

STATEMENT

From Prof. Irena Dimitrova Kostadinova, MD, DSc

Clinic of Nuclear Medicine, Acibadem City Clinic – Oncology, Sofia, member of the Academic Advancement Board, appointed by Order No. № P-109-199/29.04.2022 for the defense of a PhD thesis on "68Ga-PSMA PET/CT IMAGING IN PROSTATIC CARCINOMA. ADVANTAGES AND POSSIBLE DIAGNOSTIC ERRORS" in 7. Health-care and sports – higher education area, 7.1. Medicine – professional field, Medical radiology, and X-ray treatment (including use of radioactive isotopes) scientific specialty for awarding the educational and scientific degree "Philosophy Doctor" of Marina Ivanova Dyankova, MD, Assistant Professor at the Department of Imaging Diagnostics, Interventional Radiology and Radiation Therapy, Faculty of Medicine, Medical University "Prof. Dr. Paraskev Stoyanov" – Varna, a physician-specialist in Nuclear Medicine at the Clinic of Nuclear Medicine and Metabolic Therapy, St. Marina University Hospital – Varna.

In addition to early diagnosis and staging of prostate cancer (PC) as the most common tumor in men, a fundamental problem for clinicians is the early detection and visualization of recurrences after prostatectomy, radiotherapy, or other local treatment and the values of prostate-specific antigen over 0.2 µg/L are challenging in modern imaging methods. The ultimate goal is an adequate treatment, including surgery, to achieve complete or partial remission. Contrast-enhanced MRI and CT are most commonly used today for a visualization of recurrences, but they are not always with sufficient sensitivity and specificity, especially at low tumor marker values. With the introduction of high-sensitivity molecular imaging by PET-CT, it has become possible to obtain early functional information for the disease development and detection of recurrences, which in many cases is more accurate than CT or MRI scans. In 2013, the first encouraging results were reported for using a new radiopharmaceutical that binds to molecular target receptors overexpressed on the surface of cancer cells in prostate cancer – in 100 - 1000 times higher than normal cells and covering 95% of the tumors. This is the prostate-specific membrane antigen PSMA, with the possibility of using the positron source 68Ga as a marker and the use of PET-CT. Thus, revolutionary progress was made in diagnosing PC and determining an optimal personalized therapy for patients.

Despite numerous studies on the role of 68Ga-PSMA PET-CT in PC patients, there are ambiguous data concerning the advantages of the method in restaging at different levels of tumor differentiation, incl. in those with ISUP grade 5 (Gleason score 9 and 10), in patients with PSA levels below the levels of biochemical recurrence, the staging of intermediate and high-risk patients, and the comparison with conventional imaging methods, especially concerning the local

nodal status and bone/bone marrow metastasis and possible sources of errors in interpreting the results.

In this aspect, the subject of Dr. Dyankova's thesis "68Ga-PSMA PET/CT IMAGING IN PROSTATIC CARCINOMA. ADVANTAGES AND POSSIBLE DIAGNOSTIC ERRORS," is fully up-to-date with a research on the application possibilities of the most modern and promising method in staging and restaging a large group of PC patients – 386 and presenting a comparison with conventional imaging methods, making theoretical and practical recommendations to optimize and individualize therapy.

The dissertation contains 197 pages and 3 appendices and is illustrated with 85 figures and 50 tables.

The bibliography includes 212 cited literature sources, of which 11 are in Cyrillic and 201 in Latin, the majority of them published in the last 5-6 years when the method was introduced in diagnostic practice.

The inclusion criteria for the examination of patients are entirely in line with the recommendations of the EANM for the main indications of the study. Very professionally, with in-depth knowledge of the subject, 5 groups are defined in order to formulate precisely the indicators in view of the diagnostic benefit and respective individualization of the therapy, namely:

Group I patients – with suspected recurrence of PC and PSA values above 0.2 ng/mL to 10 ng/mL, and those above 10 ng/mL if there is an unclear/uncertain result from other imaging methods.

Group II patients – with tumor marker levels below the biochemical recurrence values, as well as those with persistently elevated PSA values (biochemical persistence).

Group III patients – with intermediate and high-risk PC for staging

Group IV patients with performed comparative conventional imaging studies.

Group V patients – with high-risk PC (ISUP grade 5).

In Group I patients, there is an established dependence of the tests' sensitivity on the actual and initial PSA levels and the stage. The results are comparable to the world practice, regardless of the time of doubling of PSA.

Interesting and important for practice are the results in Group II patients with increasing PSA levels but below the limit of biochemical recurrence. A positive result is found in 16.1%, dependent on GS, with sensitivity and specificity of 58.0% and 87.0%.

The results showed a significantly higher detection rate of metastatic lesions in Group III patients – in high-risk patients (42.6%) compared to 6.6% in intermediate-risk patients. With increasing PSA values and increasing ISUP grade, the detection rate of metastatic lesions for regional and distant LN, bone, visceral and distant metastases also increased. The reasons for false negative and positive results are discussed very professionally. In 26.1% of patients, the (M) stage

increased, and in 11.6%, it decreased, which is of predictive significance with regard to further therapy.

For the first time in our country, the possibilities of the method are compared with those of conventional imaging studies. It has been proved to exceed them in detecting nodal and distant metastatic lesions, both in initial staging and restaging.

In Group V patients with ISUP grade 5, ^{68}Ga -PSMA PET/CT was found to show high potential with a sensitivity of 92.3% to 98.9% and a specificity of 97.7% and 100%.

The thesis is illustrated with many qualitative and informative images from the applied hybrid nuclear medicine studies in PC patients. The tables and figures are also very professionally prepared and contain the essential diagnostic elements of the studied patients and the results obtained.

The discussion of the results and conclusions reveals the author of the thesis as a very experienced professional in nuclear medicine, with in-depth knowledge of imaging capabilities and the whole range of clinical and paraclinical studies related to PC.

The main contributions of the research are as follows:

1. For the first time in our country, a comprehensive, in-depth study has been conducted on the application of the hybrid imaging method ^{68}Ga -PSMA PET/CT in a large group of PC patients:

- in restaging – the prognostic factors for positivity of the results, the factors related to the detection rate, as well as the advantages of the method over CT, with emphasis on low PSA levels, including in patients with values <0.2 ng/mL have been determined;

- in the initial regional nodal and distant metastatic staging of patients with primary PC with intermediate and high risk before radical therapy;

- in patients with large tumor volume and with ISUP grade;

- the precision of the study with a detection rate, sensitivity, specificity, PPV, NPV, and accuracy was studied.

2. For the first time, the possibilities of the method are reliably compared with the conventional imaging methods to achieve an optimal diagnostic algorithm in patients with PC.

3. For the first time in our country, the possible diagnostic errors have been investigated, both in terms of a false positive and a false negative result, incl. the visualization of a metachronous tumor with ^{68}Ga -PSMA PET/CT to achieve a reliable assessment of the disease.

Dr. Dyankova has complied with all my preliminary recommendations for the PhD thesis.

I would like to emphasize my excellent assessment of the proposed research-both in selecting patients to achieve optimal diagnostic benefit from the study and in terms of in-depth analysis of data, excellent visualization, and important theoretical and practical conclusions for all professionals. A monograph on the

subject could be considered, pointing out the most important indications and advantages of the method in the overall diagnostic algorithm in PC patients.

Related to the subject of the thesis, there is one full-text publication presented, along with participation in a national conference and the most prestigious European Forum – the European Congress of Nuclear Medicine with the publication of a summary report in an impact factor journal.

IN CONCLUSION, I think, that the presented by Dr. Dyankova PhD thesis on "68Ga-PSMA IMAGING IN PROSTATIC CARCINOMA. ADVANTAGES AND POSSIBLE DIAGNOSTIC ERRORS" considers this issue for the first time in Bulgaria. Significant scientific and practical contributions have been made at a national level. There is a precise rationale for applying the method in restaging and staging of PC patients, indicating its advantages over the conventional imaging methods and the possible sources of errors in its application. The research can be a very reliable guide for the therapeutic behavior of specialists in nuclear medicine, oncology, radiotherapy and imaging. In view of the above, I strongly recommend to the members of the Academic Advancement Board to vote positively for the PHD degree of MARINA IVANOVA DYANKOVA, MD

Date: 04.05.2022

Statement by:


Prof. I. Kostadinova, MD, DSC