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Surgery for *MutYH*-associated polyposis (systematic review, meta-analysis)

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ABSTRACT *BACKGROUND: to date, there are no clear guidelines for MutYH-associated polyposis (MAP) surgery.*
AIM: to study the world literature on MutYH-associated polyposis surgery using a meta-analysis.
MATERIALS AND METHODS: the systematic review was carried out in accordance with the practice and guidelines of PRISMA. The meta-analysis included the results of 14 case studies, 4 cohort studies, as well as own data on patients with MAP. A total of 474 patients with MAP were analyzed.
RESULTS: when analyzing the number of colorectal polyps, the total occurrence value (95% CI: 0-14) of less than 10 polyps was 10%, in 52% cases (95% CI: 0-100) from 10 to 100 polyps were detected, in the remaining cases there were more than 100 polyps. Colorectal cancer was diagnosed in 56% of patients (95% CI: 45–66) of patients, while tumors with the T1-T3 were found in 38% of cases, tumors with the T4 were found in 7% of cases, lesions of the regional lymph nodes N + were found in 8%. The synchronous tumors were detected in 12%, and metachronous — in 5%. In 87%, some parts of the large intestine were preserved, in 38% [95% CI: 0-100] — colectomy with ileorectal anastomosis, in 27% [95% CI: 23-31] — colorectal resection, in 22% [95% CI: 16-27] — polypectomy), in other cases total removal of all parts of the large bowel was performed.
CONCLUSION: patients with MAP who have been diagnosed with less than 100 colorectal polyps may undergo endoscopic polypectomy, if technically possible. Despite the risk of developing CRC, which in most cases has a non-aggressive course, the clinical course of MutYH-associated polyposis is relatively favorable. For this category of patients, it is possible to limit colorectal resection with annual endoscopic control and removal of detectable polyps in the remaining parts of the large bowel.

KEYWORDS: *MutYH gene, MutYH-associated polyposis, familial colon adenomatosis, surgical treatment, colorectal cancer*

CONFLICTS OF INTEREST: *The authors declare no conflicts of interest*

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INTRODUCTION

MutYH-associated polyposis is a rare hereditary polyposis syndrome with an autosomal recessive type of inheritance, which is based on biallel mutations in the *MutYH* gene. The disease is characterized by the development of multiple colorectal polyps with a high risk of their malignant transformation.

According to a number of authors, the risk of developing colorectal cancer by the age of 70 in patients with biallel mutations in the *MutYH* gene reaches 80% [1–5].

It is known that 1–2% of people in Northern Europe, Australia and the USA are carriers of heterozygous mutations in the *MutYH* gene [4–7]. The database gnomAD reports a slightly lower frequency of pathogenic variants (~0.8%). Using these figures, it is possible to calculate the prevalence of *MutYH*-associated polyposis (MAP) from 1:20,000 to 1:60,000 for individuals who are carriers of biallel germinal mutations [8]. According to researchers, MAP accounts for 0.7% of all cases of colorectal cancer and up to 6% of cases of colorectal cancer at an early age in patients with a small number (< 15–20) of adenomas and

Table 1. *Characteristics of the studies included in the meta-analysis*

Author	Year	Type	N patients
Toboeva M.Kh. [17]	2021	Retrospective	24
Nascimbeni, R [18]	2010	Retrospective	11
Morak, M [19]	2010	Retrospective	33
Patel, R [20]	2020	Prospective	134
Nieuwenhuis, M [21]	2012	Retrospective	254
Casper, M [22]	2010	Clinical case	1
Nielsen, M [23]	2006	Clinical case	2
De Schepper, H [24]	2012	Clinical case	2
Kidambi, T [25]	2018	Clinical case	1
Pervaiz, M [26]	2010	Clinical case	1
Buisine, M [27]	2013	Clinical case	1
Casper, M [28]	2018	Clinical case	1
De Mesquita, G [29]	2019	Clinical case	1
Fostira, F [30]	2010	Clinical case	2
Kacerovska, D [31]	2016	Clinical case	1
Reggoug, S [32]	2009	Clinical case	1
Tricarico, R [33]	2009	Clinical case	2
Weidner, T [34]	2018	Clinical case	1
Volkov, N [35]	2020	Clinical case	1
TOTAL	-	-	474

in families with a burdened hereditary history [6, 11–16].

An extremely urgent problem is the tactics of treating patients with MAP in the absence of colon cancer. It is also an important task to choose the optimal volume of surgery in the development of colorectal cancer, taking into account the risk of metachronous tumors and the high probability of continued growth of polyps in the remaining parts of the large intestine. The available literature data indicate that the basic principles of treatment for patients with *MutYH*-associated polyposis are similar to the recommendations for patients with an attenuated form of familial adenomatous polyposis (FAP). However, there are no clear guidelines for this particular category of patients to date.

Given the difficulties in choosing the approach of surgical treatment, we decided to make a meta-analysis for treatment of *MutYH*-associated polyposis.

Getting Data

Search strategy and the meta-analysis of data was carried out in accordance with the preferred reporting items for systematic reviews

Figure 1. *Article Search Chart*

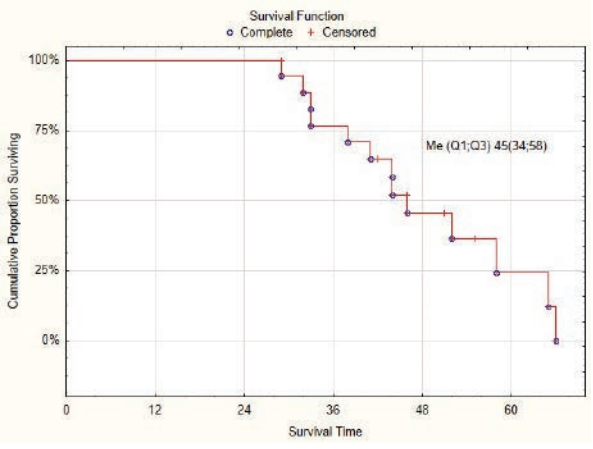

Figure 2. *Median age of diagnosis of CRC in patients with MAP*

Table 2. *Characteristics of the combined group of patients with MAP, made up of individual clinical cases without taking into account the own data*

Indicator	Patients with MAP, N = 18
Age	44 (33;55) (29–76)
Gender – Male – Female	 11 (61%) 7 (39%)
Family medical history: – autosomal dominant – autosomal recessive – no medical history – no information available	 6 (33%) 5 (28%) 6 (33%) 1 (6%)
Mutations: – compound-heterozygous – homozygous	 12 (67%) 6 (33%)
The number of polyps in one patient Quantity not specified	30 (10;100) (0–103) 6
The presence of colorectal cancer: – patients with CRC – patients without CRC	 13 5
Localization of cancer: – caecum – ascending colon – sigmoid colon – rectum – localization is not specified	 3 4 5 3 1
Synchronous cancer Metachronous cancer	3 –
Surgeries: – PE, dissection – resection – CE with IRA – CPE	 3 (cancer in the polyp) 5 3 7
T – 1 – 2 – 3 – 4a – no data available	 2 1 2 1 7
N – 0 – + – no data available	 5 1 7
M – 0 – + – no data available	 5 1 7

and meta-analyses checklist (PRISMA) [14] in the Medline electronic database using Pubmed queries among English-language literature without restrictions on the publication date (up to 10.05.2021) by keywords: "*MutYH*-associated polyposis", "*MutYH*-gene", "*MutYH*". The main criterion for the selection of articles included in the meta-analysis was the presence of a description of surgical decision-making in patients with MAP. In addition, the following data were extracted from the scientific publications: author, year of publication, study design, number of patients in groups, characteristics of groups, median overall survival.

Statistical Analysis

Continuous data was described by the median (Q1; Q3) (min-max). The time before the onset of colorectal cancer was calculated by Kaplan-Mayer's method (Statistica, TIBCO 2013). Single-group and subgroup analysis for categorical data was carried out by the random effects method (Rstatistica, metaphor package). The combined median in the single-group analysis was calculated using the meta medium (Rstatistica) package. Statistical heterogeneity among the studies was assessed using the χ^2 test. Heterogeneity was considered statistically significant at $I^2 > 50\%$ and $p < 0.1$.

Search Results

Using the PubMed search engine, 725 studies were found in the Medline database for a query containing the above keywords (Fig. 1). Sixty-two studies were selected during screening. Then the works that did not contain information about treatment tactics were excluded — 44. As a result, the analysis included 14 studies describing clinical cases and 4 group studies (Table 1). Thus, data on 474 patients with MAP were included in the meta-analysis.

Рисунок 3. *Структура описания результатов*
Figure 3. *Results description structure*

Analysis of Individual Cases within the Combined Group

For a detailed analysis of the clinical and genetic features of MAP, the data on patients described in individual clinical cases were grouped (Table 2). Subsequently, this group was included in the meta-analysis along with the other studies.

The combined group included 11 men and 7 women. When analyzing this group of patients, CRC was diagnosed in 13 patients. The median number of polyps was 30 (0–103) (10;100). Mutations in the compound heterozygous state were most common in 12/18 (67%) cases, and in homozygous — in 6/18 (33%) patients. Family medical history was observed in 11/18 (61%) patients, while 6 families had a horizontal type of inheritance, 5 — vertical. According to the pathomorphological study, tumors within the intestinal wall (T1-T3) were diagnosed in 5/6 patients. N + regional lymph node lesion and metastatic lung lesion were found in 1/6 patient. There were no data on the results of histology in 7 patients.

The median age of diagnosis of colorectal cancer in patients with *MutYH*-associated polyposis in the combined group of patients was 45 (34; 58) years (Fig. 2).

Thus, according to the analysis of the data from the combined group of patients, colorectal cancer against the background of MAP develops at a late age, while in most patients, tumors are limited to the intestinal wall without affected regional lymph nodes. The data of the above group are further included in the meta-analysis within the framework of the combined group.

Meta-Analysis Results

The structure of the meta-analysis results description is shown in Figure 3.

The rate of occurrence of *MutYH*-associated polyposis (with a risk of inheritance of the disease

of 25%) in men and women is distributed equally (Fig. 4).

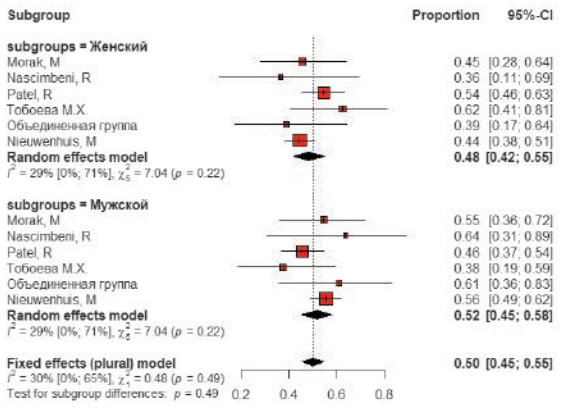

Figure 4. *Forest plot distribution of patients by gender*

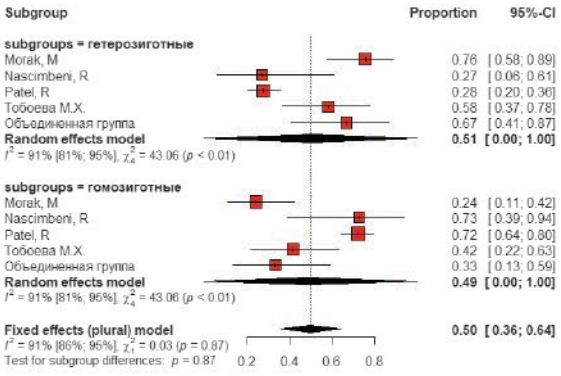

Figure 5. *Forest plot distribution of patients depending on the presence of homozygous/compound heterozygous mutations*

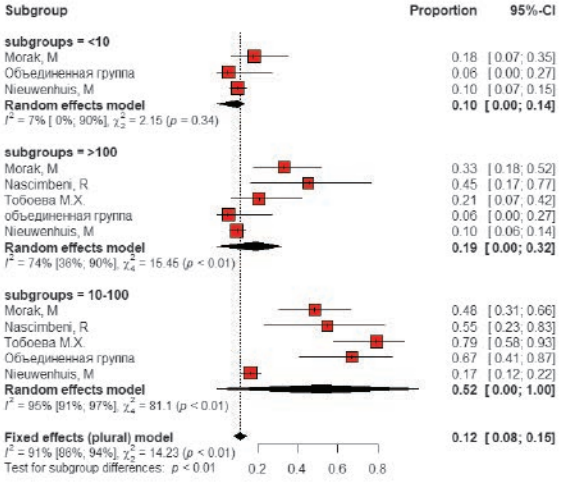

Figure 6. *Forest plot distribution of patients by the number of polyps in the colon*

Similar data were obtained by analyzing the occurrence of mutations in homozygous and compound-heterozygous states. At the same time, their uniform distribution in groups (49% and 51%) was revealed (Fig. 5).

When studying the number of polyps in patients with MAP, it was revealed that the total occurrence (95% CI: 0–14) of less than 10 polyps in the large bowel was 10%. 52% of patients (95% CI: 0–100) had from 10 to 100 polyps, 19% (95% CI: 0–32) of patients had more than 100 colorectal polyps.

It should be noted that in the Russian patient population, the minimum number of colorectal polyps was 22 (Fig. 6).

Colorectal cancer in the initial treatment of patients with MAP was diagnosed in 56% (95% CI: 45–66) (Fig. 7).

At the same time, synchronous tumors were revealed in 12% of cases, and metachronous tumors — in 5%. The timing of the occurrence of metachronous cancer is not indicated in the

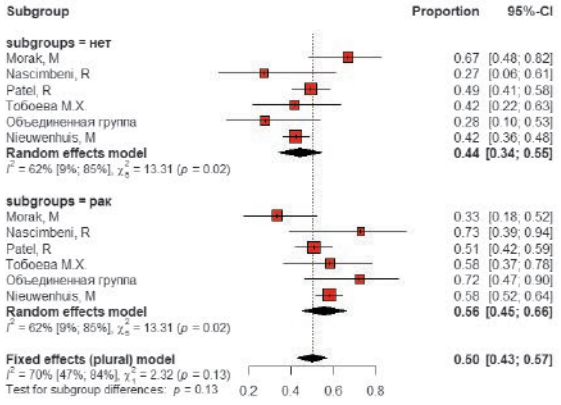

Figure 7. *Forest plot distribution of patients by the presence of colorectal cancer*

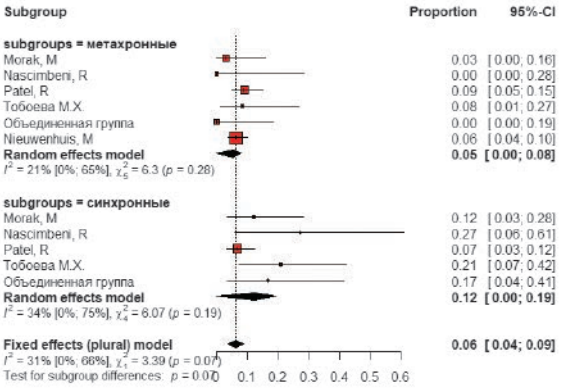

Figure 8. *Forest plot distribution of patients depending on the presence of synchronous, metachronous CRC*

publications, but the average follow-up period was 5 (0–13) years (Fig. 8).

By location, the tumors were distributed almost evenly in all parts of the large intestine (Fig. 9).

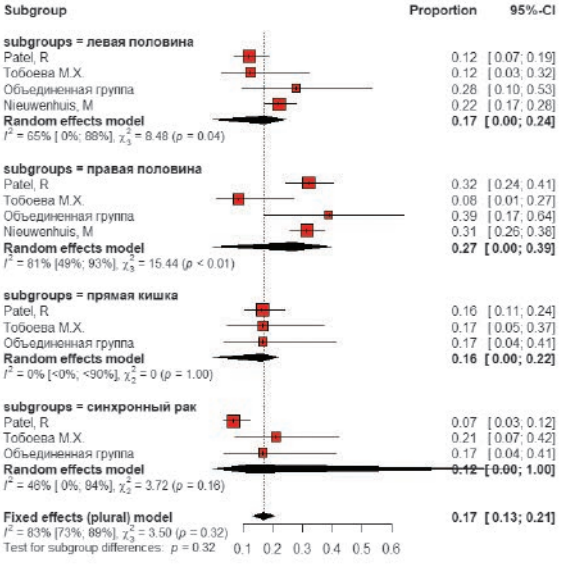

Figure 9. *Forest plot distribution of patients by CRC localization*

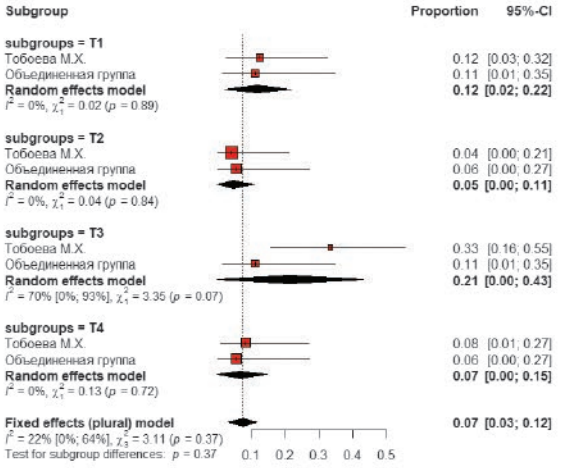

Figure 10. *Forest plot distribution of patients depending on the degree of CRC invasion into the intestinal wall*

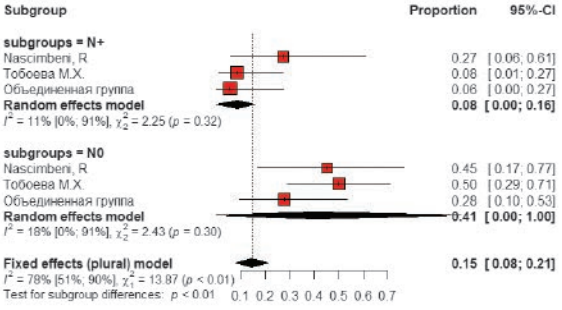

Figure 11. *Forest plot distribution of patients depending on the involvement of regional lymph nodes*

When analyzing the results of pathomorphological studies, it was found that tumors with the T1-T3 index were present in 38% of patients, and with the T4 index — in 7% of patients (Fig. 10).

The lesion of regional lymph nodes N + was found in 8% of patients.

Distant metastases were found only in 4% of cases. (Fig. 11, 12).

When analyzing the surgical tactics of patients with MAP, total removal of the entire large intestine was performed in 19% of cases (95% CI: 0–33), and in 87% of cases, certain parts of the large intestine were preserved (Fig. 13).

The median age of detection of colorectal cancer was 48 years (Fig. 14).

DISCUSSION

As a result of our study, it was revealed that the rate of *MutYH*-associated polyposis in patients with multiple colorectal polyps (> 20) in the Russian population is 7%.

It should be noted that according to the meta-analysis, in one of the studies performed in 2010, less than 10 colorectal polyps were diagnosed in some patients (14%) [26]. However, according to the study in 2017 at the RNMRC of Coloproctology of the Health Ministry of Russia, among patients with less than 20 adenomatous colorectal polyps, mutations in the *APC* and *MutYH* genes were not detected in any case, and therefore this criterion was chosen as the lower bound and was the basis for the examination of patients with MAP included in the study in the Russian population [36]. This limit of the number of polyps is currently generally accepted both in Russia and in the USA [37, 38].

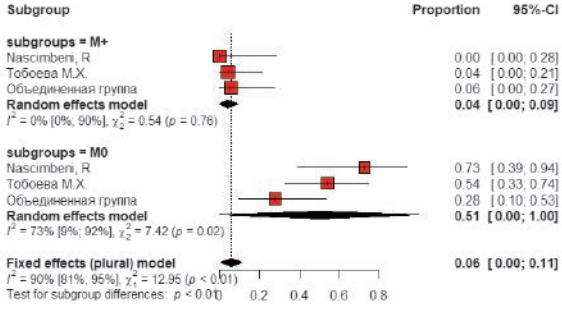

Figure 12. *Forest plot distribution of patients by the presence of distant metastases*

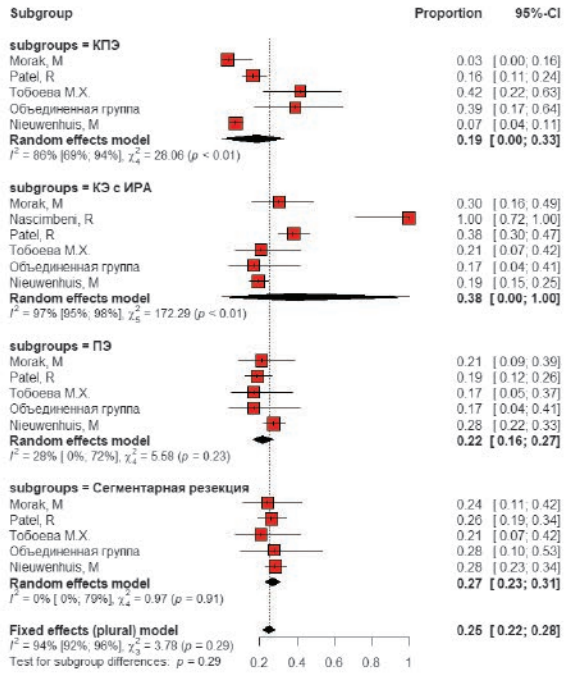

Figure 13. *Forest plot distribution of patients depending on the volume of surgical interventions*

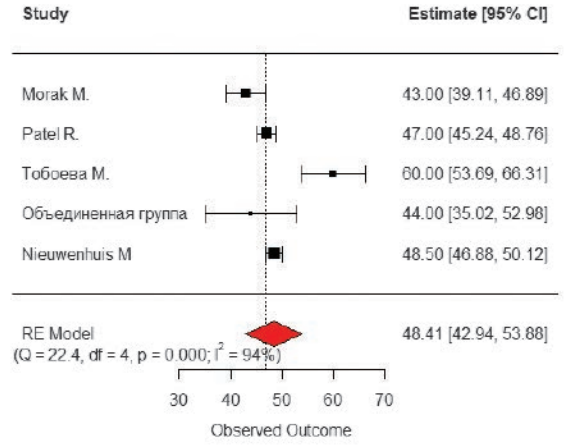

Figure 14. *Median age of CRC detection in patients with MAP*

When analyzing the results of a pathomorphological study, it was revealed that in most patients the tumor is located within the intestinal wall (T1-T3), while the lesion of regional lymph nodes is in 8% of cases. Extremely rarely, distant metastases are detected (in 7% of patients). Metachronous cancers, according to the meta-analysis, were found only in 5% of observations. According to our data, metachronous colorectal cancer was diagnosed in 2/14 cases in 15 and 16 years after the detection of the first colorectal tumor and was represented by a moderately differentiated adenocarcinoma pT1N0cM0, while all patients included in the study by the RNMRC of Coloproctology were alive for 10 years of follow-up. These facts indicate that cancer against the background of *MutYH*-associated polyposis has a relatively non-aggressive course.

The meta-analysis showed that 87% of patients underwent organ-preserving procedures. In our study, a detailed analysis was carried out in a group of patients who had one or another part of the large intestine preserved (14/24 patients). At the same time, it was found that dynamic observation with endoscopic sanitation of colorectal polyps suspends the process of malignant transformation of colorectal polyps and helps to reduce the risks of colorectal cancer.

Colorectal cancer in patients with MAP occurs exponentially; therefore, there cannot be a normal distribution of the age of development of CRC in this category of patients. In this regard, the description of age by average numbers found in group studies is not correct [26–28].

Thus, regarding the age of occurrence of CRC, we can refer only to the data obtained in our study, namely, the median age of occurrence of colorectal cancer in Russian patients with *MutYH*-associated polyposis was 60 (47; 63) years. In addition, ROC analysis revealed that colorectal cancer develops in patients aged > 41 years with a sensitivity of 93%, specificity of 80% (area under the curve of 89.6, $p < 0.001$).

Taking into account the above facts, in patients with less than 100 colorectal polyps endoscopic polypectomy of the largest of them (more than 5 mm) with constant dynamic monitoringcan be performed. If endoscopic sanitation is technically impossible due to the high rate of growth of polyps, a large number and large size, colorectal resection is performed, followed by constant dynamic control of the remaining parts of the large intestine or colectomy [39].

CONCLUSION

Patients with MAP who have been diagnosed with less than 100 colorectal polyps may undergo endoscopic sanitation if it is technically possible. Despite the risk of developing CRC, which in most cases has a non-aggressive course, the clinical

course of *MutYH*-associated polyposis is relatively favorable. For this category of patients, it is possible to make only segmental colorectal resection with annual endoscopic control and removal of detectable polyps in the remaining parts of the large intestine.

AUTHORS CONTRIBUTION

Concept and design of the study: *Aleksey S. Tsukanov, Aleksey A. Ponomarenko*
Collection and processing of the material: *Margarita Kh. Toboeva*
Statistical processing: *Aleksey A. Ponomarenko*
Writing of the text: *Margarita Kh. Toboeva*
Editing: *Dmitry Yu. Pikunov, Yuri A. Shelygin, Sergey A. Frolov*

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