Review

from **Prof. Dr. Aneliya Klisarova, MD, PhD, DSc**
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for dissertation thesis for obtaining the educational and scientific degree
"Philosophy Doctor"
in the field of higher education 7. Healthcare and sports,
professional division 7.1. Medicine, scientific specialty "Medical radiology and X-ray treatment (including use of radioactive isotopes)".

Dr. Marina Ivanova Dyankova,
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Title of the dissertation thesis:

68Ga-PSMA PET/CT IMAGING IN PROSTATIC CARCINOMA. ADVANTAGES AND POSSIBLE DIAGNOSTIC ERRORS

Dear members of the scientific jury,

By Order № P-109-199 from 29.04.2022 of the Rector of the Medical University of Varna and as a member of the scientific jury, I was selected to participate with a review regarding the defense of the PhD thesis of Dr. Marina Ivanova Dyankova

1. Significance of the problem and formulation of the purpose and tasks:

Prostate cancer is a heterogeneous tumor with a presence of hormone dependent and hormone resistant populations possessing their own biology, prognosis and treatment. Prostate cancer is the most commonly diagnosed malignant disease in males globally. The early diagnosing, the reccurent and metastatic lesions is of paramount importance as regards the determination of the clinical stage, the therapeutic approach, the risk stratification and the prognosis for the patient. The topicality and the significance of the problem are determined by the difficulties in diagnosing, staging and early detection of a biochemical reccurence (BCR) in prostate cancer. This dissertation thesis examines the latest hybrid method ^{68}Ga-PSMA

PET/CT, demonstrating its advantages in comparison to the other imaging methods and the possible diagnostic errors in the interpretation of results.

The aim is clearly formulated following logically from the literary review. The tasks set by the candidate are 6. They are formulated correctly and correspond to the purpose of the study.

2. Dissertation structure:

The dissertation thesis has a classical structure. It covers 197 pages, contains 3 appendices and is visualized with 85 figures and 50 tables, with the following chapters: literature review, purpose and tasks, material and methods, results and discussion, conclusions, contributions and recommendations. The proportions between the different chapters are observed. I would like to emphasize the fact that every chapter of the dissertation paper follows the logic of the set tasks and objective, and the conclusions follow naturally from own results, the statistical data processing and the discussions.

3. Literary awareness of the candidate:

The bibliography contains 212 cited literary sources, of which 11 in Cyrillic and 201 in Latin, the majority being dated after 2014.

The literary review of the dissertation thesis covers 36 pages, in which the author makes a profound analysis of the current application of ^{68}Ga-PSMA PET/CT, proving that summarized and systematic data are lacking for the application of the method in prostate cancer in combination with other methods as well as the possible diagnostic errors. The conclusions from the literary review are concrete and directly related to the aim and tasks of the scientific study.

4. Methodological level and design of the scientific research:

The study includes 386 patients for a period of two years between 2019 and 2021, who underwent staging and re-staging ^{68}Ga-PSMA PET/CT investigations. The study includes patients distributed in different groups according to rigorous criteria, closely associated with the set tasks and allowing for the drawing of the corresponding conclusions. The results were processed by means of appropriate statistical methods.

The investigation methods and the clinical material selected by the author have enabled her to achieve the set goal and the tasks determined to be solved have obtained an adequate answer.

5. Correspondence between the aim, results and conclusions:

There is a logical correspondence between the set objective, the obtained results, the discussion and the drawn conclusions. The own results and the discussion are presented on 118 pages and are richly illustrated. The patients' groups follow the course of the set tasks and are presented clearly and in detail. The significance, the advantages and the possible diagnostic errors of the ^{68}Ga-PSMA PET/CT method are examined, including different variations of the physiological PSMA-activity, the pathological expression of PSMA antigen which is not associated with prostate cancer as well as the false negative findings.

In the algorithm for diagnosing and staging of prostate cancer, the presented data show an in-depth and detailed analysis made by the author for the different patients' groups according to the disease stage and the PSA values as well as the possible diagnostic difficulties and errors, which prove the truthfulness of the conclusions drawn.

The application of ^{68}Ga-PSMA PET/CT is studied in a large cohort of patients with BCR of prostate cancer after radical therapy (n=133). The prognostic factors are determined for the positivity of PSMA-PET results, the factors related to the detection frequency as well as the advantages of the method in comparison to CT. The application of PSMA-PET/CT method is studied in patients with biochemical progression after radical prostatectomy (n=144) in the wide range of the tumor marker values (with an emphasis on the low PSA levels, including <0.2 ng/ml), the impact is determined of the PSA values on the sensitivity and PSMA-PET detection rate. The application of PSMA-PET is thoroughly analysed in primary regional nodal (N) and distant metastatic (M) staging of patients with primary prostate cancer with intermediate and high risk (n=109), the advantages of PSMA-PET are specified as compared to the conventional CT, the possible diagnostic errors are also studied. The influence of ^{68}Ga-PSMA PET/CT is examined on (N, M) staging of primary prostate cancer with intermediate and high risk before radical therapy (n=69) in comparison to conventional imaging methods (CT, MRT and bone scintigraphy). The application of the method was studied in patients with ISUP grade 5 (n=61), analyzing the peculiarities of the nodal and bone metastasizing, the relation between the detection rate for various localisations of the malignant involvement from prostate cancer and the PSA values as well as the clinical T stage.

The various anatomical models are examined of the metastatic involvement in the recurrent and primary prostate cancer in ^{68}Ga-PSMA PET/CT scanning (in a total of 386 patients). A detailed study is carried out on the connection between a pathological PSMA PET/CT result and the values of PSA, Gleason score/ ISUP grade, the clinical T stage and other factors in patients with BCR after radical therapy (n=133), with biochemical progression after

radical prostatectomy (n=144), as well as with primary prostate cancer (n=109) in a total of 386 patients. The parameters of the hybrid method are calculated and analysed in depth, e.g. detection rate, sensitivity, specificity, positive predictive value, negative predictive value and accuracy, including the risk for false positive and false negative results in the investigated diagnostic groups of patients.

6. Analysis of the conclusions and the contributions:

The dissertation thesis finishes with 10 conclusions and 10 contributions formulated in great detail and with clarity. I accept the contributions stated in the self-assessment made by the author and I would like to point out that the dissertation work is the first of its kind in Bulgaria on the diagnostic possibilities of ^{68}Ga-PSMA PET/CT in prostate cancer. For the first time in Bulgaria, of utmost practical significance are the presented recommendations for the application of the hybrid imaging method in various clinical cases as well as in patients with biochemical progression after radical prostatectomy (in low PSA values), in primary staging of high risk prostate cancer and in patients with ISUP grade 5.

7. Nature of the critical remarks and recommendations:

I have no critical remarks to make, which could possibly question the methods, the evidence material, the discussion of the obtained results and the drawn conclusions.

8. Publications and participation in scientific events:

The results of the scientific research of the candidate on the topic have found their way in 1 scientific journal and 2 scientific fora, after being reviewed published in the European Journal of Nuclear Medicine (2020).

Personal impressions from the candidate:

Dr. Marina Ivanova Dyankova is a recognized specialist in nuclear medicine. She is among the young colleagues, who are not only responsible, profound and constantly self-improving, but also exhibiting their pronounced interest both in their everyday work and the latest developments in our field. She is accurate, loyal to her colleagues and responsible not only to the members of the team of the Clinic of Nuclear Medicine but also to her colleagues from the other specialties.

9. Conclusion:

Bearing in mind the scientific merits of the dissertation thesis, namely the topicality of the problem and the obtained results, the significant conclusions and contributions of the candidate, I firmly recommend to the members of the scientific jury to confer the educational and scientific degree "Philosophy Doctor" to Dr. Marina Ivanova Dyankova for her dissertation work entitled *68Ga-PSMA PET/CT IMAGING IN PROSTATIC CARCINOMA ADVANTAGES AND POSSIBLE DIAGNOSTIC ERRORS.*

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Varna

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