To the Chairman of the Scientific Jury
Prof. Dr. Stoyan Handjiev, MD,
determined by Order No. 11-07-31# 5/12.09.2025
of the Governor of the University hospital
Acibadem « City Clinic »
Mr. Andrey Markov and
Mr. Mehmet Orkun Sarabıyık - Procurator

REVIEW

by **Prof. Dr. Elena Nikolova Piperkova, MD, PhD**
Head of the Nuclear Medicine Clinic
University Specialized Hospital for Active Treatment in Oncology
"Prof. Ivan Chernozemski" - Sofia

of the dissertation work, for the acquisition of an educational and scientific degree
"Doctor"
in the field of higher education 7. Health and sports,
professional field 7.1. Medicine,
Scientific specialty " Nuclear Medicine".

Dr. Gabriela Hristova Mateva

On the topic:

The role of positron emission computed tomography (18F-FDG PET/CT) in patients with colorectal cancer.

Dear members of the scientific jury , with Order No. 11-07-31 # 5/12.09.2025 and as a member of the Scientific Jury, I have been assigned to participate with a statement on the defense of the dissertation work of Dr. Gabriela Hristova Mateva.

1. Significance of the problem and formulation of the goal and objectives:

Colorectal carcinoma (CRC) has statistically shown a high increase in incidence in the last decade worldwide, including in our country, ranking third among malignant diseases. Early diagnosis, accurate staging and restaging of clinically asymptomatic metastases in regional and distant LNs or in visceral organs, with the highest frequency in the liver, planning and monitoring the effect of complex treatment, as well as establishing biochemical relapse, are of key importance for the individualized therapeutic approach, for risk stratification, improving

the prognosis and quality of life of each individual patient. Studies in the field of refining and increasing diagnostic accuracy in CRC are a very relevant problem for solving the prediction, improving survival and quality of life of patients with this disease. The issue of early prediction of therapeutic response to various chemotherapy regimens, as well as the possibilities for metabolic imaging guidance in the implementation of various local therapeutic procedures, as well as in subsequent reporting of the effect of their application, has not been resolved.
The present dissertation was provoked precisely by the less studied, niche indications, with the aim of exploring the possibilities of the methodology, analyzing patients entirely from the daily clinical practice of the dissertation candidate.

The goal stems from extensive research , reflected in the detailed and at the same time "tight" and accurate literature review. The goal is clearly formulated and to achieve it, the dissertationist synthesizes and correctly sets her four tasks. The tasks are formulated clearly, correctly and meet the purpose of the study.

2. Structure of the dissertation:

The dissertation is structured clearly and precisely, meeting the requirements. It contains 126 standard pages, 65 figures and 9 tables, and is structured in the following sections: Introduction (1 page), literature review (29 pages), aim and objectives (1 page), material and methods (7 pages), results and discussion (67 pages), conclusions, contributions and recommendations. It is preceded by a list of abbreviations for better perception and understanding of the text. A bibliography of 145 sources is presented, 15 of which are in Cyrillic, by Bulgarian authors and 130 in English, from the international scientific press. The proportions between the individual sections are respected. Each section of the dissertation follows the logic of the tasks set to achieve the set goal, and the conclusions naturally arise from the own results, the statistical processing of the data and the discussions.

3. Literary awareness of the dissertation candidate:

The bibliographic reference is sufficiently in-depth and up-to-date, with included 145 cited literary sources , of which 15 are by Bulgarian authors and 130 in Latin , the majority after 2014 , without neglecting previous published experience.

The literature review of the dissertation is 29 pages, with an in-depth analysis of the current application of PET/CT and proves that there are still missing generalized and standardized data on the application of the method in CRC, an algorithm of diagnostic methods has not been developed, there is no personalized approach in arranging the diagnostic methods

according to their appropriateness at the different stages of monitoring the disease and taking into account the effect of treatment. The conclusions from the literature review are specific and justify the goal and objectives of the scientific work.

4. Methodological level and design of scientific research:

The scientific study included 110 patients with histologically verified colorectal carcinoma, examined at the Nuclear Medicine Clinic of Acibadem City Clinic Mladost for the period 2017-2024. The study covers patients, who are very precisely distributed into separate groups according to strict criteria related to the tasks set and allow the relevant conclusions to be drawn.

To fulfill the first of the tasks, a total of 50 patients who underwent consecutive PET/CT examinations with 18F-FDG in a randomly selected period were analyzed. In addition to the PET/CT examination in the specified time interval, which is an inclusion criterion, all available imaging examinations of the patients in the group were additionally examined and processed - a total of 277, of which 109 PET/CT (39%) , 144 CT (52%) and 24 MRI (9%), as well as the results of tumor markers examined.

For the second of the tasks, 26 patients with a total of 42 metastatic liver lesions from colorectal carcinoma were studied. All patients underwent 18F-FDG PET/CT up to two months before radiosurgery for the liver metastatic lesions, as well as restaging 18F-FDG PET/CT three to six months after the procedure, and a total of 52 PET/CT studies were analyzed, comparing metastatic lesions before and after SBRT, assessing the effect of the therapy and looking for correlations between it and various metabolic parameters.

For the third task, 18 F - FDG PET/CT was performed in 23 patients, evaluating a total of 28 liver lesions treated with radiofrequency ablation (RFA). The task 3 group also included 16 patients with liver metastases from other primary tumors (2 with primary hepatocellular carcinoma, 1 with papillae of Vateri carcinoma, 3 with pancreatic carcinoma, 6 with breast carcinoma, 2 with gastric carcinoma, 1 with epipharyngeal carcinoma, 1 with submandibular salivary gland carcinoma), as part of a proof-of-concept study. Contrast-enhanced ultrasound (CEUS) was performed in all patients before and after, and in 11 patients during the RFA itself. The sensitivity of PET/CT and CEUS was evaluated and compared. to assess the effect of RFA on liver lesions.

For the implementation of the fourth task, 18 patients with metastatic CRC were studied. 18 F - FDG was performed in all patients. PET/CT and metabolic parameters (SUVmax , SUVmean , MTV , TLG and sum of the diameters) for all metabolically active malignant lesions were

examined. The obtained values being correlated with the values of the tumor markers CEA and CA 19-9, which were measured within one month before or after the PET/CT examination. Without conducting systemic or local therapy in the time intervals between the measurement and comparison of the metabolic semiquantitative indicators and serum levels of tumor markers.

The results are processed with appropriate statistical methods.

The research methods chosen by the author and the clinical material allow achieving the set goal, and the set tasks have received an adequate response.

5. Correspondence between the goal, results and conclusions:

There is a logical correspondence between the set goal, the obtained results, the discussion and the conclusions drawn. The own results and discussion are presented on 67 pages and are richly illustrated. The patient groups follow the course of the set tasks, presented clearly and in detail. The importance, advantages and possible diagnostic errors of the 18 F - FDG - PET/CT method are indicated, including different variations of physiological and artifactual activity . Indicated are FN and FP findings.

The presented data from the applied diagnostic algorithm for staging CRC show a thorough analysis of the dissertation in the individual groups of patients, according to the stage and values of tumor markers, with regard to possible diagnostic limitations and errors, and this ensures high reliability of the conclusions drawn.

The application of 18F - FDG PET/CT has been studied with big enough cohort of patients with CRC. The prognostic factors for positivity of 18 F - FDG PET results were determined, and the advantages of the method over CT has been specified. The application of 18F - FDG PET/CT in patients with biochemical progression after radical surgical therapy in the wide range of tumor values has been studied. Analysis of the results obtained in patients with liver metastases shows PET/CT sensitivity 80%, specificity 100%, PPV 100%, NPV 30%, which is of significantly higher diagnostic value than CT, which shows slightly higher sensitivity with sensitivity 84%, but significantly lower specificity 33%, PPV 89%, NPV 25%.

The doctoral candidate analyzed the results of the hybrid examination of the patients, in addition to visual (qualitative) and semi-quantitative assessment, through the standardized degree of accumulation of 18 F - FDG. in pathological and therapeutically removed or treated lesions - SUV max , the degree and change in monitoring of disease foci after treatment of tumor glycolysis - TLG and the metabolic tumor volume – MTV. The dissertation confirms that

metabolic changes precede structural-anatomical, dimensional-density changes, both in the assessment of the effect of CRC treatment and the early detection of biochemical recurrences.

6. Analysis of conclusions and contributions:

The dissertation ends with 14 conclusions and 8 contributions, which are formulated in detail and clearly. The contributions are of high importance, due to the fact that this is the first in depth study in our country of the diagnostic contributions of 18 F - FDG PET/CT in CRC on such a broad and in-depth scale . For the first time road to Bulgaria, recommendations have been made for practical application of this high-tech hybrid imaging method, after research on large enough number of patients with CRC, including biochemical progression after radical surgery or complex treatment .

7. Nature of critical remarks and recommendations:

I have no critical remarks that would question the methods, the evidence, the discussion of the results obtained, and the conclusions drawn. The conclusions could be combined and reduced in number, but presented in this way they are highly informative and give weight to each result obtained.

8. Publications and scientific events:

The results of the doctoral student's scientific research on the topic of the dissertation have been published in **2 prestigious scientific journals** , respectively: in "Mol Imaging Radionucl Therapy " and in "Roentgenology and Radiology", as well as **5 scientific reports** , 4 of which have been published in the materials of Eur JNMM - 1917,1919, 2020, 2024) , as well as in Clinica Chimica Acta - 2022 , **carrying an impact factor** .

9. Personal impressions of the candidate:

Dr. Gabriela Hristova Mateva is already an established specialist in Nuclear Medicine. I have direct impressions of the practical and theoretical training in Nuclear Medicine. She is responsible, thorough in her work, in clinical and scientific research. She shows interest not only in her daily work, but also in the innovations in our field, with a desire for the rapid implementation of innovative diagnostics for the benefit of patients. She treats managers, colleagues and patients with respect, is correct, ethical, has qualities for teamwork and improvement.

10. Conclusion:

Based on the stated scientific merits of the dissertation work of Dr. Gabriela Hristova Mateva , the relevance of the problem and the significance of the results obtained, the precise conclusions and useful contributions of the dissertation candidate, I fully convincedly vote "YES" and recommend to the members of the esteemed Scientific Jury to give a positive assessment and award the educational and scientific degree "DOCTOR" to Dr. Gabriela Hristova Mateva for her dissertation work " **The role of positron emission computed tomography (18F-FDG PET/CT) in patients with colorectal carcinoma".**

8.10.2024

Sofia

Prof. Dr. Elena Piperkova, PhD