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Translation of the article

Factors limiting the endoscopic submucosal dissection in colorectal tumors

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ABSTRACT *AIM: to identify the risk factors for conversion of endoscopic submucosal dissection to abdominal surgery.*
PATIENTS AND METHODS: the prospective cohort study included 405 patients: 166 (40.9%) males and 239 (59.1%) females. The median age was 66 (59;72) years old; the patients underwent endoscopic submucosal dissection of colorectal epithelial neoplasms.
RESULTS: the median size of the removed neoplasms was 3.0 (2.4;4) cm, tumor was removed en bloc in 324/363 (89.2%) cases; and R0 resection margins were detected in 218/324 (67.3%) cases. Significant risk factors for conversion were: the tumor size ⩾ 3.2 cm (OR 2.9, 95% CI: 1.2–7.1, p = 0.017), lifting ⩽ 3 mm (OR 41.95% CI: 15–105, p = 0.000002) and the tumor vascular pattern IIIa according Sano's capillary pattern classification (OR 4.0, 95%: CI: 1.3–11.9, p = 0.013).
CONCLUSION: endoscopic submucosal dissection is safe for colorectal neoplasms. However, the presence of conversion risk factors can influence the outcome of endoscopic treatment.

KEYWORDS: *ESD, conversion, colorectal polyps, colorectal cancer, submucosal dissection, adenoma, adenocarcinoma*

CONFLICT OF INTEREST: *The authors declare no conflict of interest.*

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INTRODUCTION

Endoscopic submucosal dissection (ESD) is the method of choice for the removal of epithelial colorectal neoplasms [1].
The ESD method is hard to perform, it requires special equipment and a long learning curve, which creates certain difficulties for its wide implementation in clinical practice. In addition, in a certain category of patients, there is a risk of conversion to transabdominal surgery, which complicates the treatment itself, and at the same time increases the risk of postoperative complications [2].
The identification of predictive risk factors and complexities in performing dissection will increase the effectiveness of the method and contribute to its wider implementation.

AIM

To identify risk factors for the ESD conversion to transabdominal surgery.

PATIENTS AND METHODS

From January 2017 to January 2020, 405 epithelial colorectal neoplasms were removed by the ESD method.

To determine the indications for ESD, all the patients underwent diagnostic colonoscopy using high-resolution video endoscopes.

In the endoscopic description of the identified neoplasms, the Paris-Japanese macroscopic classification, the Kudo S. pit pattern and the Sano Y. vascular pattern classifications were used [3–5].

If an irregular pit pattern with a demarcation line was detected during magnifying endoscopy, or it was structureless (corresponding to the Vn tumor as per Kudo and IIIb as per Sano), the lesions were interpreted as invasive cancer (with a distance of less than 1,000 μm from the muscle plate of the mucous layer) with the risk of metastasis to the lymph nodes. In these cases, ESD was not performed [6]. Only in 6 patients, an attempt of ESD was made. However, at the stage of lifting, due to its unsatisfactory result, the continuation of ESD was refused.

In order to determine the metastatic lymph nodes close to the tumor site, all the patients underwent computed tomography or ultrasound of the abdominal cavity. The biopsy was not performed due to the high risk of fibrosis and the associated subsequent complexities in performing ESD.

In most cases (87%), a two-stage laxative drug regimen was used for bowel cleansing before performing dissection. It consisted in following a special diet — a fiber-free diet for 2 days and a two-stage intake of the laxative. Given that all the procedures were performed as planned under intravenous sedation, the last fluid intake was to be done at least 3 hours before the surgery. The quality of preparation was assessed as per the Boston scale [7]. Excellent or good quality of cleansing was in 91%.

The dissection in the submucosal layer began with determining the tumor location: with the help of a water test, the tumor site at the circumference of the intestinal wall was assessed, after which the patient was located optimally on the operative table so that the tumor was located on top and hung down under the gravity force in the separation process.

The ESD was performed using a pediatric colonoscope (in the case of tumor site in the rectum — a gastroscope) Pentax, combined with a video processor EPK-i7010.

After determining (if necessary, marking) the margins of the tumor, an injection of a gelatin solution with a small amount of indigocarmine into the submucosal layer was performed. For the incision of the mucosa and further separation of the tumor, an uninsulated knife (Dual Knife, Olympus) was used in the End-cut Q mode (action 3, duration 2, interval 2) using the VIO300D, ERBE operating unit.

If necessary, repeated injection was performed to maintain optimal lifting. To ensure hemostasis during the manipulation, hemostatic forceps (Coagrasper, Olympus) were used in the fast coagulation mode (effect 2, 40–60 W). After removing the specimen, the postoperative defect was also treated with a coagrasper, and if necessary, covered with endoclips. The surgical team consisted of 2 endoscopist-surgeons and a nurse.

The removed specimen was spread out on a special platform and fixed in a 10% solution of neutral buffered formalin for 24 hours. After removal, the specimen was cut into plates with a thickness of 2 mm with the marking of the resection margins. The samples were stained with hematoxylin and eosin. The pathomorphological diagnosis was established in accordance with the Vienna classification [8].

The statistical data processing was performed using the Statistica TIBCO, USA.

The quantitative data with a non-Gaussian distribution was described by the median and quartiles, and the comparison was done using the Mann-Whitney test.

To determine the risk factors, a univariate and multivariate regression analyses were done.

The factors that had continuous indicators and statistical significance in the univariate analysis using ROC analysis were reduced to binary values that were used in the multivariate analysis. The results at $p < 0.05$ were considered significant.

RESULTS

The study included 405 patients: 239 (59.1%) women and 166 (40.9%) men. The median age of the patients was 66 (59; 72) years. The median size of the tumors was 3.0 ± 1.2 cm. Most of the neoplasms were laterally spreading tumors (LST-G) and were located in the right colon (Table

Table 1. *Characteristics of patients and neoplasms*

Age (years), (Q)		66 (59; 72)
Gender	male	166 (40.9%)
	female	239 (59.1%)
Tumor site	Right colon	223 (55%)
	Left colon	136 (33.5%)
	Rectum	46 (11.5%)
Macroscopic type according to the Paris classification	LST-G	198 (48.8%)
	LST-NG	125 (30.8%)
	0-Is	42 (10.3%)
	0-Ip	17 (4.1%)
	0-IIa	10 (2.4%)
	0-IIc	13 (3.2%)
Median tumor size, cm (M ± SD)		3.0 ± 1.2
Classification of the pit pattern changes as per Kudo, S.	IIIS	73 (18%)
	IIIL	117 (28.8%)
	IV	115 (28.3%)
	Vi	57 (14%)
	Vn	6 (1.4%)
	II (II-O Kimura)	37 (9.1%)
Classification of the vascular pattern as per Sano Y.	I	33 (8%)
	II	277 (68.3%)
	IIIa	89 (21.9%)
	IIIb	6 (1.4%)
Lifting less than 3 mm		72/405 (17.7%)

Table 2. *Indications for converting ESD to abdominal surgery*

Conversion rate	42/405 (10.3%)
Lifting < 3 mm	22 (5.4%)
Technical complexities	10 (2.4%)
Complications:	
Bleeding	5 (1.2%)
Perforation	5 (1.2%)

1). The neoplasms less than 20 mm were removed by dissection in the cases where endoscopic signs of superficial invasion were detected, or a scar was present due to the previous manipulation.

The study assessed the extent of the tumor lifting. It turned out that in 72/405 (17.7%) patients, lifting was found to be unsatisfactory — less than 3 mm. In most cases (89%) of unsatisfactory tumor lifting, the continuation of ESD was refused. If the reason for the poor lifting was a previous endoscopic manipulation (a biopsy or an attempt to remove the lesion), the endoscopic surgery was continued.

The conversion to transabdominal surgery occurred in 42/405 (10.3%) patients. In half of the 22/42 patients (52.3%), the ESD rejection occurred at the stage of injection and lifting evaluation. In the remaining cases, the conversion is associated with technical complexities or complications (bleeding, perforation) that occurred in the ESD process (Table 2).

To determine the risk factors for the conversion of submucosal dissection to abdominal surgery, a univariate and multivariate analyses were done. To determine the effect of tumor size on the risk of conversion, a ROC analysis was done and a cut-off point of 3.2 cm (Youden Index 0.17) was determined (Fig. 1). Thus, for tumors of 3.2 cm or more, there is a significant dependence of the incidence of dissection conversion to transabdominal procedure.

In a univariate analysis, significant conversion risk factors were: male sex (OR 1.91, 95%: CI: 1.0–3.63,

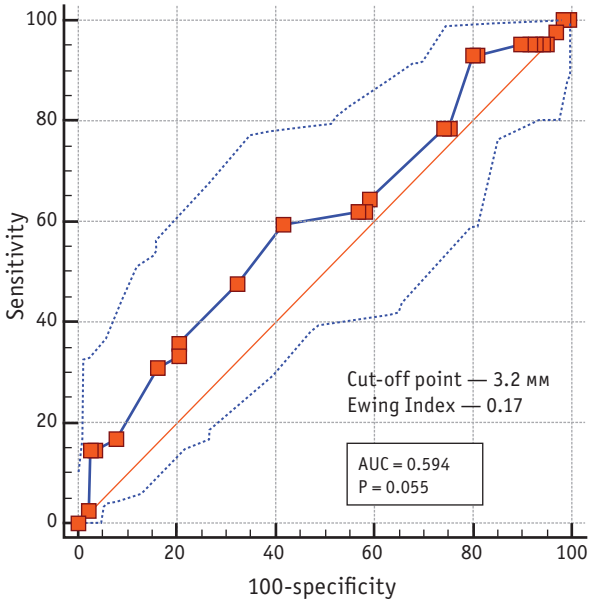

Figure 1. *ROC analysis of the effect of removed tumor size on the risk of conversion to abdominal surgery. Cut-off point 3.2 cm, Ewing index — 0.17, sensitivity — 59.5%, specificity — 58.4%*

Table 3. *Univariate and multivariate analysis of risk factors for ESD conversion to open surgery*

	Univariate analysis			Multivariate analysis		
Factor	**OR**	**CI: 95%**	***p***	**OR**	**CI: 95%**	***p***
Male/female	1.91	1.00–3.63	0.049	1.17	0.48–2.86	0.73
Patient position: on the side/back	0.18	0.056–0.614	0.006	0.162	0.042–0.619	0.008
Operative time	0.001	0.000001–11.736	0.153			
Age	1.02	0.99–1.05	0.20			
Tumor size	1.24	1.03–1.50	0.02			
The tumor size of over 3.2 cm	2.06	1.08–3.96	0.03	2.939	1.210–7.135	0.017
The tumor site (compared to the rectum): sigmoid colon	1.25	0.32–4.85	0.74			
Descending colon	3.58	0.72–17.81	0.12			
Transverse colon	3.58	0.88–14.58	0.07			
Ascending colon	1.21	0.31–4.67	0.79			
Caecum	1.41	0.33–5.95	0.64			
Lifting less than 3 mm	36.35	15.69–84.22	0.0000001	41	15.8–105	0.0000002
Kudo S. (compared to IIIL): IV	1.44	0.56–3.72	0.45			
Vi	2.90	1.08–7.81	0.04	2.9	0.79–10.91	0.1
IIIS	2.45	0.89–6.73	0.08			
Vn	6.81	1.08–43.02	0.04	7.9	0.72–87.7	0.09
Sano Y. (compared to II): IIIa	4.66	2.29–9.46	0.00002	4.0	1.33–11.9	0.01
IIIB	16.06	3.00–86.02	0.001	9.64	0.83–112.45	0.07
I	0.50	0.06–3.91	0.51			
Intravenous anesthesia with spontaneous breathing/ intravenous with ventilator	2.80	0.88–8.86	0.08			
The tumor morphology (compared to the tubular one) is Tubulo-villous	1.12	0.49–2.57	0.78			
Villous	1.35	0.40–4.57	0.63			
Adenocarcinoma	4.32	1.46–12.80	0.01	1.10	0.23–5.24	0.91
Dysplasia (compared to mild): moderate	1.39	0.63–3.02	0.41			
Severedysplasia	1.03	0.31–3.48	0.96			
Intraepithelial neoplasia	1.87	0.47–7.50	0.38			

$p = 0.049$), tumor size ⩾ 3.2 cm (OR 1.24 95%: CI: 1.08–3.96, $p = 0.03$), lifting ⩽ 3 mm (OR 36.3 95%: CI: 15.6–84.2, $p = 0.0000001$), Kudo Vi tumor pit pattern (OR 2.9, 95%: CI: 1.08–43, $p = 0.04$), and Vn (OR 6.81 95%: CI: 1.08–7.81, $p = 0.04$), the vascular pattern of the tumor according to Sano IIIa (OR 4.6, 95%: CI: 2.2–9.4, $p = 0.00002$) and IIIb (OR 16, 95%: CI: 3–86, $p = 0.001$), the presence of elements of adenocarcinoma according to the pathomorphological study of the removed specimens

Table 4. *Results of pathomorphological examination*

Tumor Structure	N = 363	
Adenoma	**345/363 (95.1%)**	
	Tubular	111 (30.5%)
	Tubulo-villous	161 (44.3%)
	Villous	33 (9%)
	Serrated	40 (11%)
Adenocarcinoma	**18/363 (4.9%)**	
	Sm1	12 (3.1%)
	Sm2	3 (0.9%)
	Sm3	3 (0.9%)

(OR 4.32 95%: CI: 1.46–12.8, $p = 0.01$). The patient position on the side opposite to the tumor intestine circumference localization was associated with a reduced risk of conversion (OR 0.18, 95%: CI: 0.05–0.6, $p = 0.006$). Such factors as the operative time, the patient's age, the tumor site, the anesthesia type (spontaneous respiration, ventilator), the degree of tumor dysplasia (moderate, severe, intraepithelial neoplasia) did not significantly affect the risk of conversion (Table 3).

In the multivariate analysis, the independent risk factors for conversion were: tumor size ⩾ 3.2 cm (OR 2.9, 95% CI: 1.2–7.1, $p = 0.017$), lifting ⩽ 3 mm (OR 41.95% CI: 15–105, $p = 0.000002$) and vascular pattern of the tumor according to Sano IIIa (OR 4.0, 95%: CI: 1.3–11.9, $p = 0.013$).

The patient position on the operative table was also significantly associated with a reduced risk of conversion (OR 0.16, 95% CI: 0.04–0.6, $p = 0.008$) (Table 3).

The postoperative complications were observed in 11/363 (3%) patients. The most often complication was bleeding — 9/363 (2.4%) cases, 2/363 (0.6%) patients had perforations.

The bleeding was stopped endoscopically and was clinically insignificant. In patients with perforation, laparotomy, abdominal cavity sanitation, closure of the defect with the diverting stoma were performed.

According to the pathomorphology: among 363 patients who underwent the ESD, the tumor was removed *en bloc* in 324 (89.2%) cases. In the remaining cases, the tumors were fragmented.

The risk factors for fragmentation were: tumor size ⩾ 3.2 cm, lifting ⩽ 3 mm, and vascular pattern of the tumor according to Sano IIIa.

The incidence of R0 resection was 60% (218/363), and in 29% (106/363) the lateral resection was < 1 mm, which was regarded as R1 resection. In patients with fragmentation (10.8%), the lateral margins were estimated as Rx.

Adenomas were detected in 345/363 (95.1%) cases, and adenocarcinomas — in 18/363 (4.9%). All 18 patients had invasive pT1 adenocarcinomas: in 12/18 observations pT1sm1, in 3/18 — pT1sm2 and in 3/12 — pT1sm3. Lymphovascular invasion was detected only in 4/18 tumors with a depth of pT1Sm1L1 invasion (Table 4).

Out of the patients with adenocarcinomas, 8/18 (44.4%) cases showed a positive resection margins along the deep edge (< 1), and 10/18 (55.5%) cases showed R0 resection. It is extremely important to emphasize that of 8 patients with R1 resection, in 3 cases there was a pT1sm3 tumor, in 4 cases there was a lymphovascular invasion, and in 1 case the tumor had the structure of a low-grade adenocarcinoma. In all the 8 patients, 4–8 weeks after the ESD, a traditional resection was done. None of the cases revealed residual tumor tissue at the ESD site, as well as regional lymph nodes involvement.

DISCUSSION

According to univariate and multivariate regression analyses, the significant risk factors for the conversion of ESD to abdominal approach were the size of the lesion ⩾ 3.2 cm (OR 2.9, 95% CI: 1.2–7.1, $p = 0.017$) and the vascular pattern of the tumor IIIa according to Sano (OR 4.0, 95%: CI: 1.3–11.9, $p = 0.013$), as well as lifting < 3 mm. Inadequate lifting was often observed in the presence of a scar from previous endoscopic manipulations (biopsy or attempt of removal). Similar results in their study were obtained by Horiko et al. [9]. Fibrous changes were the most significant intraoperative conversion risk factor both in the recent and in a number of other studies, as well as a risk factor for postoperative complications (95% CI: = 1.0–1.2; $p = 0.007$) [13]. Perhaps, in the presence of recurrent tumor and/or unsatisfactory lifting, endoscopic removal should be abandoned in favor of resection.

The results obtained show that with careful selection of patients, the incidence of postoperative complications in ESD does not exceed 4% [13]. According to Buddingh K. et al. [18], the most common complication was bleeding, and in all cases, hemostasis was performed endoscopically. The most serious complication was perforation.

Iacopini F. [14] and Imai K, et al. [15] found that the non-granular type of lesion (LST-NG), as well as the large size of the tumor were predictors of the technical complexities of ESD associated with the high prevalence of submucous fibrosis.

The complexity of large tumors removal may be due to the difficulty in recognizing the submucosal layer, its lesser thickness, as well as the torsion of the residual tumor in the final stage of the procedure.

Thus, we can predict that in patients with tumors larger than 3.2 cm, with unsatisfactory lifting (less than 3 mm), with neoplasms corresponding to type IIIa as per Sano Y., ESD may not be safe due to the risk of intraoperative complications or a high risk of conversion.

At the moment, a number of countries are developing special scales that allow predicting the success of the ESD with a high degree of confidence at the outpatient stage [15–17]. However, these scales have a number of significant drawbacks. The British scale was developed primarily to determine the complexity of polypectomy and assessed only 4 parameters — size, macroscopic characteristics, the tumor site and operative approach. As the study showed, to predict the success of dissection, it is necessary to have data on the severity of submucosal fibrosis. Also, these studies have methodological shortcomings that do not take into account the experience of an endoscopic surgeon.

Thus, there is a need to develop an original scale for assessing the gradient of the dissection complexity and the risk of its conversion to resection. The key point of this scale should be the possibility of its application at the outpatient stage.

CONCLUSION

ESD is a safe and standardized method for removing epithelial colorectal neoplasms. The presence of risk factors for conversion: tumor size ⩾ 3.2 cm (OR 2.9, 95% CI: 1.2–7.1, p = 0.017), lifting ⩽ 3 mm (OR 41.95% CI: 15–105, p = 0.000002, and the vascular pattern of the tumor according to Sano IIIa (OR 4.0, 95%: CI: 1.3–11.9, p = 0.013) may increase the likelihood of intra- and postoperative complications.

AUTHORS CONTRIBUTION

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Statistical processing: *Marat A. Nagudov*
Writing of the text: *Alexey A. Likutov, Oleg M. Yugai*
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