According to order № P-109-199, 29.04.2022 of the Rector of the Medical University - Varna

STATEMENT

From Prof. Dr. Antonia Dencheva Tsonevska, Ph.D.

Head of Clinic of Nuclear Medicine,

UMHAT Acibadem City Clinic, Tokuda Hospital EAD, Sofia

The dissertation on the topic:

68Ga-PSMA PET / CT IN PROSTATIC CARCINOMA,

ADVANTAGES AND POSSIBLE DIAGNOSTIC ERRORS

for obtaining the scientific and educational degree "Doctor",

Field of higher education: Health and Sport

Professional field: "Medicine" (code 7.1)

Scientific specialty: 03.01.28. Medical radiology and radiology

(incl. use of radioactive isotopes)

of   Dr. MARINA IVANOVA DYANKOVA

SUPERVISOR:

Assoc. Prof. Dr. Borislav Chaushev, Ph.D.

Dr. Marina Ivanova Dyankova works as a doctor at the Clinic of Nuclear Medicine and Metabolic Therapy, MHAT "St. Marina EAD, Varna since 2015. until. In 2018 is enrolled as a doctoral student under the supervision of Prof. Dr. Anelia Klisarova, MD. In 2019 acquires a degree in Nuclear Medicine. In 01.2020 holds the position of assistant at the Department of Imaging Diagnostics, Interventional Radiology and Radiation Therapy at the Medical University - Varna. She takes an active part in continuing education courses conducted by the IAEA and EANM in Latvia and Bulgaria, as well as annual European congresses EANM, ESOR, BAR and the international symposium WARMTH.

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

Prostate cancer is currently the most common cancer in men worldwide (over 30% of men in their 50s and 80% of men in their 80s have molecularly detectable prostate cancer). Prostate cancer is the second most common cause of cancer-related deaths after lung cancer. Since the end of the last century, prostate cancer has gone from a neglected problem of research in the field of oncology to one of the main and leading objects of study by urologists, biochemists, molecular biologists, geneticists, oncologists, radiotherapists.

There is currently no consensus on the true biological progression of prostate cancer, its screening, diagnosis, treatment and follow-up. The main dilemma in the current behavior of prostate cancer is the inability to differentiate clinically significant cases of the disease (cases with metastatic potential that would determine the duration and quality of life of the patient) in stages when they are localized in the gland before invasive and metastatic development.

On the other hand, patients with clinically insignificant prostate cancer (anatomically localized who have not yet developed a potentially metastatic phenotype) do not require aggressive behavior in terms of diagnosis and treatment, and by saving patients unnecessary medical and diagnostic procedures significantly reduces their associated morbidity.

Early diagnosis of PC, recurrent and metastatic lesions is of utmost importance in determining the clinical stage, therapeutic approach, risk stratification and patient prognosis. Imaging methods are the main means of confirming the diagnosis, referral for prostate biopsy, staging, determining the optimal treatment tactics for primary PC, as well as re-staging in case of suspicion of recurrence after radical prostatectomy or radiation therapy. Morphological imaging methods have significant limitations due to the relatively low sensitivity and specificity. The need for more sensitive and specific imaging methods for PC detection, early recurrence and early metastatic progression stimulates technological advances in diagnostic imaging and in particular positron emission tomography with various radiopharmaceuticals. Recently, different RFs with different targets for PC have been developed, among which 11C- and 18F-labeled choline have become widespread, as markers of membrane metabolism as well as 68Ga-PSMA. The high sensitivity and specificity of 68Ga-PSMA PET-CT allow for early detection of recurrences, for initial staging of high-risk primary PC, for detection of occult metastases in lymph nodes and bones, although the role of the method is not well studied and defined . Literature data on the role of 68Ga-PSMA PET-CT are ambiguous and in some respects contradictory. There is no definite answer in the scientific literature to current questions concerning the indications for conducting 68Ga-PSMA PET-CT and the accuracy of the method. Nuclear medical studies are needed to compare the available preliminary results and to confirm the world experience in the application of 68Ga-PSMA PET-CT,

to define the advantages and disadvantages and to optimize the indications.

In this regard, the dissertation proposed to me for an opinion is a topical and timely work of theoretical and practical importance and has contributed to the diagnosis of PC.

2. Structure of the dissertation:

The dissertation under the above title is written on 197 pages, contains 3 appendices and is illustrated with 85 figures and 50 tables.

The bibliography includes 212 cited literature sources, of which 11 in Cyrillic and 201 in Latin, most of them after 2014.

The dissertation is properly structured and meets the generally accepted criteria and contains a literature review of 35 pages, purpose, tasks, material and methods 13 pages, results and discussion 117 pages and conclusions and contributions 6 pages. The individual sections are well balanced.

3. Literary awareness of the dissertation:

The literature review consistently addresses the issues of epidemiology, morbidity, mortality and risk factors in PC, basic methods for early screening and diagnosis. The possibilities of different radiopharmaceuticals for PET-CT in the diagnosis of PC, their advantages and disadvantages have been studied in detail. Special attention is paid to 68Ga-PSMA PET-CT. The literature is systematically analyzed critically, highlighting the main problems and unresolved issues in the diagnosis of PC.

The dissertation student handles scientific information expertly, the details present the advantages and disadvantages of the described methods. The literary review is focused on the topic of the dissertation. All this is presented by Dr. Dyankova as a multifaceted excellently prepared researcher A critical look at the detailed literature logically leads to the formulation of the aim of the dissertation, namely: To evaluate the role of 68Ga-PSMA PET-CT in the study of patients with PC, examining the advantages of the hybrid imaging method and possible diagnostic errors . The set goal is specific, well-structured, corresponding to the considered problem.

The set tasks correspond to the set goal and are clearly and precisely defined:

1. To study the use of 68Ga-PSMA PET-CT in patients with BHR on PC after radical therapy and to discover the advantages of the method compared to conventional CT.

2. To determine the role of 68Ga-PSMA PET-CT in the study of patients with biochemical progression after RP in a wide range of PSA (with emphasis on low tumor marker values), including PSA <0.2 ng / ml.

3. To study the application of the method in the initial regional nodal (N) and distant metastatic (M) staging of patients with primary PC with moderate and high risk before radical therapy; to detect possible diagnostic errors of the hybrid method, as well as to determine the advantages over CT.

4. To determine the effect of 68Ga-PSMA PET-CT on regional nodal (N) and distant metastatic (M) staging compared to conventional imaging methods (CT, MRI and CS) in patients with newly diagnosed histologically verified primary PC with moderate and high risk.

5. To study the application of the method in patients with high-risk PC-ISUP grade 5 (Gleason score 9 and 10).

6. To determine the parameters of 68Ga-PSMA PET-CT: frequency of detection, sensitivity, specificity, accuracy, positive predictive value (PPS), negative predictive value (NPS) in different diagnostic groups of patients.

4. Methodological level and design of scientific research:

The section Material and methods presents the patients included in the scientific work with correctly defined inclusion and exclusion criteria. 386 patients with PC were included in the study

and analyzed, divided into 5 groups according to the set tasks. The number of patients is quite sufficient to achieve the objectives of the study. The used diagnostic methods, their advantages and disadvantages are described in detail.

The statistical analysis of the obtained results was carried out using modern appropriate methods.

The results of the dissertation are described exhaustively in 6 sections, which purposefully, in detail and correctly prove the set tasks. At the end of each section there is a preliminary discussion of results with a critical attitude to the advantages and disadvantages of the method as well as the sources of errors.

5. Correspondence between the goal, the results and the conclusions

There is a logical connection between the set goal, the obtained results, the discussion and the conclusions made. The obtained results are presented consistently, accurately and convincingly, based on the individual tasks. The own results are presented on 127 pages and are richly illustrated, following the course of the set tasks and are presented in detail. They are illustrated with statistically processed digital tables and color figures.

The expression of the author's own opinion, the critical attitude to the results, pointing out the reasons for possible diagnostic errors are impressive. The discussion is analytical, diverse and at the same time well focused on the main goal and tasks. The comparative examination of one's own results compared to the published data of other authors is extremely valuable

6. Analysis of the conclusions and contributions:

Based on the obtained results, the author synthesizes 11 conclusions, which are written specifically and are relevant to the goal and the tasks developed.

I accept the contributions formulated by the dissertation, which I would define as theoretical and practical.

I accept the contributions formulated by the dissertation, which I would define as theoretical and practical. In general, they validate the application of the innovations for the country hybrid imaging method 68Ga-PSMA PET / CT in a large number of patients with prostate cancer, define the indications for the study and its benefits, determine the parameters of 68Ga-PSMA PET / CT (for the first time in the country): frequency of detection, sensitivity, specificity, PPP, NPS and accuracy, including the risk of false-positive and false-negative results in different diagnostic groups of patients, an in-depth study of the relationship between pathological PSMA PET / CT score and PSA values, Gleason score / ISUP grade, clinical T stage and other factors in patients with BHR after radical therapy, with biochemical progression after RP, as well as with primary PC, an in-depth analysis of possible diagnostic errors was performed, including various variations in physiological PSMA activity, pathological PSMA antigen expression not related to PC, and false-negative findings.

The dissertation is written clearly and concisely, in good literary Bulgarian. All recommendations made at the preliminary discussion have been implemented.

In connection with the dissertation Dr. Dyankova presented 1 real publication in which she is the first author and 2 presentations at scientific forums, all related to the topic of the dissertation.

The summary corresponds to the content of the dissertation, fully and reliably reflects the main results obtained and their analysis, the conclusions made and the derived scientific and scientific-applied contributions.

Conclusion:

The dissertation of Dr. Marina Dyankova is a topical and in-depth scientific work of scientific and applied value. The dissertation fully covers the qualitative and quantitative criteria for obtaining the educational and scientific degree "Doctor".

Having in mind the above, I give a positive assessment of the dissertation of Dr. Marina Dyankova and recommend to the esteemed Scientific Jury to award her the scientific and educational degree "DOCTOR".

16.05.2022   Prof. Dr. Antonia Tsonevska, Ph.D.