Review
From Prof. Dr. Diana Vasileva Stefanova - Petrova, DSc
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Subject: Dissertation on the topic: "Heredity, precancerous lesions and monitoring in patients with colorectal cancer" for obtaining the educational and scientific degree "PhD" in the field of higher education 7. Health and sports, professional field 7.1. Medicine, doctoral program "Internal Medicine"

PhD student: Dr. Girgina Manolova Stoyanova, PhD student in self-study at the Clinic of Gastroenterology at Acibadem City Clinic Tokuda Hospital.
Supervisor: Associate Professor Dr. Stoyan Handjiev, PhD

According to Order №164 of March 29, 2021 of the Executive Director of Acibadem City Clinic Tokuda Hospital EAD, Sofia, pursuant to Art. 4 of ZRASRB, art. 31 of PPZRASRB, art. 29 of the Regulations for the development of the academic staff of Acibadem City Clinic Tokuda Hospital and Decision of the Scientific Council (Minutes № 35 / 18.03. 2021).

Brief biographical data
Dr. Girgina Stoyanova was born on November 11, 1957. in the city of Sofia, in 1981 she graduated medicine at the Medical Academy - Sofia. From 1982 to 1985 she worked as an intern and nutritionist in the Gastroenterology Department of the District Hospital in Yambol. Since 1985 she has been working in the Gastroenterology Department at the FIFTH MHAT - Sofia, initially as an endoscopist, from 1991 to 1992 she was the Head of the Department, from 1992 to 2002 she was a doctor, from 2002. until 2012 - senior doctor, and since 2012 she has held the position of "Head of Gastroenterology" at the Fifth Hospital - Sofia.
In 1986 she acquired the first specialty in "Internal Medicine" and in 1990 - the second specialty "Gastroenterology and Dietetics". Dr. Stoyanova has a professional qualification in gastrointestinal endoscopy - II level (1986 and 2004), laser therapeutic endoscopy (1992) and specializations in abdominal ultrasound, endoscopy with international participation in specialized thematic conferences and congresses. She is a member of the Bulgarian Medical Union, Society of Gastroenterology, ESO, EASL and IASGO. Fluent in French, English, Latin and Russian.

Data on the selected topic of the dissertation
Colorectal cancer is a socially significant disease due to its increasing incidence worldwide. In the European Union, the incidence is 58/100000 and the death rate is 30/100 000 per year. In Bulgaria, colorectal cancer is second in oncological cause of death after lung cancer in men and in women after breast cancer. The newly discovered cases of colorectal cancer in our country are between 50 and 55 / 100,000 per year. In the last three decades, the incidence of colorectal cancer in Bulgaria has quadrupled.
Early detection and treatment of precancerous lesions in the colon, followed by monitoring, can lead to a real reduction in the incidence and decrease in the incidence of colorectal cancer.
The endoscopic method is crucial for early diagnosis and treatment, as well as for dynamic follow-up after surgery in patients with colorectal cancer.
The dissertation is the result of many years of clinical experience, observation and study of the causes associated with intestinal inflammation, dysplasia and the development of colorectal cancer.

Scientific significance of the chosen topic and innovation

The developed dissertation justifies the need to introduce early screening (before the age of 50) for colorectal cancer; development of an algorithm for monitoring early colorectal cancer; updating a program for systematic monitoring of precancerous lesions and colorectal cancer with a view to prolonging the survival and quality of life of these patients; updating follow-up control intervals with a view to early detection of recurrences after surgical treatment; offering an individualized follow-up approach in patients with precancerous lesions, such as familial polyposis, Lynch syndrome, serat colorectal lesions, and inflammatory bowel disease. A balanced, systematic approach to diagnosis, treatment and follow-up has been proposed in patients with colorectal precancerous lesions and operated on for colorectal cancer.

Structure of the dissertation

The dissertation is presented on 203 standard pages. Of which: title page; description of the content on 5 pages; abbreviations used -1 page; introduction on 1 page; 45 pages - literature review; 1 page - purpose and tasks, 3 pages - material and methods; 116 pages - results and discussion; 3 pages - conclusions and recommendations; 5 pages for clinical cases; 2 pages conclusion; 2 pages for contribution and 18 pages with bibliography. The structure of the dissertation is well balanced, meeting the requirements for such research. The text is perfectly illustrated with 134 figures and 24 tables. The bibliography includes 257 publications, ten of which are in Bulgarian; 222 of them have been published since 2010.

The literature review and its conclusions correspond to the topic of the dissertation. Current literature data on the links between dysplasia and inflammation, precancerous lesions and hereditary factors associated with the evolution of colorectal cancer are analyzed. The problem of early colorectal cancer in patients under 55 years of age has been studied. The need for early screening of precancerous lesions with chromendoscopy, high-resolution i-scan / endoscopic techniques, in combination with modern biochemical studies, fecal calprotectin, tumor markers, molecular analysis and immunohistochemistry; optimization of the conditions for endoscopic observation, both in patients with precancerous lesions and in already operated patients; individualization of observation according to the nature of the disease process.

The aim of the dissertation is to study the morphogenesis of colorectal cancer developing from precancerous lesions and to propose an optimal algorithm for early diagnosis, timely treatment and follow-up of patients. Formed five tasks that meet the goal.

The study was conducted on the territory of the Fifth Hospital - Sofia in patients from the departments of gastroenterology and abdominal surgery of the hospital. The follow-up period is 5 years. 213 patients were included, divided into the following groups: (1) a group of patients who underwent colorectal surgery with a subgroup of early colorectal cancer up to 55 years - 87 patients; (2) group of inflammatory bowel diseases in ulcerative colitis and Crohn's disease - 45 patients (3) group of patients with intestinal polyps and adenomas 71 patients (4) group of patients with intestinal polyposis - 5% of the total number of subjects; (5) patients with individual follow-up. Examination methods include a physical examination every 3-6 months for the first three years and every 6 months for the fourth and fifth years; follow-up of tumor markers CEA and CEA19-9 at each visit for 3-5 years after surgery; examination of serum CD26 in isolated cases. The main method of examination is endoscopy. Biopsy material from endoscopies was analyzed histologically to assess the severity of dysplasia, to determine the type of precancerous lesions and the depth of invasion in the transition to colorectal cancer. A selective immunohistochemical study of CEA and Ki67, chromogranin, neuronospecific enolase and cytokeratins was performed. Genetic tissue biomarkers - KRAS and BRAF typing - were studied selectively. In some cases, endoluminal ultrasound is performed. Computed tomography scans are performed in the sixth month to one year after surgery and then annually for three to five years in patients with colorectal cancer. A PET scan

was performed in patients with suspected extracolonary involvement. For statistical analysis of the data were used: descriptive statistics; graphical analysis; Kolmogorov-Smirnov method for frequency distribution; nonparametric Mann-Whitney analysis to test hypotheses for difference between ranks; non-parametric Kruskal-Wallis method for dependencies; one-way analysis of variance; parametric and nonparametric correlation with Pearson or Spearman coefficients; regression analysis.

The results in the group of operated patients with colorectal cancer show a more frequent participation of men aged between 56 and 65 years. The most common histological variant is that of moderately differentiated carcinoma. The left hemicolon is more commonly affected. In 16.09% of the cases the heredity was established in a straight line. Postoperative follow-up revealed polyps in 70% of cases. Early colorectal cancer occurs mainly in women under the age of 55; in 2/3 of the patients it is moderately differentiated carcinoma, the leading localization is that in the rectum, in 44%, heredity is established in a straight line. Polyps were found in 70% of patients with chronic inflammatory bowel disease, of which 6.67% were serat adenomas. The results in the group with colon polyps show a higher incidence in men and in the age group between 62-68 years, affecting mainly the left hemicolon. Histologically, adenomas (tubular, villous, etc.) predominate.

Serum polyps are found in 9% of cases. The results in the group with intestinal polyps show involvement of the left hemicolon - in 40%, location in the rectum and sigmoid - in 20%, complete involvement of the colon - in 40% of cases with an increase in their frequency between 48 and 68 years of age. The female sex is more often affected. Of these, 30% with serata histological characteristics, tubular - 30% and mixed polyposis - 30%. A high degree of dysplasia was found in 40% of patients with polyps. Intraepithelial neoplasia (G1- carcinoma in situ) is observed in 10%. Heredity in a straight line is found in 20% of cases.

Conclusions and contributions of the dissertation

Based on these data, the need for early and longer active monitoring in patients with inflammatory bowel disease, followed by patients with intestinal polyps; colon polyps and patients operated for colorectal cancer. The main recommended method of observation is endoscopic with high definition devices, and targeted biopsies should be taken in each patient to record parameters such as inflammatory activity, presence and degree of dysplasia and transition to neoplasia. The aim is to achieve early prevention of colorectal cancer and its recurrence after surgery by introducing an individualized approach to control the activity of intestinal inflammation and control intestinal dysplasia.

The "quality of life" index is introduced in the dissertation and are distinguished: very good, good and satisfactory quality of life index. The term reflects the quality of life of patients according to the duration of their active follow-up. The average value of the index (61.46) in the group with polyps shows the best quality of life compared to the other groups. In second place in terms of quality of life are the monitored patients after surgery, in third place are the monitored patients with inflammatory bowel diseases and in fourth place are the monitored patients with intestinal polyps.

The need to create a national program for active long-term monitoring of colorectal cancer surgeons in order to effectively treat emerging lesions and improve their quality and life expectancy. For this purpose, it is proposed to perform early postoperative endoscopy (one to three months after surgery) to detect early anastomotic recurrences, synchronous and metachronous tumors. Active follow-up is proposed until the end of the fifth year after colorectal cancer surgery. A differentiated approach to high-risk cases with the need for more frequent monitoring is shown (operated for colorectal cancer with two or more polyps, with the presence of serat and / or high-grade dysplasia and sizes over 10 mm)

It is proposed to create a register of patients with FAP / MAP, Lynch syndrome and IBD in order to build individualized monitoring programs and the ability to perform high definition endoscopy from 10 to 12 years of age.

Style and presentation of the dissertation

The dissertation is written in correct Bulgarian. The work is presented clearly and understandably, as the tables and figures presented in the text illustrate the presented work perfectly. The dissertation is well structured. The numbering of the chapters, sections and paragraphs is done diligently and facilitates the perception of the presented material.

Conclusion

The dissertation of Dr. Stoyanova is scientifically sound and solves an important and current problem in clinical practice, related to building a model of medical behavior in the observation and treatment of colorectal precancers, colorectal cancer and related heredity.

The dissertation meets all the requirements of the Law for the Development of the Academic Staff in the Republic of Bulgaria (ZRASRB) and corresponds to the specific requirements of the Regulations for the Development of the Academic Staff of Acibadem City Clinic Tokuda Hospital, Sofia.

The dissertation shows that Dr. Stoyanova has in-depth theoretical knowledge and professional skills, demonstrating qualities for independent research.

That is why I confidently give my positive assessment and offer the esteemed scientific jury to award the educational and scientific degree ‘PhD’ in the field of higher education 7. Healthcare and sports, professional field 7.1. Medicine, doctoral program "Internal Medicine" by Dr. Girgina Manolova Stoyanova,

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Reviewer:
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