

REVIEW

by **Prof. Zhasmina Mihailova, MD, PhD**

According to the order №P-109-567/19.12.2023 of the Rector of Medical University-Varna and Protocol №1/20.12.2023, I have been selected to prepare a review on the dissertation of Dr. Maria Ivanova Penkova-Ivanova.

About the dissertation on:

"Expression of tumor reversion markers in colorectal cancer".

For the award of the Education and Scientific degree „Doctor“ in the scientific specialty "Oncology", in the field of higher education "Health and Sport", professional field 7.1 "Medicine".

Author: Mariya Ivanova Penkova-Ivanova, MD

Scientific supervisor: Assoc. Prof. Eleonora Georgieva Dimitrova-Gospodinova, MD, PhD

The review was prepared in accordance with the requirements of:

- Law for the Development of the Academic Staff of the Republic of Bulgaria
- the Regulations for the implementation of the RRBA
- The Regulations for the Development of the Academic Staff of MU-Varna and the Specific Requirements for the Acquisition of the Doctoral Degree

Candidate's biography: Dr. Maria Penkova-Ivanova graduated with honors in Medicine from Medical University "Prof. Dr. Paraskev Stoyanov" - Varna in 2016. Since 2018 she has been appointed as a resident at the Clinic of Medical Oncology of the University Hospital "St. Marina" - Varna and as a regular assistant at the Department of Propaedeutics Internal Medicine of Medical University - Varna, English-speaking training. Since 2020 she has been reassigned to the newly formed Department of Oncology, where she is also enrolled as a regular PhD student after successfully passing the competitive examination. Dr. Maria Penkova-Ivanova is fluent in English and German. She is a member of the European Society of Medical Oncology (ESMO).

Characteristics of the submitted dissertation:

The dissertation has a classical structure. The dissertation contains 117 standard pages with the following sections: "Introduction" - 2 pages, "Literature review" - 58 pages, "Aim and objectives of the study" - 1 page, "Patient population and study methods" - 11 pages, "Results" - 12 pages, "Discussion" - 4 pages, "Conclusion" - 1 page, "Contributions" - 1 page, "Contributions of the dissertation" - 1 page, "Scientific publications and communications related to the dissertation" - 2 pages (5 scientific publications are presented, of which 3 are published in international journals). The work is illustrated with 18 tables and 17 figures of high quality and informative. The reference list includes 274 references, of which 273 are in Latin. The dissertation has a balanced structure, the proportions between the different sections are respected and meet the requirements of the Law for the Development of Scientific Staff of the Republic of Bulgaria.

Today, despite advances in modern approaches to the diagnosis and treatment of patients with metastatic colorectal cancer, 5-year survival in this group of patients remains low. In recent years, there has been increasing interest in discovering new prognostic biomarkers to predict and monitor response to treatment. In **her literature review**, Dr. Penkova has presented in detail the main points in the etiology, epidemiology, pathogenesis, staging, diagnosis and treatment of CRC.

The detailed and expert presentation by the dissertation student of the essence of the tumor reversion process is impressive. Dr. Penkova thoroughly and precisely presents the mechanisms of tumor reversion, the structural characteristics of the mediators of the process and the influence of the tumor microenvironment on its course. The structure and function of TSTR (Translational control tumor protein), its role in carcinogenesis, is explained in detail. tumor progression and reversion. The topicality and innovation of the topic is also determined by the fact that a search in Pubmed for the terms "Translational control tumor protein and CRC" yields only 520 results, for the terms "TCTP and CRC" - 4 publications, and for the terms "tumor reversion and TCTP" are released - 63 results.

The main goal of the dissertation is the discovery and introduction of a new prognostic biomarker in these patients. The dissertation examines the relationship between TSTR expression levels as a marker of tumor reversion in patients with CRC and some clinicopathological characteristics of the patients such as gender, age, degree of tumor differentiation, RAS mutational status, progression-free survival and overall survival. The purpose of the dissertation is a logical continuation of the literature review.

The realization of this goal is related to the fulfillment of the main tasks set by the dissertant, namely:

- Selection of patients with histologically verified CRC.
- Comparative study of immunohistochemical expression levels of TCTP in primary tumor cells.
- Analysis of correlations between immunohistochemical levels of TCTP expression and clinicopathological characteristics of patients.
- Analysis of the prognostic potential of TCTP expression in primary tumors in terms of progression-free survival and overall survival.

The set tasks are clearly and accurately formulated and correspond to the set goal, which shows the good theoretical preparation and mastery of the problem by the dissertant.

The materials and research methods are well chosen and comprehensively explained. The analysis of the collected data was performed by applying the methods of medical-statistical data processing.

This dissertation is based on a retrospective study of 74 patients with histologically verified CRC followed up between January 2015 and December 2015. The dissertator has summarized and illustrated with tables and figures the distribution of the selected patients by groups according to gender, age, performance status, RAS mutation status, primary tumor localization and tumor differentiation grade.

The actual results are presented in detail on 12 pages and are illustrated with statistically processed numerical tables and graphs. The analysis of the results shows that there is no association between the expression levels of TCTP in the primary tumor and some clinicopathological characteristics such as: gender, age, pathological status, tumor localization and stage at diagnosis. According to the results presented by the dissertator, higher nuclear levels of TCTR expression are associated with the presence of a greater number of metastatic foci at diagnosis and a higher degree of tumor differentiation. A significantly shorter progression-free time was found for the high nuclear expression group compared to the low nuclear expression group of TCTP. A significant

difference was also reported in terms of overall survival in both groups, with significantly shorter survival in the high nuclear expression TCTP group compared to the low TCTP expression group.

In the **discussion**, Dr. Penkova compares the results of her study with similar studies worldwide, thus highlighting the innovativeness and relevance of the research.

The contributions of the thesis show the importance of the conducted study due to the fact that for the first time in Bulgaria the association between the level of expression of TCTP in patients with histologically verified CRC and progression-free survival and overall survival in the above group of patients was investigated. His contribution is also impressive worldwide, as it is the first time in the world literature to investigate and report the role of TCTP expression levels in the primary tumor as a prognostic factor regarding progression-free survival and overall survival in patients with histologically verified CRC.

The abstract, which runs to 52 pages, is a summary of the main points of the thesis - materials and methods, aim and objectives, results, discussion, contributions and conclusions of the thesis. A list of Dr. Penkova's publications related to the dissertation is presented.

Conclusion:

The dissertation work of Dr. Maria Penkova-Ivanova on "Expression of tumor reversion markers in colorectal cancer" is a precise and thorough scientific work on a topical problem in the field of oncology.

Dr. Maria Ivanova Penkova-Ivanova has set well-formulated goals and objectives, which are precisely implemented. The analysed conclusions are comprehensive and well justified. The contributions of the dissertation have theoretical and practical value and can be used as a basis for future developments. The dissertation fulfils all the requirements for obtaining the degree of Doctor of Education and Science and fully complies with the requirements of the Law on Doctor of Education and Science and the Regulations for its implementation.

In view of the above, I give a positive evaluation to the dissertation work of Dr. Maria Ivanova Penkova-Ivanova and recommend the Scientific Jury to award her the educational and scientific degree "DOCTOR".



Prof. Zhasmina Mihailova, MD, PhD