DOES LESION SITE AFFECT OUTCOMES OF ENDOSCOPIC SUBMUCOSAL DISSECTION FOR COLON NEOPLASIA?

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AIM: to assess results of endoscopic submucosal dissection (ESD) for colon neoplasms due to lesion site.

PATIENTS AND METHODS: One-hundred thirteen patients (66 females, aged 65,7±11,0 years) with colon neoplasms which underwent ESD for one year (January 2017 – January 2018) were included in the study. All patients were divided in two groups depending on lesion site. The first group included patients with lesions in caecum, ascending colon and proximal third of tranverse colon, the second group – other colon parts and intraperitoneal part of the rectum. All patients underwent preoperative tests including colonoscopy, gastroscopy and transabdominal ultrasound. ESD included lesion marking, injection, circular incision and dissection. The results obtained were analyzed statistically using Graph Pad 7 for Mac.

RESULTS: the 1st group included 61 (54.0%) patients and the 2nd – 52 (46.0%). Laterally spreading tumors (LST) were detected more often in the 1st group (56 patients of the 1st group vs 38 – in the 2nd, p=0.03). The lesion size in the 1st group was 31±13 (7-80) mm and 29±11 (8-76) in the 2nd one (p=0.3). Conversion from ESD to resection occurred in 9 (8.0%) patients, in 5 patients of the 1st group and in 4 – the 2nd one (p=1.0). The only reason for conversion was unfavorable lesion lifting (⩽2 mm).

Most of the lesions were removed en bloc, specimen fragmentation after ESD occurred in 10 (9.6%) patients: in 5 (9.0%) in the 1st group and in 5 (10.4%) in the 2nd (p=1.0). Intraoperative complications during ESD in the 1st group occurred in 2 (3.5%) cases and in 2 (4.1%) – in the 2nd (p=1.0). Postoperative complications were detected in 2 (1.9%) patients. Histopathology showed adenocarcinoma in 9 (8.0%) patients. Two (1.7%) patients produced local recurrence.

CONCLUSION: ESD is a safe method removal of colon ademonas. The intra- and postoperative complications rate is 3.5% and 1.9% for the 1st and the 2nd group. Local recurrences occurred in 2,04%. Unfavorable lesion lifting (⩽2 mm) in right colon is a risk factor for specimen fragmentation or conversion.

[Key words: endoscopy, endoscopic submucosal dissection, colon, neoplasms, adenocarcinoma, lesion, piecemeal resection, local recurrence, right part of the colon]

INTRODUCTION

Endoscopic submucosal dissection (ESD), developed in Japan as a method of removing tumors of the upper gastrointestinal tract (GIT), only a few years later was presented by Yamamoto N. (2003) and Fujishiro M. (2005) as a promising method for colon tumors [3,5,9,18]. Currently, ESD along with endoscopic mucosal resection (EMR) is a safe method for benign tumors and early colorectal cancer (CRC) with a postoperative morbidity rate not exceeding 3-6% [12].

At the same time, endoscopic submucosal dissection, unlike endoscopic mucosal loop resection is more effective for large tumors, not less than 20-40 mm in size, which is realized in a significantly higher rate of *en bloc* resections (93% and 12%, respectively) and leads to less recurrence rate (2% and 14%, respectively) [4,6,12,13]. In addition, the precision of the surgery and the level of dissection with the possibility of creating negative deep resection margin, like in transanal endoscopic microsurgery, make ESD an attractive alternative for resection method for early CRC [1,2,6,11].

However, despite the advantages of ESD, the method is difficult to implement, especially in the proximal colon, requires expensive equipment and a long period of training, which creates obstacles to its wide implication. Moreover, a relatively small number of publications and the fragmentation of available data on the technical complexity of the ESD, the rate of intraoperative and postoperative complications depending on the lesion site in the colon are the subject of discussion today.

The study systematized the results of endoscopic submucosal dissection (ESD) for colon neoplasms due to lesion site, specified endoscopic interventions and described complications obtained.

PATIENTS AND METHODS

For the period of between January 2017 and January 2018, onehundred and thirteen (113) patients (66 females, 58%, aged 65.73±11.05 years) with colon neoplasms were included in the study. The study was prospective, non-randomized and single-centered. All patients were divided into two groups depending on the lesion site. The first group included patients with lesions in caecum, ascending colon and proximal third of transverse colon, the second group –inleft colon and intraperitoneal part of the rectum. As the conditional border was considered the middle third of

the transverse colon. Thus, 61/113 (54%) patients were included in group I with thelesion site in the right part, and 52/113 (46%) patients in group II with the lesion site in theleft parts of the patient.

All patients underwent standard preoperative examination, which included: proctoscopy, colonoscopy, esophagogastroduodenoscopy, abdominal and pelvic ultrasound. It should be noted that when planning ESD, we refused to perform a preoperative biopsy due to the risk of edema/sclerosis in the submucosal layer and problems with tumor lifting. A colonoscopy was performed on the video processors Pentax (Japan) EPC I 7000 and EPC 7010 with a resolution of HD+ and with the possibility of a narrow-band mode, i-scan, as well as the video processors Olympus (Japan) Evis Exera III with video resolution HD+ and NBI mode. When performing colonoscopy, all detected formations were assessed according to the following classifications:

- Kudo-Fujii was used to assess the pit pattern and, if necessary, was supplemented with chromoscopy (0.4% solution of indigocarmin), in the mode of 100× magnification (Pentax EC 3890 LZi). By the nature of the pit pattern, the presence of dysplasia formation or its malignancy was detected [8].
- Sano Y. was used to assess capillary (vascular structure) relief of formations using narrow spectral regime (NBI), Olympus CF-H190L apparatus, as well as the extent of dysplasia and malignancy in the revealed tumors [14,15].
- Paris classification – macroscopic structure of formations was assessed, special attention was paid to planar forms (LST), as well as the presence/absence of depression (deepening) in the formations, which, in turn, allowed to assess the surface or deep invasion [10,17].

When the pathomorphological study of the removed specimenrevealed invasive early cancer, the depth of tumor invasion (pT1) was specifiedaccording to the sm-classification proposed by Kikuchi R. [7].

All ESDs were elective. Colon cleansing was carried out in two stages, using osmotic agents based on polyethylene glycol. All interventions were performed under intravenousanesthesia with spontaneous breathing, in some cases tracheal intubation was used. Equipment for ESD included: video endoscopic rack Pentax EPC 7000, operating colonoscope Pentax EC 34i10L/EC 34 I 10 M with a diameter of 12 mm, length 160/130 cm with biopsy channel of 3.8 mm, operating unit 300D made by the company Erbe (Germany), insufflator Olympus. The bestlocation of thelesion site for dissection is the projection in the interval between 5 and 8 hours according to the "conventional" dial, in connection with which all patients were placed on the operating table in the appropriate position for localization of the tumor in the given projection (in the position on the back, on the stomach, on the side). ESD was performed as follows: at first, colonoscopy was carried out to perform a visual assessment of the tumor. For better visualization and additional traction (tension) of the submucosallayer, as well as control of the muscle layer and in order to minimize the risk of perforation during the operation, a special soft cap up to 4-6 mm long with a side hole was used, which was fixed on the distal end of the colonoscope. Further, in carboxycolono with the injection needle 25G injection was performed to create a "cushion" (lifting), while in the submucosallayer in the area of the tumor formation a solution of plasma-substituting agent (gelofusin), dyed with a dye of 0.4% Indigo Carmine (in dilution of 0.5/10 ml to thelight blue color),was used (Fig.1A). The extent of tumor lifting was assessed according to the

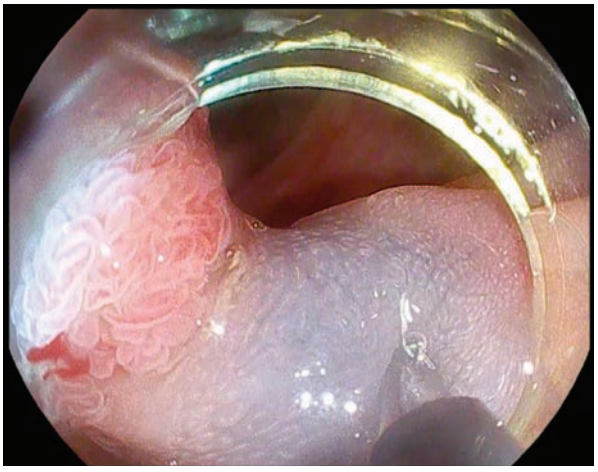

Figure 1A. *ESD stage. Injection of gelofuzinsolution diluted in Indigo Carmine*

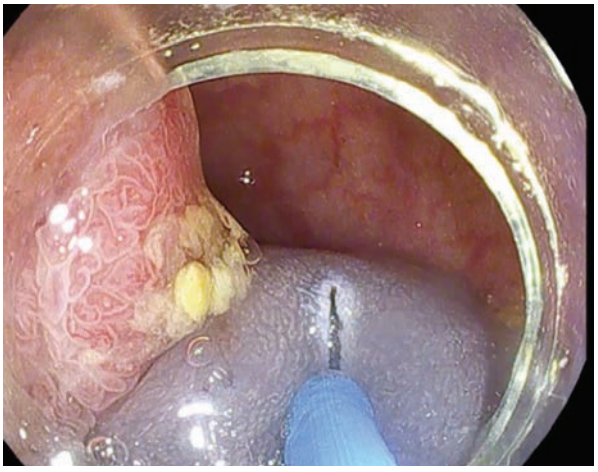

Figure 1B. *ESD stage. Circumferential incision of the mucous layer indented from the edge of the tumor with the help of Dual Knife*

Table 1. *Distribution of tumors by site in accordance with the endoscopic classification*

Type of endoscopic classification	Tumor site		p
	Right colon n=61	Left colon & rectum n=52	
Paris classification			
0-IIa, 0-IIb	1 (0,9%)	1 (0,9%)	–
0-IIa + 0-IIc	–	2 (1,8%)	–
0-Is	4 (3,5%)	11 (9,7%)	–
LST	56 (49,6%)	38 (33,6%)	0,01
Kudo classification			
II	5 (4,4%)	–	–
III, IV	51 (45,1%)	40 (35,4%)	–
Vi	4 (3,5%)	11 (9,7%)	0,02
Vn	1 (0,9%)	1 (0,9%)	–
Sano classification			
II	53 (46,9%)	36 (31,9%)	–
IIIa	8 (7,1%)	15 (13,3%)	–
IIIb	–	1 (0,9%)	–

following criteria:

- unsatisfactorylifting – 0-2 mm from its base;
- satisfactorylifting –3-4 mm;
- sufficientlifting –5 mm.

With adequate lifting, dissection was performed with the electrical unit Erbe 300D and with an electrosurgical knife Dual Knife (Olympus) the resection margins were marked, retreating 5-6 mm from the visible edges of the tumor.

After marking, the circumferential cut and intervention into the submucosallayer were performed, simultaneously creating its tension with a cap (Fig. 1B). In the detection oflarge vessels ofthe submucosallayer, coagulation was carried out with hemostatic forceps (Coagrasper Hemostatic Forceps, Olympus). Then, in turn, the solution was injected into the submucosal layer to maintain thelifting, and the expansion of both the circumferential cut (up to the circular) and the dissection of the submucosal layer were performed (Fig. 2A).

In all patients, the intervention was performed within the submucosallayer. After removal of the tumor, the postoperative defect was not covered, the resected specimen was fixed on a plastic screen in the operating room (Fig. 2B).

Statistical analysis was performed using Graph Pad 7 for Mac. In Gaussian distribution, continuous values were described by standard deviation and amplitude, in non-Gaussian distribution – by median and quartiles. Accordingly, the comparison of the average and

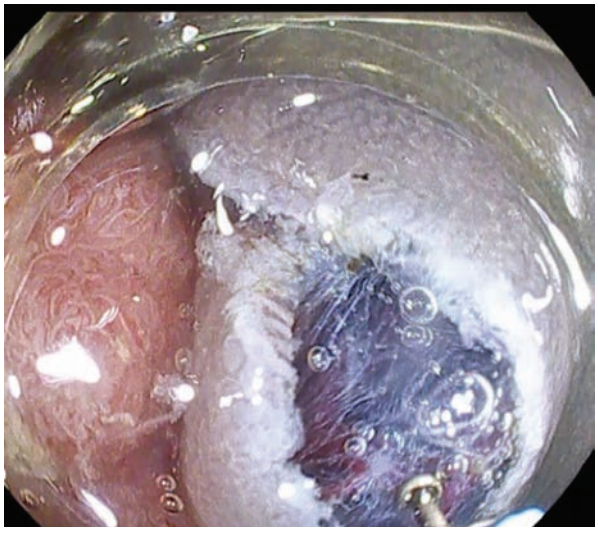

Figure 2A. *ESD stage. Entry of 5-6 mm into the submucosal layer with the help of Dual Knife and its dissection*

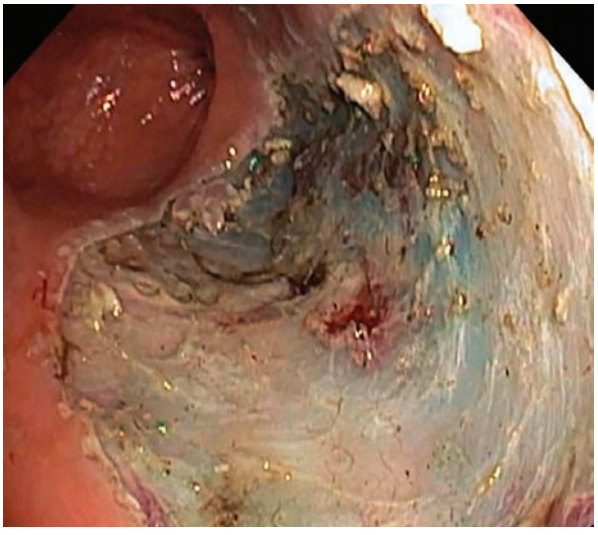

Figure 2B. *ESD stage.The mucosal defect after colorectal ESD*

median – using unpaired t-test and Mann-Whitney test. Discrete values were compared using Fisher's exact test. The odds ratio (oddsratio, OR) was calculated to assess risk factors.

RESULTS

As presented above, after distribution by groups, it was found that patients with tumors located in the right colon were slightly more 61/113 (54%) than patients with tumorslocated in theleft – 52/113 (46%). Depending on the type of endoscopic classifications, the groups did not differ, except that adenomas with lateral spreading (LST – laterally creeping tumors) were more common in group I than in group II – 56/62 (49.6%) and 38/52 (33.6%), p=0.01. Tumors with endoscopic signs of superficial malignancy (Vi) according to the Kudo classification (pit pattern) were more common in theleft than in the right colon– 11/52 (21.1%) and 4/61 (6.5%), respectively, p=0.02 (Table. 1). The mean size (M±SD) of tumors in the right colon was 31±13 (7-80) mm, in theleft one – 29±11 (8-76), the differences are not significant, p=0.3.

According to the principles of ESD, in all cases, the intervention began with an injection of the solution into the submucosal layer to create a tumor lifting, after which, even with unsatisfactorylifting of no more than 2 mm, an attempt was made to dissect the tumor (Table 2). Most patients (104/113, 92%) underwent complete ESD without changing intervention plan. In the remaining patients 9/113 (8%) there was a conversion of ESD into resection, while in all cases the cause was unsatisfactory lifting – less than 2 mm. It was also found that unsatisfactory lifting was more common in patients with tumors located in the right colon than in the left one: 10/61 (16.4%) and 6/52 (11.5%), p=0.0001.

In tumors of the right colon after conversion, in most cases, right-sided hemicolectomy was performed (in three out of five). It should be noted that in group II in three of the four patients subjected to conversion, tumors were located in the peritoneal part of the rectum and in one – in the sigmoid colon. Three patients underwent resection of the upper rectum, and the fourth – resection of the sigmoid colon (Table 3). Histology of removed specimens in patients with conversion revealed adenocarcinoma with invasion of the submucosa of the pT1sm1only in one case. As to conversion rate, the groups of patients did not significantlydiffer (p=1.0). The mean duration of the surgery in patients with tumor site in the right colon was 124.3±8.2 min. and did not differ significantly from this in group II – 119.1±7.0 min., p=0.7.

As follows from table 3, in both groups, the majority of tumors were removed *enbloc*, the fragmentation rate in the right colon after ESD was 9%, and in the left – 10.4%, p=1.0. It should be noted that the main causes of tumor fragmentation were: severe fibrosis at the tumor base, even with satisfactory and sufficient lifting; the presence of active bowel movements, tolerant to medical correction; tumor site on the antimesenterial edge, especially in the right colon. These difficultiesled to a significantlengthening of the dissection time (more than 4 hours) andled to theloop fragmentation (Fig. 3A,B).

Intraoperative complications developed in 2/56 (3.5%) patients with tumors in the right colon and 2/48 (4.1%) patients – in the left colon, p=1.0. It should be noted that in patients to whom ESD was performed

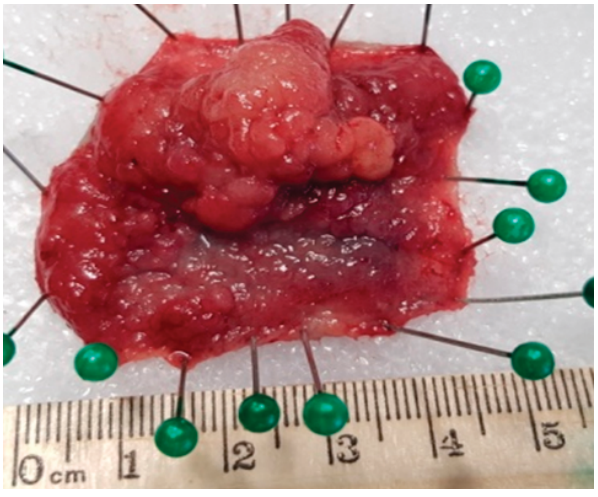

Figure 3A. *Resected specimen removed en bloc after ESD*

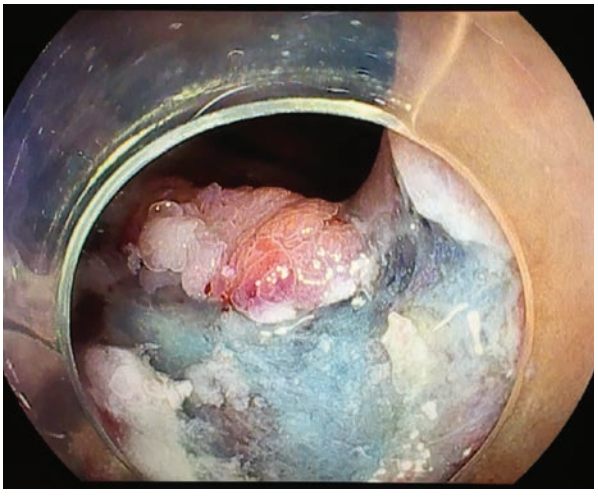

Figure 3B. *Tumor fragmentation. In the photo – residual adenoma after submucosa dissection. The remaining fragment will be removed by the next loop excision.*

Table 2. *The lifting characteristics of tumors depending on the localization*

Tumor lifting	Tumor site		p
	Right colon n=61	Left colon n=52	
Unsatisfactory 0-2 мм	10/61 (16,4%)	6/ 52 (11,5%)	0,001
Satisfactory 3-4 мм	3/61 (4,9%)	1/52 (2%)	0,6
Sufficient 5 mm or more	48/61 (78,7%)	45/52 (86,5%)	0,4

Table 3. *Features of surgical procedures*

Peculiarities of surgical interventions	Tumor site		p
	Right colon n=61	Left colon n=52	
ESD conversion	5/61 (8,2%)	4/52 (7,7%)	1,0
Right hemicolectomy	3/5		
Ileocaecal resection	1/5		
Transverse colon resection	1/5		
Resection of the upper rectum		3/4	
Sigmoid resection		1/4	
En bloc*	51/56 (91%)	43/48 (89,6%)	1,0
Fragmentation *	5/56 (9%)	5/48 (10,4%)	

** converted patients are excluded*

due to the neoplasmsin the right colon, there was only intraoperative arterial bleeding. While in one case it was possible to stop it by clipping, in the second clipping an attempt was unsuccessful, which required a right-sided hemicolectomy. In both cases, the further postoperative period was without complications. In two patients after ESD of tumors in the left parts, perforation of the bowel wall was detected. During the ESD, there were difficulties associated with increased fibrosis in the area of the tumor base, and after removal of the specimen, it turned out that the dissection of the formations was performed not in the submucosal, but deep in the muscular layer of the intestinal wall. The defect of the intestinal wall failed to be restored by clipping. So, laparoscopic resection was performed, in one case – in the left colon, in the other – in the sigmoid colon. Postoperative period in these patients was uneventful.

Two patients (1.9%) developed postoperative complications. One patient (0.95%), after ESD performed due to the adenomas of the caecum up to 45 mm,had profuse defecation with blood clots on the 3rd day. Urgent endoscopy and hemostasis by clipping were performed. The further postoperative period was uneventful. Another patient (0.95%) of group II on the 3rd day after ESD developed perforation of the sigmoid colon. Abdominal radiology revealed free gas under the dome of the diaphragm. The patient was urgently operated on, a perforation of the sigmoid colon wall in the ESD region was revealed, resection of the sigmoid colon by *Mikulicz*was performed. The further postoperative period was uneventful. Currently, the patient is waiting for a stoma closure.

Pathologic morphological study of resected specimens

According to the histology ofresected specimens in most patients of both groups (98/104, 94%) tumors were adenomas (Table 4). Serrated adenomas in the right colon were more common than in theleft – 5/61 (8.2%) and 1/ (2.0%), p=0.1

In group I, invasive adenocarcinomas were detected in 5 (8.2%) patients, and in four patients tumors had the depth of invasion of Sm1, and in one – Sm2. In group II, invasive early cancer was detected in 4/52 (11.6%) patients, in one case, the patient revealed the depth of invasion of Sm3, the tumor was localized in the sigmoid colon. This patient underwentlaparoscopic sigmoid resection. At the same time, according to the final histological study of the resected specimen, no signs of residual tumor in the area of ESD were revealed, but adenocarcinoma metastasis was detected in one of the lymph nodes (1/12 lymph nodes) of the mesentery of the sigmoid colon, the pT1sm3N1aM0 stage was detected. Currently, the patient receives adjuvant XELOX chemotherapy. In the remaining patients with adenocarcinomas, according to the data of the pathomorphological study, ESD wasperformed as R0 resection.

The rate of R0 resections in groups I and II was 52/61 (85%) and 42/52 (80.7%), p=0.6. The middle lateral margin was 1.7±0.9 (0-7).

The majority of patients 85/104 (81%) were followed up. Median follow-up was 6 (2-9) months. In two patients with adenomas in the proximal third of the transverse colon and in the sigmoid colon after 6 months local recurrence of the tumor up to 1.0 cm in size was revealed. They were treated mucosectomy. Thus, the rate oflocal recurrence of adenomas after ESD was 2.04%.

Table 4. *Characteristics of removed tumors according to the pathomorphological study of resected specimens*

Criteria	Tumor site		p
	Right colon n=61	Left colon n=52	
Morphology			
Adenomas with different grade of dysplasia	51 (83,6%)	47 (90,4%)	0,6
Serrated adenoma	5 (8,2%)	1 (2,0%)	0,1
Adenocarcinoma pT1 Sm1 Sm2 Sm3	5 (8,2%) 4 1 –	4 (11,6%) 2 1 1	1,0
Morphology of the resection margins after ESD			
R0 resection	52/61 (85%)	42/52 (80,7%)	0,6
R1 resection	9/61 (15%)	10/52 (19,3%)	

DISCUSSION

In the current decade already, endoscopic dissection in the submucosal layer is a priority and safe trend in organ-preserving treatment for epithelial tumors of the colon. In the present study, the incidence of intraoperative and postoperative complications after ESD was 3.5% and 1.9%. The most frequent complications were bleeding and perforation of the colon in the dissection area. It should be noted that the data obtained correlate with the results of other papers [5,12,13,19]. However, the Swedish researchers Rönnow Carl Fredrik et al. [11] showed that the most frequent complication is intraoperative perforation of the intestinal wall – 14%. At the same time, in almost all cases, except for one, it was possible to close perforating hole by endoscopic clipping, which allowed to avoid conversion with transabdominal resection. In this study, perforation was not such a frequent complication. It occurred in two cases during the ESD, and in one – on the 3rd day after. Moreover, all patients underwent bowel resection due to an unsuccessful attempt to clip the defect. In our opinion, this is due to insufficient experience of clipping perforation of the intestinal wall and it is thought that with accumulation of experience, attempts to restore the defect will be more successful. However, Isomoto H. et al. [4], analyzing the results of ESD in 278 patients, showed that statistically significant factors leading to postoperative complications (perforation and bleeding) are the large tumor size more than 50 mm and the fibrosis in the submucosal base, when there are difficulties with differentiation of layers during dissection. In addition, the other authors showed that risk factors for R1 resection were tumor site in the right colon with the presence of fibrosis in the submucosal base. In the present study, we did not obtain statistically significant differences in the incidence of complications, R1-resection rate, and tumor fragmentation between groups depending on the tumor site. But it should be noted that bleeding developed only in patients with tumors located in the right colon. In addition, the tumor site in the right colon showed a significant high rate of unsatisfactory tumor lifting, which became a frequent cause of conversion to resection.

It is interesting that Tanaka N. et al. [16]encountered difficulties arising in ESD in the right colon. According to these data, excessive development of adipose tissue in the submucosal layer of the intestinal wall is an unfavorable factor for the development of intra- and postoperative complications, fragmentation of tumors and R1 resections. Multivariant analysis by Tanaka, N. showed that the tumor site in the right colon, malegender and body mass index >25 kg/m^2 are independent risk factors for excessive development of adipose tissue in the submucosal base. Thus, despite the growing interest in endoscopic submucosal dissection in the last decade, a number of issues that have arisen with the accumulation of experience of its implementation require further discussions. This is especially true for the removal of epithelial tumors of the right colon.

CONCLUSION

Endoscopic submucosal dissection is a fairly safe method of removing colon adenomas with the rate of intra-and postoperative complications of 3.5% and 1.9%, respectively, and the level of local recurrences of 2.04%. A tumor lifting of less than 2 mm in the right colon is a risk factor for tumor fragmentation and conversion to bowel resection.

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