or very limited prior experience in animal models and were very closely supervised by an expert while doing every ESD.

Method

Procedures

All ESD procedures performed by an expert endoscopist or one of 3 novices in a single non-academic center from September 2015 until February 2022 were retrospectively collected. The procedures performed by the expert were defined as an eESD. An ESD in which a novice was involved, was defined as a supervised ESD (sESD). The decision to involve a novice in the endoscopy was influenced by the lesion's appearance during the procedure, with key factors being a straight scope position, easy lesion accessibility, a "folded" presentation in the colon due to the absence of haustrations, and an assessment of the potential

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complications of perforation. Direct supervision by an expert endoscopist with continuous feedback was a prerequisite. If the expert wasn't comfortable with the novice initiating the ESD or tackling a specific step, he would intervene and demonstrate how to handle the challenging part. The expert would then return control of the scope to the novice and continue to offer instructions in order to progressively train dexterity. As the trainees' skills progressed, they then could be entrusted with additional steps in the procedure. Throughout the learning process, the expert always remained side-by-side with the trainee, providing feedback, guidance and intervention if necessary. In short, the expert certified a smooth and safe process of the procedure, taking over from the novice only if needed, ensuring a minimal risk and allowing the novice to improve while performing the ESD. Patient safety was always the top priority.

The trainees had a comprehensive knowledge of ESD theory, instrumentation and excellent basic endoscopic techniques (routine interventional colonoscopies and gastroscopies). They underwent a one-year training program under the constant supervision of an expert endoscopist. All 3 trainees were in an interventional endoscopy training curriculum. The novices had none or very limited prior experience in animal models.

Data collection

Patient characteristics, such as age, gender, comorbidities and relevant medication use were registered. Along with lesion characteristics, including location, JNET/NICE Classification and size of the lesion. If JNET or NICE classification was missing, such classification was retrospectively added through the images in the endoscopy records.

The surface area of the neoplastic area was calculated, based on its long and short axis and the assumption that the polyps have an ellipsoidal form. The short and long axis were obtained from histopathological reports.

Esophageal lesions were classified into two groups, lesions originating from Barrett epithelium and lesions originating from squamous epithelium. Furthermore, histopathological parameters were registered, including depth of infiltration; lymph vascular invasion; differentiation grade and vertical and horizontal margins. Recurrence was monitored after 4 months and one year. Finally, all complications were recorded. The AGREE classification was used to assess severity of adverse events (AE) (15). A distinction was made between minor complications (AGREE I) and clinically relevant complications, which is defined as a complication at least AGREE II or more. In addition, analysis for serious AE, which are defined as complications with at least an AGREE IIIb classification, was performed. Some patients underwent more than one endoscopic procedure, in those cases each procedure was included as a separate entity. Anticoagulants and P2Y12 receptor antagonists were discontinued before the procedure and restarted according to recommendations from ESGE guidelines.

Outcomes

The primary outcomes of the study were rate of en-bloc resection and clinically relevant adverse events (AE). The secondary outcomes of this study were R0 resection, procedure time, recurrence rate and delayed adverse events (DAE). Recurrence rates were analyzed at 4 months and 1 year.

Statistical analysis

All data were analyzed with Statistical Package for the Social Sciences (SPSS, v29.0.1.1). Continuous data were expressed as the median and categorical data were expressed as counts and percentages. Data between the groups was compared using crosstabs and significance tested with Chi square tests. If the conditions for the Chi-square test were not met, the Fisher exact test was used. P values of <0.05 were determined to be statistically significant. For comparing means the independent T test was used.

Results

Baseline characteristics

Between September 2015 and February 2022, a total of 210 ESD procedures were included of which 97 sESD (46.2%) were performed by a novice endoscopist under strict supervision. In the eESD group there were 69 male patients (61.1%) versus 75 in the sESD group (77.3%). There were significantly more males in the sESD group in comparison with the expert group ($p=0.011$). The median age was 69.5 [range 59.8–79.2] years in the eESD group compared to 70.7 [59.2–82.3] years in the sESD group. In the eESD group 29 (25.7%) of the patients were under acetylsalicylic acid compared to 22 (22.7%) in the sESD group, 11 (9.7%) patients under anticoagulation versus 11 (11.3%) in the sESD group, 4 patients in the eESD group were taking P2Y12 receptor antagonists (3.5%) versus 3 patients in the sESD group (3.1%).

Three patients in the eESD group (2.7%) and one patient in the sESD group (1%) received combination (anticoagulants and antiplatelet) anticoagulation therapy. Two patients in eESD group were taking steroids at the time of procedure (1.8%), and none of the patients in the sESD group. No statistically significant differences were observed in the utilization of anticoagulants, antiplatelet agents or steroids between the two groups. In addition, the comorbidities between the expert and novice group were analyzed. No significant difference in rate of patients with diabetes mellitus type 1 or 2, chronic kidney failure, arterial hypertension, cirrhosis, chronic obstructive pulmonary disease (COPD) and active malignancy on the moment of the procedure was noted between the groups. There were significantly more patients included with cardiovascular disease in the sESD group in comparison with the expert group ($p=0.035$), but there was no significant difference after multivariable analysis (Table 1).

Table 1. — Overview clinical characteristics

	eESD (n = 113)	sESD (n = 97)	p
Sex			
Male, n %	69 (61.1)	75 (77.3)	0.011
Female, n %	44 (38.9)	22 (22.7)	0.83
Age median (age)	69.5	70.7	
Anti-aggregantia/coagulant therapy			
Acetylsalicylic acid, n (%)	29 (25.7)	22 (22.7)	0.615
P2Y12 receptor antagonist, n (%)	4 (3.5)	3 (3.1)	0.857
Anticoagulant, n (%)	11 (9.7)	11 (11.3)	0.705
Combination therapy, n (%)	3 (2.7)	1 (1.0)	0.391
Comorbidities			
Cardiovascular disease, n (%)	31 (27.4)	40 (41.2)	0.035
Renal disease, n (%)	5 (4.4)	2 (2.1)	0.342
Diabetes Mellitus, n (%)	19 (16.8)	15 (15.5)	0.791
Arterial hypertension, n (%)	39 (34.5)	34 (35.1)	0.935
Cirrhosis, n (%)	2 (1.8)	0 (0)	0.188
COPD, n (%)	5 (4.4)	10 (10.3)	0.099
Malignancy, n (%)	5 (4.4)	4 (4.1)	0.914
Steroids, n (%)	2 (1.8)	0 (0)	0.188
Dimension lesion			
Length mean in mm (SD)	38.9 (22.4)	40.2 (24.3)	0.716
Width mean in mm (SD)	27.6 (19.3)	27.6 (16.8)	
Estimated surface mean in cm ² (SD)	11.4 (20.6)	11.4 (15.0)	0.499
Esophagus (SD)	7.6 (5.2)	6.9 (4.0)	
Stomach (SD)	2.7 (2.8)	7.7 (6.6)	
Duodenum (SD)	6.9 (/)	0 (0)	
Left colon (SD)	10.1 (12.3)	10.0 (12.0)	
Right colon (SD)	7.2 (5.8)	3.9 (3.5)	
Rectum (SD)	18.3	16.4	0.016
Location			
Esophagus, n (%)	28 (24.8)	27 (27.8)	
Stomach, n (%)	2 (1.8)	7 (7.2)	
Duodenum, n (%)	1 (0.9)	0 (0)	
Left colon, n (%)	40 (35.4)	16 (16.5)	
Right colon, n (%)	10 (8.8)	6 (6.2)	
Rectum, n (%)	32 (28.3)	41 (42.3)	
Total colorectal lesions, n (%)	82 (56.6)	63 (43.3)	
JNET			
JNET 1, n (%)	0 (0)	0 (0)	0.046
JNET 2A, n (%)	40 (58)	20 (35.7)	
JNET 2B, n (%)	24 (34.8)	30 (53.6)	
JNET 3, n (%)	5 (7.2)	6 (10.7)	
NICE			
NICE 1, n (%)	6 (9.0)	0 (0)	0.004
NICE 2, n (%)	53 (79.1)	43 (72.9)	
NICE 3, n (%)	8 (11.9)	16 (27.1)	

Lesions

The surface area of the neoplasias was similar between groups, at approximately 11.4 cm². When examining the size of the lesions in relation to their location, we found that in both groups the largest lesions were located in the rectum. There was a significant difference between the locations of the lesion between the two groups ($p=0.016$). Most lesions in the eESD group were located in the left colon (35.4%), followed by the rectum (28.3%), Barrett esophagus (19.5%), right colon (8.8%), squamous esophagus (5.3%), stomach (1.8%) and duodenum (0.9%). In contrast to the sESD group where most lesions were in the rectum (42.3%) followed by Barrett esophagus (19.6%), left colon (16.5%), squamous esophagus (8.2%), stomach (7.2%) and right colon (6.2%). There were no lesions resected in the duodenum in the sESD group.

A total of 145 colorectal neoplasia's were resected, 56.6% in de eESD group. A more detailed look at the

classifications of these colorectal polyps shows a significant difference in JNET classification ($p=0.048$).

In the eESD group, 58% of the polyps were classified as JNET 2A, compared to 35.7% in the sESD group. On the other hand, JNET 2B was more frequently observed in the sESD group, accounting for 53.6% of the lesions. This trend was also reflected in the NICE classification. An overview can be found in table 1.

Procedure

En-bloc resection was achieved in 99.1% in the eESD group and 99% in the sESD group. ($p=ns$). Furthermore, the R0 resection rate was 80.5% in the eESD group versus 79.4% in the sESD group ($p=ns$). Comparing the procedural time between the two groups, the procedure took significantly longer in the sESD group compared to the eESD group, with an average of 110 minutes (SD 74.08) versus 79 minutes (SD 56.95) ($p=0.002$). The median resection speed in the eESD group was 14.68

Table 2. — Overview outcomes

	eESD (n = 113)	sESD (n = 97)	p
En Bloc, n (%)	112 (99.1)	96 (99.0)	0.364
R0 resection, n (%)	91 (80.5)	77 (79.4)	0.836
Procedural time (minutes, SD)	79.22 (56.95)	110.09 (74.08)	0.011
Procedural speed (mm ² /min, SD)	14.68 (10.62)	9.08 (7.67)	0.001
Recurrence, n (%)	7 (6.2)	3 (3.1)	0.293

± 10.62 mm² per minute, versus 9.08 ± 7.67 mm² per minute in the sESD group ($p < 0.001$) (Table 2). When we look in more detail at the cases where an R0 resection was not achieved, we see that these are mainly due to deeply invasive ($>T1sm1$) tumors. In the expert group this accounted for 7 lesions, in the novice group this was the case for 9.

Recurrence

The recurrence rate was 6.2% in the eESD group and 3.1% in the sESD group ($p = ns$). Recurrence was observed in 10 cases total, 7 of these were observed in the Barrett esophagus group. Excluding Barrett, recurrence rates dropped to 2.2% in the eESD group and 1.3% in the sESD group.

Eight out of 10 patients with recurrence could be treated endoscopically, in 2 patients with Barrett's subsequent surgery was performed.

Adverse events

A total of 32 complications were registered, 22 (19.5%) in the eESD group and 10 in the sESD group

(10.3%) ($p = ns$). Of these, 22 were clinically relevant, i.e. 16 in the eESD group (14.2%) and 6 in the sESD group (6.2%) ($p = 0.04$).

The most common complication in the eESD group was delayed bleeding in 7 cases (6.2%), followed by 6 perforations (5.3%), 5 cases of post-procedural pain (4.4%) and 3 urinary retentions (2.7%). In the sESD group there were 4 cases of post-procedural pain (4.1%), 3 perforations (3%), 2 patients with delayed bleeding (2%) and one urinary retention (1%). No significant differences were recorded in subtype of complication between the 2 groups (Table 3).

Interestingly, all recorded AGREE IIb complications were perforations; 5 (4.4%) in the eESD group and 2 (2.1%) in the sESD group ($p = ns$). In the eESD group, the majority of the perforations occurred in the left colon, in the sESD group one perforation occurred in the stomach and one in the esophagus. Only 4 patients required additional surgery after these perforations, two of them had undergone a colonic ESD, one in the stomach and the last one in the esophagus. All other perforations were managed endoscopically (Table 4). Finally, 12 late stenosis occurred due to fibrotic structuring, 6 in each group (5.3% vs 6.2%). In both groups, we observed that strictures occurred predominantly in the esophageal (50 % vs 66.6%) lesions spanning >75 % of the circumference. No procedure related deaths were reported in either group.

Discussion

ESD is a technically challenging technique, with an extended learning curve. It is time-consuming and

Table 3. — Overview of AE and DAE

	eESD (n = 113)	sESD (n = 97)	P
Total complications, n %	22 (19.5)	10 (10.3)	0.066
Type of complications			
Bleeding < 24h, n(%)	0 (0)	0 (0)	0.806
Bleeding > 24h, n (%)	7 (6.2)	2 (2.0)	
Perforation, n (%)	6 (5.3)	3 (3.0)	
Pain, n (%)	5 (4.4)	4 (4.1)	
Urine retention, n (%)	3 (2.7)	1 (1.0)	
Others, n (%)	1 (0.9)	0 (0)	
Clinically relevant complications, n (%)	16 (14.2)	6 (6.2)	0.040
Bleeding < 24h, n(%)	0 (0)	0 (0)	
Bleeding > 24h, n (%)	6 (5.3)	2 (2.0)	
Perforation, n (%)	6 (5.3)	3 (3.0)	
Pain, n (%)	1 (0.9)	1 (1.0)	
Urine retention, n (%)	2 (1.8)	0 (0)	
Others, n (%)	1 (0.9)	0 (0)	
Severe complications, n (%)	5 (4.4)	2 (2.1)	0.455
Perforation, n (%)	5 (4.4)	2 (2.1)	
Esophagus, n (%*)	1 (3.6)	1 (3.7)	
Stomach, n (%*)	0 (0)	1 (14.2)	
Left colon, n (%*)	3 (7.5)	0 (0)	
Rectum, n (%*)	1 (0.9)	0 (0)	
Surgical intervention, n (%)	3 (3.1)	1 (1.0)	1.0
Death, n (%)	0 (0)	0 (0)	
Late strictures, n (%)	6 (5.3)	6 (6.2)	0.074
Esophagus, n (%)	3 (2.7)	4 (4.1)	
Left colon, n (%)	2 (1.8)	0 (0)	
Rectum, n (%)	1 (0.9)	2 (2.1)	

%%* = the percentage expressed as the rate of complications at this specific location compared to all ESDs performed at the same location.

carries a high procedural risk, especially of perforation. As a result, there is ongoing development of devices and training models to make ESD safer and more successful (16,17). Studies consistently highlight the critical role of practicing ESD techniques on animal models (both ex-vivo and in-vivo) before performing the procedure clinically. This was also stressed in the current 2019 ESGE curriculum guideline for ESD training (18). This learning model however comes with several challenges. The limited availability of ESD training facilities that can offer live tissue training and cadaveric animal models limits the training options and these trainings come with a significant economic burden. Also, there are important ethical questions surrounding the use of animal models. (14)

In this retrospective study, we investigate the efficiency and complication rate of ESD by novices without such prior animal experience, but under strict direct expert supervision. Suitable ESD cases were selected by the supervisor based on expected difficulty to remove the lesion, and experience of the novice.

This study shows that in our master-apprentice ESD training model novices performed ESDs with an excellent en-bloc resection rate and an acceptable adverse event rate.

However, the study has significant limitations given the wide variety of lesions in the gastrointestinal tract, the case selection in the eESD group and the overall low R0 resection rate. Our study shows that there are no more complications (AEs) in the trainee group. On the contrary, significantly more clinically relevant AEs were seen in the expert group. This increased presence of clinically relevant AEs in the eESD group can be explained by the aforementioned case selection, where the more challenging cases are reserved for the expert. Importantly, there was no difference observed in en-bloc resection, R0 resection or recurrence rate between both groups. The en-bloc results did meet the quality indicators of ESGE set for ESD. The perforations in the eESD group can be explained by case selection, as some lesions were beyond criteria for expected curative endoscopic resection. However, these patients were not considered fit enough to undergo surgery and an endoscopic attempt was made regardless after multidisciplinary team discussion. It is evident that such procedures are associated with a higher risk of complications and fewer R0 resections (18).

In our study, the R0 resection rate is only 80 %, while the en-bloc resection rate is much higher. This can be partially explained by our preference to limit the extent of ESD and thereby accepting a small margin of normal mucosa in order to limit the risk of stricture formation. However, this can make accurate pinning of the specimen cumbersome, leading to a more difficult interpretation of the lateral margins histopathologically with higher chance of false positive resection margins. This hypothesis is supported by our low recurrence rate on follow up. The recurrence rate drops to approximately 2 %, if, ESD procedures in Barrett's epithelium are

omitted. The very low risk for recurrence is compatible with the very high en-bloc resection rates in both groups.

Studies have revealed a higher recurrence rate following esophageal ESD compared to stomach or colon procedures. This can be attributed to two key challenges; accurately defining the margins of the lesions in Barrett's esophagus (which is more complex than in the stomach or colon) and the potential difficulty of endoscopically identifying high-grade dysplasia (19,20).

The procedure time is significantly longer in the sESD group, this was expected as it is well known that procedural speed increases as proficiency in ESD is gained (21,22). It is however important to grant novices this extra time and even support a lower dissection speed, allowing novices to consciously work themselves through the procedures in a safe and controlled manner.

Some other limitations also need to be addressed. First, due to the retrospective design, there is a risk of underreporting of complications. However, to minimize this risk, all medical files were retrospectively scrutinized for possible adverse events.

Second, not for all procedures, structured and standardized endoscopy reports were available. However, all lesion characteristics were obtained directly from the endoscopy reports. Data not documented within these reports were categorized as missing data.

A last limitation is the absence of proven competence in ESD of the trainees after completing the one-year training period due to a lack of objective competence measurement. To our current knowledge this however stands for all current ESD traineeships in the absence of a recognized certification. Also, no formal testing is suggested in the 2019 ESGE curriculum guideline either. We can however attest that all 3 trainees were at the end of their training competent to reliably perform ESD on their own.

The master-apprentice training in this model can serve as an alternative to the ESGE curriculum guideline on training in ESD in selected expert centers. It allows trainees to learn from experienced experts under strict conditions. It allows to develop the confidence and skills needed to do a successful ESD. Our data show that this method allows for equally qualitative and safe procedures, with similar rates of R0 resections, recurrences or complications between the novice and expert group. The value of our approach is confirmed by a recent study from Japan, which also shows excellent results in terms of safety and efficiency. Trainees here were allowed to perform ESD limited to the stomach once they had demonstrated adequate knowledge and ability to assess invasion depth and this without prior ESD animal training (9,16). It is important to note that while the presented data suggest that sparing animal models could be viable alternative to the current training guidelines, further validation on a larger scale and replication of these findings are necessary to draw definitive conclusions.

Nevertheless, there are some challenges associated with the master-apprentice training model. The most

important challenges being the selection of training centers and the significant time investment of the expert endoscopist. He or she must be able to estimate the risk of a complication for each action the trainee makes so he can warn the novice in advance and prevent the complication all together. The supervisor must be extremely comfortable with the risk of dealing with a complication and be able to solve a perprocedural problem induced by a novice. Finally, the selected training centers should be obliged to evaluate their training programs based on accepted criteria of quality and outcome.

Conflict of interest

The authors declare that they have no conflict of interest.

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