Review

by **Prof. Dr. Anelia Klisarova, MD**
Head of the Department of Nuclear Medicine and Radiotherapy
Faculty of Medicine
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of the dissertation work for acquiring an educational scientific degree
"Doctor"
in a district on higher education 7. Health and sports ,
professionally direction 7.1.
Medicine , scientific specialty " Medical Radiology and X-rays (including the use of radioactive isotopes)".

Dr. Gabriela Hristova Mateva,
Clinic of Nuclear Medicine
Acibadem City Clinic UMBAL Mladost

Topic on the dissertation labor :

The role on positron emission tomography computer tomography (18 F- FDG PET/CT) at patients with colorectal carcinoma

Dear members of the scientific jury,

With order on The managers of Acibadem City Clinic UMBAL No. № 11-07-81/ 12.09.2025 and as a member of the scientific jury I am assigned to participate in the defense of Dr. Gabriela Mateva's dissertation with a review.

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

Colorectal carcinoma (CRC) is the third most frequent malignant disease in the world. There is a trend for increase of the number of diagnosed cases each year and despite the significant improvement in diagnostics opportunities and therapeutic options , the curve on mortality is also increasing. The current role of 18 F-FDG PET/CT in CRC is formulated in the recommendations of the major oncological societies as complementary to morphological imaging studies - CT and MRI, at least as far as the standard staging, restaging and follow-up of these patients are concerned. At the same time, the method is recommended as a possible alternative in specific clinical indications - assessment of the effect of radiofrequency ablation or radiotherapy, especially for liver lesions, as well as in the context of assessment of the effect of therapy in patients with metastatic disease, unsuitable for assessment according to RECIST 1.1.

Relevance and significance on the problem is determine namely from the less studied specific indications, as well as from the need for a comprehensive approach to patients and combining metabolic parameters with clinical and biochemical ones, for a better understanding and optimization of the assessment of the effect of the applied treatment.
This dissertation examines the hybrid imaging method 18F-FDG PET/CT, showing its advantages, comparing it with other imaging methods, investigating its capabilities in taking into account the effect of radiofrequency ablation and radiosurgery of liver lesions, and looking for relationships between various metabolic parameters and tumor marker levels.

The goal is clearly formulated, arising naturally from the literature review. The tasks that the dissertation candidate sets for himself are 4 in number. They are formulated correctly and correspond to the goal of the study.

2. Structure of the dissertation:

The dissertation has a classical structure. It is written on 142 pages, illustrated with 65 figures and 9 tables and contains the following sections: literature review, aim and objectives, material and methods, results and discussion, conclusions, contributions. The proportions between the individual sections are respected. I would like to draw attention to the fact that each of the parts of the dissertation follows the logic of the set tasks and objective, 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 includes 145 quoted literary sources, from which 15 in Bulgarian and 130 in English, the majority published after 2012.

The literature review of the topic of the dissertation is presented on 35 pages, where the author makes an in-depth analysis of the current application 18 F-FDG PET/CT and proves that there is still a lack of summarized and systematized data on the application of the method in colorectal carcinoma in combination with other imaging and laboratory methods, as well as the issues of early prediction of therapeutic response and the possibilities for metabolic imaging guidance in the conduct of various local therapeutic procedures, as well as in subsequent reporting of the effect of their application. The conclusions from the literature review are specific and directly related to the goal and objectives of the scientific work.

4. Methodological level and design of scientific research:

The scientific study included 110 patients over a seven-year period from 2017 to 2024, in whom we performed staging and restaging 18F-FDG PET/CT. The study covers patients, divided into different groups according to strict criteria that are closely related to the tasks set and allow for the relevant conclusions to be drawn. The results are processed using suitable statistical methods.

The chosen from the author methods of research and clinical material has allowed the achievement on the set goal, and the assigned tasks has received adequate answer.

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 76 pages and are richly illustrated. The patient groups follow the course of the set tasks and are presented clearly and in detail. For the first time in Bulgaria was conducted an in-depth study of the application of 18F-FDG PET/CT in patients with colorectal carcinoma - clinical indications, place in the diagnostic algorithm and how it is combined in practice with other imaging studies. Special attention is paid to the differences between local practices and generally accepted recommendations for the usability of imaging and laboratory studies and the need for standardization. The diagnostic accuracy of CT and PET/CT for the detection of metastatic liver lesions from colorectal carcinoma is compared, demonstrating the advantage of the hybrid method.

The application of PET/CT in the use of local therapeutic techniques - radiosurgery and radiofrequency ablation of metastatic liver lesions has been studied. Regarding radiosurgery, in addition to the effectiveness of the method for planning and evaluating the effect of the procedure, the influence of the segmental distribution of metastatic lesions, as well as their number on the overall response to therapy, has been studied, and it has been established that patients in whom only one lesion has been irradiated demonstrate the best local and systemic response. Additionally, a number of metabolic indicators - MTV, TLG, SUVmax , SUVmean - have been studied in order to search for predictive value for the effect of radiosurgery, with higher pretherapeutic median values of SUVmax, SUVmean and TLG of liver lesions being associated with a worse response to radiosurgery, without, however, proving a statistically significant value as a reliable predictor of any of the parameters studied.

Regarding radiofrequency ablation, the value of the method for assessing the effect of the procedure was studied, the importance of the segmental distribution of secondary lesions, their number, as well as the combination with systemic treatment were again studied and a higher

diagnostic accuracy of PET/CT compared to that of contrast-enhanced ultrasound was demonstrated – 96%, compared to 78 % for CEUS. Only in this group were included patients with other primary tumor localizations, although the predominant number were patients with CRC treated with RFA, in whom mostly isolated multifocal liver involvement was observed as a type of dissemination and it was in them, that the best overall response to the therapy was observed – 57%. In addition to assessing the value of PET/CT in the specific clinical situation, attention was also paid to the overall therapeutic approach, and it is striking that in the majority of patients - 78%, various chemotherapy regimens and/or targeted therapy are performed in parallel with RFA, fully in line with modern trends in the treatment of metastatic liver disease, where the multimodal approach is associated with better disease control and prolonged survival. The dissertation has conducted an in-depth study of the relationship between metabolic parameters measured by 18F-FDG PET/CT (metabolic tumor volume and total glycolysis of lesions) and serum levels of tumor markers (CEA and CA 19-9) . It has been established that at the level of an individual patient with metastatic or persistent colorectal cancer, a strong positive correlation is observed between MTV values and CEA levels, so that changes in the serum marker CEA can serve as a direct indicator of changes in tumor volume, which allows adapting the imaging monitoring regimen based on its dynamics. At the group level, no such significant correlation is established. for MTV, but TLG shows strong correlation with CEA, which emphasizes his potential role as prognostic and monitoring parameter .

6. Analysis of conclusions and contributions:

The dissertation ends with 14 conclusions and 8 contributions, which are formulated in great detail and clearly. I accept the contributions according to the author's self-assessment, and I would like to emphasize that the dissertation work is the first study in Bulgaria on diagnostic opportunities on 18 F-FDG PET/CT in colorectal carcinoma. The application of the hybrid method in practice has been thoroughly studied , and for the first time the application of PET/CT when using local therapeutic techniques to assess their effect has been examined, with a contribution to world practice, recommendations have been made and the need for individualization of the approach and combining information from clinical status, laboratory and imaging studies has been emphasized in order to achieve more effective monitoring, disease control and a better end result for the patient.

7. Nature of critical remarks and recommendations:

I have no critical remarks that would question the methods, the evidentiary material, the discussion of the results obtained, and the conclusions drawn.

8. Publications and scientific events:

The results of the doctoral student's scientific research on the topic have found a place in scientific journals and in scientific forums - 2 real publications - in a Bulgarian and an international indexed journal and 5 scientific communications in international scientific forums.

9.Personal impressions of the candidate:

Dr. Gabriela Mateva was born in the town of Karlovo. She studied medicine at the Faculty of Medicine of Sofia University "St. Kliment Ohridski", from which she graduated with excellent grades in 2016. In the same year, she started working at the Nuclear Medicine Clinic of Acibadem City Clinic Mladost, where she was enrolled as a resident in 2018 and obtained a specialty in Nuclear Medicine in 2022. She was enrolled as a doctoral student at the Clinic of Nuclear Medicine in 2023 to develop a dissertation on the topic " The Role on positron emission tomography computer tomography (18F-FDG PET/CT) in patients with colorectal carcinoma ". During the period of work at the clinic, the doctoral student has 25 publications, both printed in Bulgarian and European journals and participation in the European Congresses of Nuclear Medicine. Dr. Mateva has many active participations in scientific events in the country and abroad, as well as specializations and participations in courses of the European School of Nuclear Medicine, the International Atomic Energy Agency, as well as the European School of Radiology.

Her scientific interests are in the field of nuclear oncology, with a focus on solid tumors - especially colorectal carcinoma and theranostics, as well as in the field of nuclear cardiology. Dr. Mateva is a responsible and accomplished specialist, enjoying the trust of her colleagues and patients. She is always familiar with the latest trends in nuclear medicine and oncology. In recent years, she has shown skills and knowledge in the field of nuclear cardiology and the introduction of modern radiopharmaceuticals in theranostics. She willingly actively participates in the life of the nuclear medicine society. Loved and respected by the entire college - doctors, chemists, physicists, X-ray technicians, nurses.

9. Conclusion:

Considering the scientific merits of the dissertation work, namely: the relevance of the problem and the results obtained, the significant conclusions and contributions of the dissertation candidate, I strongly recommend that the members of the esteemed

scientific jury award the educational scientific degree "doctor" to Dr. Gabriela Hristova Mateva for the dissertation work " The Role on positron emission tomography computer tomography (18F-FDG PET/CT) in patients with colorectal carcinoma ".

15.09.2025

Varna Prof. Dr. Anelia Klisarova, MD.