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Translation of the article

Risk factors for colon adenomas recurrence after endoscopic mucosal resection

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ABSTRACT *AIM: to identify risk factors for neoplasms recurrence removed by endoscopic mucosal resection (EMR).*
PATIENTS AND METHODS: the single-center retrospective observational study included 207 patients with 260 benign colon neoplasms. There were 95 (45.9%) males and 112 (54.1%) females. The median age of the patients was 67 (27-80) years. The results obtained were assessed using following criteria: morbidity rate, complication type, hospital stay, tumor site, number of neoplasms in colon, lateral growth, fragmentation rate, technical difficulties (mucosal fold convergence)during surgery, grade of dysplasia, recurrence rate.
RESULTS: intraoperative fragmentation of the neoplasms during mucosectomy occurred in 48/260 (18.5%) cases. Postoperative complications within the period of up to 30 days occurred in 13/207 (6.3%) patients. The most frequent 9 (4.2%) postoperative complication arising after mucosectomy was post-polypectomy syndrome. Another 4 (2.0%) patients produced bleeding after the surgery, which required repeated endoscopic procedure. No mortality occurred. The tumor size exceeding 25 mm (Exp (B) = 0.179; 95% CI = 0.05-0.7; p = 0.014), severe dysplasia (Exp (B) = 0.113; 95% CI = 0.03-0.4; p = 0.001) and fold convergence (Exp (B) = 0.2; 95% CI = 0.07-0.7; p = 0.015) are independent risk factors for disease recurrence.
CONCLUSION: mucosectomy is indicated for colon adenomas if its size does not exceed 25 mm and can be removed en bloc.

KEYWORDS: *colon polyps, mucosectomy, polypectomy, relapse, adenoma*

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

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INTRODUCTION

Benign epithelial neoplasms of the colon are a significant problem of colorectal surgery and health care not only because of their malignant potential, but also because of their prevalence among the working-age population [1-3]. Inlocalized benign neoplasms of the colon mucosa, their endoscopic minimally invasive removal is a routine, standard procedure [4-6]. Endoscopic mucosectomy (EMR – endoscopic mucosal resection) was developed in 1984 as a method of removing epithelial neoplasms of the gastrointestinal tract [7]. In the modern interpretation, EMR is defined as resection of a fragment of the intestinal wall, including the mucosa to the submucosal layer, using a diathermicloop [8-9].

The EMR is quite well studied. However, there are a number of aspects that cause additional difficulties in the endoscopic removal of benign neoplasms, for example, the convergence of folds, the localization oflarge polyps between two folds, the spread of the tumor beyond the two folds, which are factors of fragmentation of neoplasms and require additional study of their impact onlong-term results.

With the purpose of identifying risk factors of recurrence tumors that were removed by mucosectomy, the Ryzhikh National Medical Research Center of Coloproctology conducted a retrospective audit of results of treatment in 207 patients operated with endoscopic resection of the mucous layer of the colon from October 2014 to December 2019.

PATIENTS AND METHODS

The study design is a single-center retrospective observational study. The study was conducted in accordance with the GCP ethical standards and approved by the local ethics committee.

The study included patients with benign neoplasms of the colon, up to 40 mm in size, who underwent endoscopic mucosectomy.

Patients with neoplasms of type 0-Ip according to the Paris classification (pedunculated polyps) and patients who underwent simultaneous endoscopic procedures using different methods were excluded from the study.

All the colonoscopies and endoscopic procedures were performed using expert-class devices Olympus Exera III or Pentax 7000 endoscopic stands.

According to the study protocol, mucosectomy (EMR) was performed in 207 patients with 260 benign neoplasms of the colon. The study included 95 (45.9%) males and 112 (54.1%) females. The median age of the patients included in the study was 67 (27-80) years.

In 164 (79.2%) patients only one benign neoplasm of the colon was detected. Another 34 (16.4%) patients had 2 synchronous neoplasms and 9 (4.4%) patients had 3 or more colon polyps.

In the analyzed group of patients, tumors were located in the right colon in 120 (46.2%) cases and 140 (53.8%) neoplasms were localized in the left colon.

Adenoma site was analyzed as a risk factor for postoperative complications and fragmentation of removed specimens.

Taking into account that the risks of fragmentation of the specimen and postoperative complications are formed independently for each neoplasm, the risks were calculated for each polyp individually.

The size of the neoplasm was estimated using the span of the branches of biopsy forceps, which is 8 mm in their unfolded state. Their median size was 13 (7-40) mm.

For endoscopic characterization of all neoplasms, the JNET classification was used. The study included patients with type 2 according to JNET. The Paris classification was used for the macroscopic description.

The lateral growth factor of adenomas, which was observed in 112/260 (43%) cases, was separately analyzed by us as a risk factor for postoperative complications or the risk of the specimen fragmentation.

The technical difficulties of performing endoscopic procedures could additionally be due to the presence of converging folds – convergence, which was evaluated endoscopically and reflected in the study protocol in 48/260 (18.5%) cases.

The preliminary sampling of biopsy material for histological confirmation of the diagnosis was not performed routinely, due to the risk of edema/fibrosis of the submucosal layer, which made it difficult to perform further endoscopic surgery.

Statistical Processing of Results

The primary patient data was entered into a Microsoft Excel 2018 spreadsheet for Windows 10.

In the normal distribution of the variation series, the quantitative parameters were described using the mean values and standard deviation. In the case of an abnormal distribution of the variation series, medians and its extreme values were used. To assess risk factors, the odds ratio (OR) was determined using four-field tables with a 95% coincidence interval. Multivariate analysis with logistic regression was performed to exclude interdependent factors. The level of logistic regression was estimated by the value of χ^2 and a standardized coefficient. Using the logistic regression, a nomogram was constructed to determine the risk of recurrence after EMR. The determination of cut-off points for quantitative parameters was performed using ROC analysis with the construction of a ROC curve (Receiver Operating Characteristic) and the determination of the Yoden criterion. The results were considered significant when the area under the ROC curve was at least 0.5. The statistical analysis was performed using SPSS 23.0 software for

Windows (SPSS Inc., USA). The differences were considered statistically significant at $p < 0.05$.

RESULTS

Postoperative complications within 30 days occurred in 13/207 (6.3%) patients. No mortality occurred.

The most common postoperative complication after EMR was the postpolypectomy syndrome.

It occurs as a result of transmural burn, which can be accompanied by hyperthermia, and requires prescribing intraluminal or systemic antibacterial drugs. Local inflammatory reaction with hyperthermia with subsequent administration of antibacterial drugs occurred in 9 (4.2%) patients after EMR.

Another 4 (2.0%) patients produced bleeding after surgery, which required repeated endoscopic procedure. At the same time, in two cases, despite the presence of blood clots in the intestinelumen, there were no signs of ongoing bleeding. In the other two patients, the bleeding was stopped by endoclips.

The incidence and structure of postoperative complications are presented in Table 1.

The mean postoperative hospital stay was 4.5±1.5 (3-6) days.

Intraoperative fragmentation of neoplasms during EMR occurred in 48/260 (18.5%) cases.

Removal of the specimen by fragments was required in 32 of 53 (60%) manipulations with neoplasms exceeding 25 mm, compared with 16 of the remaining 207 (7.7%) cases in the group of tumors with smaller sizes (OR = 18.1; 95% CI = 8.5-38, p = 0.001). The presence of severe dysplasia (n = 114; 43.8%) did not affect the risk of specimen fragmentation (p = 0.2). Fourteen neoplasms with type IIB according to the JNET out of 87 were removed in fragments. The JNET tumor type also had no significant impact on the fragmentation risk (p = 0.6). Convergence of folds was observed in 48 cases. Removal of the specimen by fragments was required in 8 (16.7%) patients with such a difficultlocalization, but we did not find statistically significant differences against the 40/212 (18.9%) patients with the standard localization of neoplasms: (p = 0.8).

Table 1. *Characteristics of postoperative complications of EMR*

Nature of complications	Severity of complication	Incidence of complications (n=207)
Post-polypectomy syndrome	I	9/207 (4.2%)
Bleeding	IIIa	4/207 (2.0%)
Total:		13/207 (6.2%)

Table 2. *Factors influencing the development of recurrence after EMR (univariate analysis)*

Factor	OR	95%CI	p
Fragmentation	3.8	1.4-10.3	0.015
Tumor size>25 mm	5.1	1.9-13.9	0.001
IIB type as per JNET	0.5	0.1-1.6	0.4
Severe dysplasia	5.5	1.7-17.4	0.002
Fold convergence	2.8	1.02-7.9	0.05
Localization in the right colon	0.6	0.2-1.6	0.5
LST type	1.0	0.3-2.7	1.0

Table 3. *Factors influencing the development of local recurrence of adenoma after EMR (multivariate analysis)*

Factor	EXP (B)	95% CI	p
Tumor size >25 mm	0.179	0.05-0.7	0.014
Severe dysplasia	0.113	0.03-0.4	0.001
Fold convergence	0.222	0.07-0.7	0.015
Fragmentation	0.38	0.1-1.4	0.1

When analyzing thelong-term results of treatment of patients with benign neoplasms of the colon, we studied the incidence oflocal recurrences.

Local recurrence was considered the appearance of a tumor in the site of the postoperative scar. Control colonoscopy was recommended for patients at discharge from hospital 6 months after removal of neoplasms *en bloc* and 3 months after fragmentation.

Thelate results were estimated in 144/207 (69.5%) patients with 173/260 (66.5%) colon polyps with a mean follow-up of 11.0±7.4 months.

Local tumor recurrence after EMR developed in 12 (8.3%) patients. They had 19/173 (10.9%) recurrent neoplasms detected in a mean period of 8.6±3.7 months.

All the patients in this group with recurrent neoplasms underwent repeated endoscopic surgery. Eight (66.0%) patients underwent repeated EMR and four underwent endoscopic submucosal dissection.

In a pathomorphological study, 10 (83.3%) repeated procedures were recognized as R0 resections. All 12 patients of this group were examined at the time of publication; there were no signs of the disease recurrence.

Given that most of the recurrences occurred after the removal oflarge neoplasms by fragmentation, we performed a ROC analysis.

According to the data obtained, the cut-off point was the size of tumors of 25 mm.

This factor was separately analyzed as a risk factor for the recurrence. Additionally, the factors of fold convergence, neoplasm site, tumor type according to the JNET, and pathomorphological structure of the tumor with severe dysplasia were evaluated (Table 2).

Univariant analysis revealed that local tumor recurrences were significantly more often in case of neoplasm fragmentation (OR = 3.8; 95% CI = 1.4-10.3; p = 0.015), in tumor sizes exceeding 25 mm (OR = 5.1; 95% CI = 1.9-13.9; p = 0.001), in severe epithelial dysplasia (OR = 5.5; 95% CI = 1.7-17.4; p = 0.002), and in technical difficulties in the form of fold convergence (OR = 2.8; 95% CI = 1.02-7.9; p = 0.05).

To identify independent risk factors forlocal recurrence of adenomas after EMR, a multivariate analysis was performed in the presented study (Table 3). In thelogistic regression model, it was found that the tumor size exceeding 25 mm (Exp (B) = 0.179; 95% CI = 0.05-0.7; p = 0.014), severe dysplasia (Exp (B) = 0.113; 95% CI = 0.03-0.4; p = 0.001) and fold convergence (Exp (B) = 0.2; 95% CI = 0.07-0.7; p = 0.015) are independent risk factors for recurrence.

To develop a visual predictive model of recurrence risk when deciding on the optimal method of tumor removal, we constructed a nomogram that includes independent risk factors for recurrence during EMR (Fig. 1).

In the presented nomogram, within the “A” area, each of the identified factors corresponds to a certain number of points on the upper scale. To obtain a quantitative assessment of the influence of a trait, a perpendicular straightline is drawn to the upper point scale. After that, the points received are summed up. Then, within the “B” area, a perpendicularline is drawn from the total number of points to the lower scale, reflecting the total risk of recurrence of the removed neoplasm, expressed as a fraction of one.

To get a numerical value as a percentage, the resulting value should be multiplied by 100.

DISCUSSION

Diagnosis and treatment of benign epithelial neoplasms of the colon is an urgent problem of colorectal surgery, since it allows to reduce the growth and mortality from malignant neoplasms of thislocalization.

The wide prevalence among the working-age population makes this task socially significant [1-2, 10].

Mucosectomy (EMR) is a safe, cost-effective and clinically effective endoscopic method for removing benign neoplasms of the colon, compared to

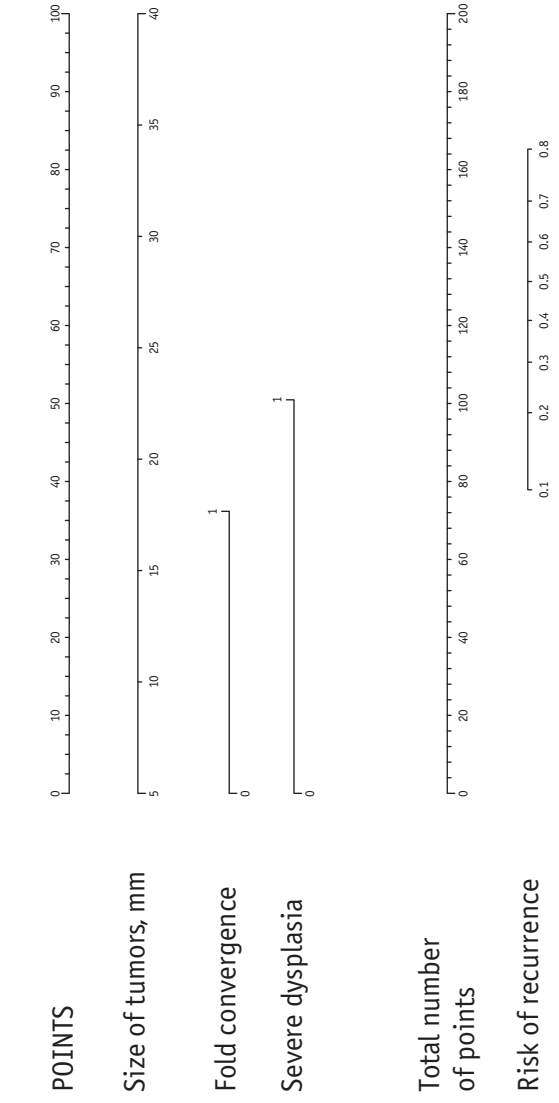

Figure 1. *Nomogram of the risk of recurrence during EMR*

surgical or other more complex endoscopic procedures [11-14].

Understanding the risk factors for recurrence of the disease will allow us to identify the category of patients in whom we should refuse to perform EMR in favor of endoscopic submucosal dissection or resection method [15-17].

In the course of the study, independent risk factors for the disease return were identified: tumor size (Exp (B) = 0.179; 95% CI = 0.05-0.7; p = 0.014), severe epithelial dysplasia (Exp (B) = 0.113; 95% CI = 0.03-0.4; p = 0.001) and fold convergence (Exp (B) = 0.2; 95% CI = 0.07-0.7; p = 0.015).

The difficulty of removing neoplasm exceeding 20 mm *en bloc* is one of the problems associated with EMR [7].

Thus, according to the multicenter study by Buchner A.M. et al., with formations smaller than 20 mm in size, EMR allows to remove 93.3% of tumors *en bloc* (78.3% – within unaffected resection margins – R0 resection). The incidence of the neoplasm *en bloc* removal progressively decreases with increasing size of the neoplasm. Thus, with a mean tumor size exceeding 22 mm, only 53.5% of tumors can be removed *en bloc* [3].

In this aspect, the results of our study correlate with the data of the worldliterature [18-19].

Risk factors for locoregional recurrence after endoscopic treatment were studied in a multicenter prospective study by Oka S. et al., summarizing the results of treatment of 1,524 patients with colon neoplasms. Tumor fragmentation,lateral tumor growth, and tumor size exceeding 40 mm were significant risk factors for recurrence [19]. However, despite thelarge sample size, the main drawback of this study is its comparative nature and the identification of risk factors for recurrence for both endoscopic submucosal dissection and EMR, with significant differences in methods.

The factor of severe epithelial dysplasia identified by us was also previously reflected in the specializedliterature. Thus, according to the Russian study based on the results of the treatment of 600 patients operated with transanal endoscopic microsurgery, the presence of severe dysplasia (p = 0.01) and the recurrent nature of the neoplasm (p = 0.04) are independent risk factors for the development oflocal recurrence [20].

The factor of convergence of folds, identified by us in the study, significantly increases the risk of recurrence of adenomas due to the technical difficulties of removing the neoplasm *en bloc*. According to some authors, the convergence of folds – a factor of fragmentation of the specimen during EMR, can also indirectly indicate the presence of malignant transformation of the tumor and invasion of the submucosallayer [21-22].

Thus, the identified risk factors for recurrence of adenomas after their endoscopic removal were previously described in the specializedliterature, which further indicates the reproducibility of the study results. However, only in the study, they were independently combined and accumulated into a joint nomogram, which allows to make decision when choosing the method of endoscopic excision, depending on the expected risk of recurrence of the neoplasm.

CONCLUSION

Mucosectomy (EMR) is indicated for colon adenomas do not exceed 25 mm, which can be removed *en bloc*. When predicting the risk of recurrence of the disease, it is advisable to use the proposed nomogram, including tumor size factors (Exp (B), to adopt the optimal method of endoscopic excision) = 0.179; 95% CI = 0.05-0.7; p = 0.014), severe dysplasia (Exp (B) = 0.113; 95% CI = 0.03-0.4; p = 0.001) and fold convergence (Exp (B) = 0.2; 95% CI = 0.07-0.7; p = 0.015).

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