

OPINION

by Prof. Dr. Kiril Vassilev Draganov, MD , DSc
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of dissertation for awarding the educational and scientific degree 'doctor'

Field of higher education 7. Healthcare and sports, field 7.1. Medicine

Scientific specialty "Internal Medicine"

Author: Dr. Girgina Manolova Stoyanova

Form the PhD: self-training

Institution: Scientific council, "Adzhibadem City Clinic Hospital Tokuda" Sofia

Topic: "Heredity, precancerous lesions and monitoring in patients with colorectal cancer"

Scientific adviser: Assoc. Prof. Dr. Stoyan Handjiev, MD

By order № 164 / 29.03.2021 of the Executive Director of ASK MHAT Tokuda and on the grounds of Art. 4 of ZRASRB, art. 31 of the Regulations for application of ZRASRB, art. 29 of the Rules for the development of the academic staff in ASK Tokuda Hospital and by Decision of the Scientific Council (Protocol №35 / 18.03.2021) I was appointed a member of the Scientific Jury for the defense of the above dissertation. At the first meetings in absentia was set to issue an opinion.

1. General presentation of the procedure and the doctoral student

The set of materials presented by the doctoral student on paper and electronic media is in full compliance with the requirements of the current regulatory framework in the country, namely - Art. 74, para 1, item 1 of the Higher Education Act, Art. 24, para. 2, para 3, para 6 of the Regulations for application of ZRASRB and art. 23, para 6 of the Regulations for development of the academic staff in "ASK MHAT Tokuda", Sofia.

This set of materials includes the following documents:

- Application to the Director of ASK Tokuda Hospital, Sofia for disclosure of the procedure for defense of the dissertation;
- CV in European format with the signature of the doctoral student;
- notarized copy of the diploma for higher education;
- orders for enrollment in doctoral studies and for expulsion with the right to defense;
- an order for conducting an examination from the individual plan and a respective protocol for passed doctoral minimum in the specialty;
- order for appointment and minutes of the meeting of the extended scientific college for preliminary discussion of the dissertation and the decisions taken for opening the procedure and for the composition of the scientific jury;
- dissertation work;
- abstract to the dissertation;

- list of scientific publications on the topic of the dissertation;
- copies of the scientific publications on the topic of the dissertation;
- list of participations in scientific forums on the topic of the dissertation;
- declaration of originality and authenticity of the attached documents;

Dr. Stoyanova has implemented four full-text publications and 2 papers presented at international scientific forums related to the topic of the thesis.

Notes and comment on the documents

The procedure for defense of the thesis and related documents in full compliance with the existing legal framework in Bulgaria.

Brief biographical data

Dr. Girgina Manolova Stoyanova graduated in medicine at the Medical Academy - Sofia in 1981.

From 1985 until now Dr. Stoyanova works as a doctor - gastroenterologist and endoscopist at the Fifth Hospital in Sofia, where the current study was conducted. She has specialties in "Internal Medicine" and "Gastroenterology", acquired in 1986 and 1990, respectively.

On June 24, 2019, Dr. Girgina Stoyanova was enrolled as a doctoral student in independent training in the scientific specialty "Internal Medicine" (order №251 /24.06.2019 of the Executive Director of "ASK MHAT Tokuda"). After successfully passing the exam for doctoral minimum (28.01.2020) and internal defense (1.02.2020) she was expelled with the right to defense (order №158 / 22.03. 2021 of the Executive Director of ASK Tokuda Hospital).

2. Relevance of the topic

The topic of the dissertation is relevant for Bulgarian medicine both in a purely scientific and in a scientifically applied aspect for a number of reasons.

Colorectal cancer (CRC), although declining in frequency, is among the socially significant cancers. In CRC, prevention, early diagnosis and proper monitoring are key to achieving good long-term results. The main role in these activities is played by the gastroenterologist-endoscopist, and at the same time he faces a number of serious challenges. The departments of gastroenterology and abdominal surgery of the Fifth Hospital - Sofia have sufficient experience in the diagnosis, treatment and monitoring of patients with precancerous lesions and CRC, which is a solid basis and the main motivation for the study.

3. Knowledge of the problem

Literature review was thorough and detailed and is represented in volume 45 pp. (Str.9-53 incl.). Dr. Stoyanova has examined in detail all current information concerning various characteristics of CRC - definitions, statistics, precancerous lesions, heredity and genetic aspects, clinical manifestations, diagnosis and behavior, incl. and monitoring.

Some of this information considered "too propaedeutic" - eg. the definition of malignant tumors (p. 9), the clinical and morphological characteristics of CRC (p. 30-31), staging (p. 31-34),

the description of colonoscopy as the main diagnostic method (p. 40-42). These are the facts and figures that are sufficiently well known.

An important place in the review borrow description and discussion of the role of screening colonoscopy (p.42) monitoring and control (p.47). I also give a high grade to the conclusion (pp. 51-53), in which 9 conclusions are formulated (their number is 10 in the abstract). This is the main motivation of the doctoral student, a prerequisite for conducting the study and last but not least proof of detailed knowledge of the problems concerning the CRC.

4. Research methodology

The purpose of the study is presented on page 54.

The study of the morphogenesis of CRC from precancerous lesions, which is part of the stated goal, is on the one hand an "too ambitious" endeavor, and on the other hand many points have been clarified here. I am referring to the appearance of aberrant glands in the epithelial crypts, leading to the development of adenoma and subsequent malignancy in adenocarcinoma, the role of K-Ras, P 53 and other mutations in tumor suppressor genes and activation of protooncogenes, the role of nuclear beta-catenin for chromosomal instability etc. Accept "... offering optimal model for the early diagnosis and timely treatment of the patients to improve survival and quality of life in these patients" as real and true purpose of the thesis.

To achieve the objective, Dr. Girgina Stoyanova sets five tasks - precise and clear.

The study included a large number of patients - a total of 213. They are divided into the following groups: undergone surgical treatment (with subgroups early arising cancer); inflammatory diseases (Crohn's disease and UK); polyps and adenomas; intestinal polyposis; patients with individual observation (the last group is not indicated in the abstract, as well as when reporting the results).

A rich arsenal of methods is used - clinical, laboratory, instrumental, statistical, which is a prerequisite for obtaining significant results.

5. Characterization and evaluation of thesis and contributions

PhD thesis has a capacity of 203 standard pages and is extremely rich illustrated with 24 tables and 134 figures. The bibliography contains 267 literary sources, 10 of which are in Cyrillic, the rest in Latin.

The opinion on the literature review, the purpose and the tasks was stated above. Here I will focus on the results achieved, their presentation and discussion, conclusions and contributions.

"Results" (str.58-157) is the largest chapter in the dissertation. They are presented sequentially for the different groups of patients (from item 3.1. To item 3.4. Incl., Pp. 58-142 incl.). Reported as a non-standard approach and the decision of the doctoral student and tutor presentation at the end of each section "Summary of the group ..." which is a practical conclusions. For the group of operated the number of these leads is 19, for IBD - 15, for the group of polyps and adenomas also 15, for polyposis - 12, or a total of 61 conclusions.

Especially for polyposis think (without being an expert in medical statistics!) That the number of cases in the group (10) is insufficient for statistical processing.

After this distribution by groups are presented "Summary data from the observed groups" (item 3.2., Pp.143-152 inclusive), as well as "Abbreviated results by groups" (item.3.3., Pp.153-157) . The information presented in item 3.3. actually represents conclusions and repeats the summaries by groups (items 3.1.1.3, items 3.1.2.3., 3.1.3.3., 3.1.4.3.), but here the conclusions are consolidated.

In the chapter "Discussion of own results" (pp.158-173) the doctoral student compares the data from his research with those from the specialized literature.

Important scientific and practical point of view, the relationship concerning the distribution by age and sex, stage of cancer, comorbidity affecting the transition from inflammation to dysplasia, quality of life, etc.

I especially appreciate the doctoral student's idea to create an "Algorithm for monitoring precancerous lesions and operations for colorectal cancer", presented on page 173. In my opinion, this is the most important and significant scientific and applied achievement and contribution of the dissertation.

It would be useful for both doctors and this contingent of patients to present the proposed algorithm at the relevant national scientific forums and to implement it in the Bulgarian gastroenterological, surgical and oncological practice after discussion and possible additions and corrections in accordance with the capabilities of our health system as a standard.

On pages 174-176 Dr. Girgina Stoyanova formulates 8 conclusions and 12 recommendations, which are based on the overall analysis of the results and are the logical conclusion of the dissertation.

Another very important merit of the development is the ones described in Chapter Six "Clinical Cases" (pp. 177-181), illustrated with photographs from colonoscopies and pathohistological preparations.

At the end of the dissertation in Chapter Eight the doctoral student presents 18 contributions.

6. Evaluation of the publications and personal contribution of the doctoral student

Dr. Girgina Stoyanova presents a list of four full-text publications and 2 papers presented at international scientific forums related to the topic of the thesis.

After a detailed acquaintance with the dissertation and the publications related to it, I give a positive assessment of the overall work of Dr. Girgina Manolova Stoyanova on the problems of colorectal cancer in terms of heredity, precancerous lesions and monitoring.

The dissertation is an in-depth study. The work on it, the obtained results, their analysis, the conclusions made and the contributions prove the personal merits of the doctoral student.

7. Critical remarks and recommendations

The critical remarks were mentioned in the above opinion, but they do not significantly reduce the qualities of the dissertation and its scientific and applied value.

8. Autoreference

The abstract to the dissertation of Dr. Girgina Stoyanova meets the requirements in terms of volume and content and gives a clear enough idea of the nature of the development, reflects in sufficient detail the results achieved and the formulated conclusions.

CONCLUSION

The dissertation of Dr. Girgina Manolova Stoyanova on "Heredity, precancerous lesions and monitoring in patients with colorectal cancer" contains scientific and applied achievements that represent an original contribution to science and meet the requirements of ZRASRB, Rules for application of ZRASRB and Rules development of the academic staff of ASK Tokuda Hospital. The presented materials and dissertation results fully comply with the specific requirements, have an original character and no plagiarism is established.

The dissertation shows that the doctoral student has in-depth theoretical knowledge and professional skills, demonstrating the qualities and capabilities to conduct independent scientific research.

Due to the above, I give *my positive assessment* of the study and *propose to the esteemed scientific jury to award the educational and scientific degree of "Doctor"* to Dr. Girgina Manolova Stoyanova in a doctoral program in "Internal Medicine", for which I confidently vote "FOR".

Prepared the opinion:

(Prof. Dr. Kiril Draganov, MD, DSc)

20.04. 2021