

STATEMENT

by Prof. Dr. Aneliya Klisarova, MD, PhD, DSc
Head of Department of Nuclear medicine, Methabolic therapy and Radiotherapy
Faculty of Medicine
Medical University "Prof. Dr. Paraskev Stoyanov" – Varna

for dissertation thesis for the acquisition of the educational and scientific degree "PhD"
in the area of higher education 7. Healthcare and sports,
professional direction 7.1.
Medicine, scientific specialty "Medical radiology and Roentgenology speciality
(including use of radioactive isotopes)"

Temenuzhka Rumenova Radeva- Petkova, MD
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Faculty of Medicine
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"INVESTIGATING THE EXPRESSION OF NECROTIC CELL DEATH MARKERS AND THEIR PREDICTIVE VALUE IN NEOADJUVANT CHEMORADIO THERAPY OF LOCALLY ADVANCED RECTAL CARCINOMA"

Dear members of the Scientific Jury,

By order No-109-131 from 20.02.2025 of the Rector of the Medical University "Prof. Dr. Paraskev Stoyanov" — Varna and as a chairman of the Scientific Jury, by Decision of the Scientific Jury in accordance with Protocol No. 1/27.02.2025 I was selected to participate with a statement regarding the PhD defense of Temenuzhka Rumenova Radeva- Petkova, MD.

1. Significance of the scientific subject and formulation of the aim and tasks:

Rectal carcinoma is one of the leading causes of death among patients with cancer. In the era of modern personalized medicine, it is not surprising that the treatment of rectal carcinoma is a subject of numerous studies exploring various ways to improve outcomes and minimize toxicity for patients and customize therapies based on the specific characteristics of each patient's tumor. Despite advances in modern medicine, the treatment of rectal carcinoma is still a challenge. The current standard for treating locally advanced rectal carcinoma is a multimodal approach, including neoadjuvant radiotherapy combined with chemotherapy, followed by total mesorectal excision and adjuvant chemotherapy based on fluoropyrimidine. Ionizing radiation can induce various types of cell death, including apoptosis, necrosis, autophagy, and mitotic catastrophe. Necrotic cell death leads to increased cell membrane permeability, resulting in the release of various intracellular molecules. One of these molecules is HMGB1 (High Mobility Group Box 1). HMGB1 is a marker of necrotic cell death. Molecular biomarkers have the potential to predict the response to neoadjuvant radiotherapy combined with chemotherapy at an early stage with sufficient sensitivity and specificity. Studying HMGB1 as a marker of necrotic cell death may contribute to a better understanding of therapeutic resistance and sensitivity in patients with rectal carcinoma.

The aim of the dissertation is clearly formulated and concerns investigating the expression of HMGB1 as a marker of necrotic cell death and its predictive value regarding the response to neoadjuvant chemoradiotherapy in patients with locally advanced rectal carcinoma. The tasks, 9 in total, are formulated correctly and align with the stated aim.

2. Dissertation structure:

The dissertation thesis follows a classical structure. It is written on 140 pages and includes the following chapters: Introduction, Literature Review, Aim and Tasks, Materials and Methods, Results, Discussion, Conclusions, and Contributions. The thesis contains 16 tables and is illustrated with 57 figures.

The structures of dissertation are well-balanced and the proportions of the individual chapters are balanced. Notably, each part of the dissertation logically follows the stated aim and tasks, and the conclusions naturally arise from the results, statistical data analysis and discussions.

3. The Ph.D. Candidate's Literature Knowledge:

The literature review covers 47 pages, where the author provides an in-depth analysis the epidemiology of rectal carcinoma, its etiology, risk factors, histological types, imaging methods for tumor staging, various treatment approaches, predictive markers, restaging, and response assessment after therapy. Various types of cell death, necrotic cell death markers, and their predictive and prognostic significance in different tumor diseases are in-depth analyzed. The review includes 262 references (2 in Bulgarian), proving the existence of a research gap and the limited availability of systematic data on the role of HMGB1 in rectal carcinoma. Globally, this is one of the few available reports that investigate and analyze the role of HMGB1 in neoadjuvant chemoradiotherapy for locally advanced rectal carcinoma in a significant number of patients. There are currently a limited number of reports on this topic, highlighting the significance and relevance of the present dissertation. The conclusions from the

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4. Methodological Level and Research Design

The study includes a total of 65 patients with histologically confirmed locally advanced rectal carcinoma. HMGB1 serum levels before and after neoadjuvant chemoradiotherapy were measured by commercial ELISA kit.

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The results were analyzed using appropriately selected statistical methods.

The methods and clinical material allowed the author to achieve the research aim, and the tasks were adequately addressed.

5. Correspondence between the aim, results and conclusions:

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There is a logical correspondence between the defined aim, the obtained results, the discussion, and the conclusions. The candidate's own results and discussions are presented on 48 pages and are illustrated with tables, figures and statistical analysis. These align closely with the outlined tasks and are comprehensively detailed. The study analyzed the clinical and pathological characteristics of patients and tumor, evaluating the response to neoadjuvant chemoradiotherapy. Serum HMGB1 concentration levels were compared before and after treatment in patients with locally advanced rectal carcinoma. Correlations were established between HMGB1 serum levels and clinical-pathological features in patients who underwent neoadjuvant chemoradiotherapy. Furthermore, the predictive potential of HMGB1 serum concentrations for treatment response was assessed. The research assessed the prognostic value of HMGB1 in relation to patient survival and analyzed the variations in its levels before and after neoadjuvant chemoradiotherapy, their dynamic over time. The findings demonstrate the detailed analysis performed by the researcher in evaluating serum HMGB1 concentrations before and after neoadjuvant chemoradiotherapy in patients with locally advanced rectal carcinoma.

6. Analysis of Conclusions and Contributions:

The dissertation concludes with 8 conclusions and 9 contributions. The contributions, as per the author's self-assessment, are accepted, highlighting that this dissertation is the first study in Bulgarian radiotherapy practice to investigate serum HMGB1 concentration levels in patients with locally advanced rectal carcinoma. For the first time in Bulgaria, the study examines HMGB1 serum levels and their dynamics in relation to the response to chemoradiotherapy. This is the first report demonstrating the potential of serum HMGB1 levels and their variations as a predictive marker for treatment response.

7. Nature of Critical Remarks and Recommendations:

I have no critical remarks that would cast doubt on the methods, evidence, discussion, or conclusions.

8. Publications and Scientific Activity

The research findings have been published in 3 full-text articles and presented in 4 scientific forum.

Personal Impressions from the Candidate:

Temenuzhka Rumenova Radeva- Petkova, MD is a recognized specialist in radiotherapy. She is among the young professionals who continuously develop and demonstrate interest not only in daily practice but also in innovations in the area. She is professional, collegial, and responsible toward her team at the Clinic of Radiotherapy and the Department of Nuclear Medicine, Metabolic Therapy, and Radiotherapy at the Medical University of Varna, but also to colleagues from other medical specialties. Dr. Radeva actively participates in various scientific forums at both national and international levels, demonstrating the ability to articulate her theses clearly and precisely. She is highly attentive and supportive toward colleagues and students alike.

9. Conclusion:

Considering the scientific merits of the dissertation thesis, namely the relevance of the problem, the obtained results, significant conclusions, and contributions, I confidently recommend that the esteemed scientific jury award the educational and scientific degree " PhD " to Temenuzhka Rumenova Radeva- Petkova, MD for her dissertation: *"INVESTIGATING THE EXPRESSION OF NECROTIC CELL DEATH MARKERS AND THEIR PREDICTIVE VALUE IN NEOADJUVANT CHEMORADIOOTHERAPY OF LOCALLY ADVANCED RECTAL CARCINOMA"*.

Заличено на основание чл. 5,
§1, б. „В“ от Регламент (ЕС)
2016/679

25.03.2025

Prof. Aneliya Klisarova, MD, PhD, Dsc