Review

by Prof. Dr. Anelia Klisarova, DMSc

Head of the Department of "Nuclear Medicine and Radiation Therapy"

Faculty of Medicine

Medical University "Prof. Dr. Paraskev Stoyanov" – Varna

of the dissertation work for the acquisition of an educational scientific degree

"Doctor"

in the field of higher education 7. Healthcare and sports,

professional direction 7.1.

Medicine, scientific specialty " Medical Radiology and rentgenology (incl. use of radioactive isotopes)".

Dr. Tanya Zhivkova Stoeva,

Department of "Nuclear Medicine, Metabolic Therapy and Radiotherapy"

Faculty of Medicine

Medical University "Dr. Paraskev Stoyanov" - Varna

Dissertation topic:

The diagnostic role of 18F-FDG PET/CT in multiple myeloma

Dear members of the scientific jury,

By order No. R-110-68/ 26.02.2024 of the Rector of the Medical University "Prof. Dr. Paraskev Stoyanov" – Varna and as a member of the Scientific Jury, I have been appointed to participate in the review of the defense of Dr. Tanya Stoeva's dissertation.

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

Multiple myeloma is a malignancy of the plasma cells in which monoclonal cells proliferate in the bone marrow, leading to an overabundance of paraproteins, bone destruction, and displacement of other hematopoietic cell lineages. Although rare, it is the second most common malignant hematological disease after Non-Hodgkin lymphomas, accounting for 1% of all occurring types of carcinoma and 13% of all hematologic neoplasms. Its early detection, assessment of bone, paraosseous and extramedullary involvement, as well as identification of pathologic fractures can be of critical importance in determining the clinical stage, therapeutic approach, risk stratification and patient prognosis. The relevance and significance of the problem are determined by the difficulties in diagnosis, staging and early detection of relapses and progression of multiple myeloma. This dissertation examines the hybrid imaging method 18F-FDG PET/CT, showing its advantages, comparing it with other imaging methods, comparing different metabolic activity assessment scales and showing its relationship with laboratory tests.

The objective is clearly formulated, arising naturally from the literature review. The Doctoral student has set six objectives. They are correctly worded and meet the purpose of the study.

2 Structure of the dissertation:

The dissertation has a classic structure. It is presented on 155 pages, illustrated with 47 figures and 22 tables and contains the following sections: literature review, goal and objectives, material and methods, results and discussion, conclusions, contributions. The proportions among the individual sections are maintained. I would like to point out that each of the parts of the dissertation work follows the logic of the set goal and objectives, and the conclusions naturally arise from the personal results, statistical analysis of the data, and discussions.

3 Literary conversance of the doctoral student:

The bibliographic reference includes 231 cited literary sources, of which 2 in Cyrillic and 229 in Latin-script, the majority after 2014.

The literature review of the dissertation is presented in 38 pages, where the author thoroughly analyzes the current application of 18F-FDG PET/CT and proves that there is still a lack of summarized and systematized data on the application of the method in multiple myeloma in combination with other methods, also a unified system for evaluating the metabolic activity of lesions. The conclusions of the literature review are specific and directly related to goal and objectives of the scientific development.

4. Methodological level and design of scientific research:

The scientific study included 125 patients for a twelve-year long period 2009-2021, in which staging and re-staging 18F-FDG PET/CT examinations were performed. The study covers patients allocated to different groups according to strict criteria, which are closely related to the established objectives and enable the drawing of relevant conclusions. The results were processed using appropriate statistical methods.

The research methods and clinical material chosen by the author have enabled the achievement of the set goal, and the objectives set to be solved have received an appropriate response.

5. Consistency between the objective, the results and the conclusions:

There is a logical correspondence between the objective, the results obtained, the discussion and the conclusions drawn. The personal results and discussion are set out in 77 pages and are richly illustrated. The patient groups follow the course of the assigned objectives and are presented clearly and in detail. The significance and role of 18F-FDG PET/CT in combination with laboratory results in different groups of patients are indicated, paraosseous and extramedullary involvement as well as pathologic fractures are studied. A comparison was made between different metabolic activity assessment scales for bone involvement with subsequent stratification of patients according to overall and progression-free survival. In the algorithm for diagnosis, staging, evaluation of the effect of treatment and restaging of multiple myeloma, the data presented show the in-depth and detailed analysis made by the PhD candidate and provide a basis for the credibility of the conclusions drawn.

The candidate conducted a thorough study of the diagnostic capabilities of 18F-FDG PET/CT in staging, evaluation of treatment effect and suspected progression/relapse of MM patients and comparison with conventional imaging methods (radiography, computed tomography, and magnetic resonance imaging) establishing, that the hybrid imaging method has significantly greater sensitivity than conventional radiography for the detection of osteolytic lesions in the skull, ribs, and pelvic bones and is recommended to be used as a complementary imaging method in combination with CT and MRI in disease staging.

For the first time in Bulgaria, the different scales for the assessment of all groups of patients with multiple myeloma are compared - semi-quantitative by SUVmax, visual by 5-PS and according to the number of osteolytic lesions (Durie-Salmon PLUS), establishing better reproducibility and stratification of the different groups of patients evaluated by 5-PS; investigates the predictive value of 18F-FDG PET/CT findings (number of osteolytic lesions and their metabolic activity) in combination with clinical parameters (stage and laboratory results) in terms of overall survival and progression-free survival in newly diagnosed, post-treated and in patients referred for restaging with MM, proving that in patients referred for staging there is a relationship between metabolic activity of lesions and β2-microglobulin values, overall survival, with visual assessment having a better diagnostic value; in patients referred to evaluate the effect of treatment, both scales for evaluating the metabolic activity of osteolytic lesions (visual or semi-quantitative) correspond to the effect of the applied treatment and have a prognostic role in terms of overall survival and time to progression; and in patients for restaging and evaluation of treatment effect, 18F-FDG PET/CT data were found to show the best correlation with β2-microglobulin.

The defined threshold values of glucose metabolism, assessed by SUVmax and FPS, to assess the tumor vitality after treatment and the recommendation for short-term follow-up of patients with results in the "gray" zone can be successfully applied in clinical practice. Excellent specificity and positive predictive value in detecting osteolytic lesions from multiple myeloma, in patients referred for an unknown primary focus, are also ably demonstrated.

6. Analysis of conclusions and contributions:

The dissertation concludes with eight detailed and clearly formulated conclusions and six contributions. I accept the contributions according to the author's self-assessment,-emphasizing that this dissertation represents the first study in Bulgaria to explore the diagnostic capabilities of 18F-FDG PET/CT in multiple myeloma. For the first time in Bulgaria, with extremely important practical importance, the recommendations for the application of the hybrid imaging method in different clinical groups of patients, their assessment according to the different scales for the metabolic activity of bone lesions and the outcome of the disease according to them, are presented.

7. Nature of critical remarks and recommendations:

I have no critical remarks that would call into question the methods, evidence, discussion of the results obtained, and the conclusions drawn.

8. Publications and Scientific Presentations:

Results of the candidates scientific research on the subject have found a place in a scientific journals and in scientific forums, after a review, published in the European Journal of Nuclear Medicine (2023).

Personal impressions of the PhD candidate:

I have known Dr. Tanya Stoeva since the first day when she started working at the Nuclear Medicine Clinic at UMHAT "St. Marina" JSC, Varna since 2019. She graduated in Medicine from our university, and during her studies she made the impression of a responsible, motivated young doctor. Already in the first days of her work in Nuclear Medicine, she showed a special interest in all the novelties in our specialty, in-depth study of basic techniques in the clinic and showed serious ambition and desire to work. She immediately got involved in the routine practice and absorbed very quickly everything shown by her colleagues. Her interest in research and studies made a special impression. She was always involved in the scientific developments of the collective. The topic she chose for her dissertation is up to date, difficult and required a lot of work and professionalism. This is an honor for a young specialist who does not seek the easy and is ready for serious scientific feats. Dr. Stoeva is an excellent colleague who works with all the specialists of the clinic, intelligent, direct and always ready to work together. She is respected by the entire team and by the colleagues she works with at the hospital and

university. All these qualities make her an excellent specialist, an excellent colleague, an excellent teacher and an excellent researcher.

9. Conclusion:

Bearing in mind the scientific merits of the dissertation work, namely: relevance of the problem and the obtained results, the significant conclusions and contributions of the doctoral student, I strongly recommend to the members of the respected scientific jury to award the educational scientific degree "Doctor" to Dr. Tanya Zhivkova Stoeva for the dissertation work "The diagnostic role of 18F-FDG PET/CT in multiple myeloma"

22/04/2024

Varna

Prof. Dr. Anelia Klisarova, DMSc