

To the Chairman of the Scientific Jury,
appointed by Order No. P-109-41/21.01.2022
of the Rector of Medical University - Varna
Prof. V. Ignatov, MD, PhD

OPINION

By Prof. Dobrinka Demireva Radoynova, MD, PhD

under the procedure for defense of the dissertation for awarding the degree of Doctor of Philosophy to *Martina Georgieva Stoeva*, area of higher education "7. Health and Sport", professional field "7.1. Medicine", scientific specialty "Pathology and Cytopathology" - PhD student in full-time education at the Department of General and Clinical Pathology, Forensic Medicine and Deontology at the Medical University - Varna. With a decision of the Department Council under protocol № 387 / 10.01.2022 of the same Department and order № P-109-41 / 21.01.2022 of the Rector of MU "Prof. Dr. P. Stoyanov", 55 M. Drinov Str., 9002 Varna, I have been appointed to prepare an opinion on the described procedure.

Based on Art. 61, para. 3, Art. 62, Art. 63 and Art. 66 of the Regulations for development of the academic staff in MU - Varna and Art. 29 of the Rules for application of the law for development of the academic staff in the Republic of Bulgaria the following decisions were made at the meeting:

I enclose my opinion on the dissertation on "*Immunohistochemical expression of the necroptosis marker RIPK3 in breast cancer*" for the award of the degree of Doctor of Philosophy to Dr. Martina Stoeva.

Area of higher education	7. Health and Sport
Professional field	7.1 Medicine
Scientific specialty	"Pathology and Cytopathology"
Department:	General and Clinical Pathology, Forensic Medicine and Deontology
Scientific supervisor:	Prof. Maria Tsaneva, MD, PhD

Prepared the opinion: Prof. Dobrinka Demireva Radoynova, MD, PhD. Contact address: Tsar Asen Str., Bl. № 68-A, ap. 7, 9002 Varna; e-mail: dradoynova@mail.bg; dobrinkaradoynova@gmail.bg; mobile phone: 0879/202927.

I. Details of the procedure

Martina Georgieva Stoeva is an assistant professor at the Department of General and Clinical Pathology, Forensic Medicine and Deontology at MU-Varna. She was enrolled as a doctoral student in a regular form of education for obtaining a scientific and educational degree

"Doctor" in the scientific specialty "Pathology and Cytopathology" by order № P-109-39 / 01.02.2019 of the Rector of MU-Varna. Based on a decision of the meeting of the Department Council at the Department of General and Clinical Pathology, Forensic Medicine and Deontology under protocol № 387 / 10.01.2022 and order № P-109-41 / 21.01.2022 of the Rector, Martina Stoeva was expelled with the right to defense.

The set of materials presented by the applicant on electronic media is in accordance with the requirements of the Law on the Protection of Scientific and Technological Information and the Regulations on the Terms and Conditions for Acquiring Scientific Degrees and Holding Academic Positions at MU-Varna.

II. Biographical data and career development

The doctoral student Martina Georgieva Stoeva was born on February 22, 1988 in Blagoevgrad.

She graduated from Maths Secondary School of Varna with intensive studying of English /2001-2006/; graduated with a Master's degree in Medicine at the Medical University of Varna /2006-2012/; in 2013 she started working as a resident at the Clinic of General and Clinical Pathology at the St. Marina University Hospital, Varna; becomes a part-time assistant in the same structure /2015-2017/; in December 2017 M. Stoeva successfully defended her specialty /diploma № 021479 / 20.2.18 MUV №3942/; from 2.10.2017 and so far she is a full-time assistant professor at the Department of General and Clinical Pathology, Forensic Medicine and Deontology.

M. Stoeva leads seminars - Bulgarian and English language program for students in the faculties of MU-Varna: Pharmacy, Dental Medicine, Medicine and the specialty Medical Laboratory Technician. She is also a pathologist at the St. Marina University Hospital, where she performs autopsies and biopsy activity.

The doctoral student is fluent in English / C1 / and has the necessary computer skills. She has declared 13 full-text articles, 5 participations in scientific forums and 59 citations. She has participated in 3 research projects.

M. Stoeva shows research interests in various fields of pathology, and her choice for her doctoral dissertation is for the mammary gland; she was approved for public defense on January 10, 2022.

III. Structure of the dissertation

The presented dissertation contains 133 standard pages for the accepted format and is illustrated with 42 figures and 50 tables. The references are from 205 literature sources, of which 4 are in Cyrillic and 201 in Latin. Most of the literature used is from recent sources.

Stoeva's dissertation is written in good and correct Bulgarian, with a well-constructed and logically consistent statement, structured according to the generally accepted way in 9 chapters: Introduction, Literature Review /42 pages/, Purpose and tasks, Materials and methods /8 pages/, Results and discussion /55 pages/, Conclusions, Contributions, Publications on the topic and References. The tables and graphs are well made, sufficiently informative in content, adequately located and do not duplicate the information from the main text.

Relevance of the topic

The relevance of the topic is defined in the first sentence: mammary carcinoma is the most common tumor in women and the most common cause of death from neoplasms (2020). Despite the great global progress of medicine with already established diagnostic and therapeutic approaches, the search for new opportunities continues. One guideline is to identify options for activating cell death in tumor cells. Therapeutically induced apoptosis, in most cases of mammary carcinoma, was considered the only strategy for inducing cell death. A new form of programmed cell death has been discovered, necroptosis, which is similar in mechanism to apoptosis and has morphological similarities to necrosis. The role of necroptosis in the progression and survival of patients with breast cancer is not fully understood, and a more detailed study of its signaling pathways would clarify its involvement in mammary carcinogenesis and provide new strategies for therapeutic response.

Literature review /42 pages/

The literature reference on the topic is multifaceted and comprehensive. General data on the modern epidemiology of breast cancer, etiology and risk factors (family, personality), morphological type of cancer, endogenous hormone levels, reproductive and other factors and the latest classification of benign and malignant breast tumors (2019) are given, as well as staging of carcinoma, prognostic and predictive factors, current treatment, necroptosis as a type of cell death and its role in the growth of mammary carcinoma. The review ends with a summary and motivating conclusion on the topic.

Purpose and tasks of the dissertation /1 page/

The purpose of the dissertation is to study the expression of the necroptotic marker RIPK3 in relation to clinical and morphological parameters, receptor status, proliferative marker Ki67 and disease free survival of patients in breast cancer. For this purpose, 6 specific tasks have been formulated.

Materials and methods /8 pages/

The basis for dissertation development, study groups, routine research, criteria for categorization of parameters, immunohistochemical protocol, levels of RIPK3 expression and the possibilities for interpretation with the used statistical methods are indicated.

Results and discussion /55 pages/

This is the most important section of Stoeva's dissertation. 79 cases were studied for a 9-year period (2010-2018), of which almost 80% had ductal carcinoma and 20% had lobular carcinoma. T-stage and grade of tumors were determined, as well as lymph node metastases and distant metastases, receptor status and Ki67 in tumor tissue; survival of patients without neoplastic progression is presented; the expression of RIPK3 in tumor tissue and non-tumor tissue in fibrocystic disease, etc.

In this section the doctoral student presents the results of her research: comparative analyzes were made between many and different indicators: nuclear expression of RIPK3 in tumor and control tissue (higher in the first); difference between cytoplasmic and nuclear

expression of RIPK3 in tumor tissue; influence of age, histological type of the tumor, the grade and metastasis; HER2 expression; tumor molecular profile; the proliferative index Ki67, etc.

Conclusions and contributions /2 pages/

M. Stoeva has drawn 12 clearly and precisely formulated conclusions that correspond to the completed tasks, and the goal of the dissertation has been achieved. The contributions are 5 in number, two with original character and 3 - with practical-applied one. They are worded concisely and concretely.

Publications on the topic

The PhD student presents 2 (two) full-text publications and 1 (one) participation in a scientific forum in Bulgaria.

Thesis summary

The thesis summary follows the content of the dissertation. It is prepared in a volume of 75 pages (it could be more compact and abbreviated) and consists of parts that accurately present the structure, content, presentation, conclusions, contributions and the list of publications and participations related to the dissertation. The material is sufficiently informative, adequately illustrated and technically correct.

Critical remarks and recommendations


I have no serious critical remarks, except for some technical omissions, probably due to lack of time. I have a recommendation, rather a wish for M. Stoeva to continue digging into the unknown but so interesting depths of the pathology.

IV. Conclusion

The dissertation of M. Stoeva is presented in a fully completed and well-structured form. It meets the requirements of the Law on the Development of the Academic Staff in the Republic of Bulgaria, the Regulations for its implementation and the Regulations on the terms and conditions for acquiring scientific degrees and holding academic positions at MU-Varna. The required procedural purity has been observed. My personal contacts with the doctoral student, although fleeting, give me a reason to say that she is an educated and responsible doctor with great potential for development.

Based on what has been written, taking into account the relevance and importance of the topic, the volume and manner of conducting the study, processing the material, results, conclusions and contributions, I declare to the members of the Scientific Jury that I strongly vote "yes" (positively) for the awarding of Martina Georgieva Stoeva the degree of Doctor of Philosophy in the scientific specialty of Pathology and Cytopathology.

14.02.2022
Varna

Prepared the opinion: 
/Prof. Dobrinka Radoyanova, MD, PhD/