

REVIEW

by competition for the academic position "*Docent*"
in the specialty *Nuclear Medicine* for the needs of the Department of Imaging, Interventional
Radiology and Radiotherapy
to the Faculty of Medicine of the Medical University
Prof. Dr. Paraskev Stoyanov – Varna

Reviewer:

Prof. Dr. Pavel Hristov Bochev
Member of the Scientific Jury under Order No. R-109-280/25/5/2023 of the Rector of the MU -
Varna as an Internal Member

Regarding: competition for the academic position "Associate Professor" in the scientific specialty "Nuclear Medicine", in the field of higher education 7. "Health and Sports", professional direction 7.1. "Medicine", for the needs of the Department "Imaging Diagnostics, interventional radiology and radiation therapy" at the Faculty of Medicine, Varna University of Medical Sciences, and Nuclear Medicine Clinic at "Sveta Marina" UMBAL EAD Varna, announced in State Gazette No. 28/28.3.2023.

Candidate (single):

Zhivka Dancheva Mezan, doctor

Technical compliance with the regulations for the development of the academic staff at MU-Varna:

1. The procedural documentation meets the requirements under Art. 123 (1)(2) and Art. 124
2. The candidate meets the conditions under Art. 125(1)
3. The documentation submitted by the applicant meets the requirements of the text of Art. 126(1).

Dr. Dancheva's application is eligible for participation and review

BIOGRAPHICAL DATA , PROFESSIONAL AND ACADEMIC DEVELOPMENT

Dr. Zhivka Dancheva Mezan, MD, graduated in medicine from Medical University - Pleven in 2005 with excellent results, diploma. series MU-2005/029852

In 2011 acquired a specialty in Nuclear Medicine, (Diploma Series MUV 3044) at the MU-Varna specialization base.

In 2012 defended a dissertation on "Metabolic radiopharmaceutical therapy with 89- Sr (Metastron) in painful bone metastases" and obtained the educational and scientific degree "Doctor of Medicine".

From 2006 to 2012, She was a full-time doctoral student at the Department of Imaging Diagnostics and Radiotherapy of the Medical University of Varna. From 2016 to the present, she holds the competitive academic position of "Chief Assistant" in the same department.

Dr. Dancheva is the deputy national delegate of Bulgaria in the European Association of Nuclear Medicine (EANM) from 2023.

RESEARCH ACTIVITY

Scientific indicators

In the current competition, the candidate participated with a total of 29 scientific works, of which actual publications - 6 nos. / 6- in Bulgarian journals/ and 22 reports presented at prestigious International Congresses with abstracts published in journals with IF/, a dissertation work for the acquisition of the ONS "Doctor", as well as a monograph that does not repeat the developments from the dissertation work. The presented scientific works, according to the requirements of the procedure, were published after occupying previous academic positions. A detailed summary of the scientific papers is presented.

Scientific indicators according to the uniform state requirements for holding academic positions, ZRAS and PRAS MU-Varna

Criteria A 1:

Presented dissertation work on "Metabolic radiopharmaceutical therapy with 89- Sr (Metastron) in painful bone metastases", defended 2012. A summary is available on the MU-Varna website.

The dissertation remains one of the very few in Bulgaria dealing with the therapeutic application of nuclear medicine methods and radiopharmaceuticals. Defended within the framework of a full-time PhD, the work is very ambitious and bold for its time, with an impressively well-structured design and substantial contributions.

Criteria C3:

Habilitation thesis-monograph.

The candidate presents a monographic work on the topic "Skin melanoma through the eyes of Nuclear Medicine". The work itself mainly contains own studies, confirming or refuting the available literature data regarding the application of FDG PET CT in patients with malignant cutaneous melanoma. Individual sub-studies illuminate some poorly or not at all studied aspects, such as the role in first relapse, which have no comparable counterpart in the current literature and the study itself has the merits to be classified as Grade 2 B in the context of evidence-based medicine and has the potential to be cited in world recommendations. (The candidate, probably deliberately and in accordance with the accepted practices of minimalism in terms of meeting the uniform state requirements, has not included those publications of his published in full text in international journals with IF)

Criteria C4:

It is replaced by the scoring for indicator B3

Criteria G7

The applicant provides a total of 22 reports with published abstracts, referenced and indexed in global databases (Scopus / WebOS) The publications provided are of a point equivalent exceeding the required one. In 4 of the publications, Dr. Dancheva is the first author, in 5 – second. Of the papers presented, 18 were published in EJMNI supplements and three in The Breast . To take into account that reports published in EJMNI undergo a refereeing process with at least two independent evaluators and in this sense are evaluated as real publications (which is permissible according to the text of Criteria D7). Seven of the works are Case reports or Case series , the rest are original studies. Of the featured publications representing Case reports / series of particular interest is G7-15, where cases of ileanal abscesses in infective endocarditis are described, which represents a practical contribution promoting a targeted search for such pathology. Very relevant to the period for which it was published is also a G7-8 report dealing with a common artefact of nodal activation after Covid vaccines (at the time of publication this type of artefact was frequently and massively misdiagnosed as nodal involvement). Also of particular interest are the presented co-authored studies in men with breast cancer published in supplements of The Breast (G7 4-6). The rest of the reports presented are co-authored dissertations of doctoral students from the clinic.

According to **Г8 criteria**, a total of 6 full-text publications were presented and with a point equivalent exceeding the required one. In one publication Dr. Dancheva is the first author and in two – second.

Criteria Д9: The criterion is not required and the applicant does not submit titles, although she has several contributions to collective monographs (which, of course, she is not obliged to declare, especially in the context of the specific features of ZRAS). Those are, however mentioned in the attached CV

Criteria group Д, the candidate presents a total of 5 citations with a point equivalent of 75pt. It should be noted that even with a basic search in the scientific database Google Scholar, Dr. Dancheva's actual number of citations is dozens of times higher than the required one, considering the specifics of ZRAS, the candidate has chosen to present only a limited number of citations to cover the scientometric norm.

List of scientific works used for filling AD" Chief Assistant"

Although not scored, the publications in this section are particularly impressive as scientific developments, including four full-text publications in international journals, with over 50 international citations. Of particular note is the publication Dual time point 18 FDG PET CT imaging May be useful in assessing local recurrent disease in high grade bone and soft tissue sarcomas (#2), which gained a wide international response and is the second most cited article of Dr. Dancheva, and the first most cited, of which she is the first author. Again, due to the imperfections of ZRAS, the scientific works in this section are not referenced (they were provided in a previous competition without such a requirement), although they are one of the most significant.

Compliance with the scientometric requirements of MU-Varna for holding the academic position of "docent"

A group of metrics	Required number of points	Number of points based on the evidence presented by the candidate
A	50	50
B	100	100
Г	200	207.05
Д	50	75

It should be noted that when checking *the* World Scientific Databases Google Scholar, ORCID, SCOPUS ID, Web of Science Researcher, Research Gate for the candidate shows a total number of publications over 50: Number of citations of scientific publications: 69 (Google Scholar) , respectively 48 in Scopus , H index: 3 (Scopus); with a total IF= 204.073 . Again, due to the specifics of the Law on the Development of the Academic Staff, some of the most significant publications are not included for participation in the competition. The very high individual impact - factor of the candidate is impressive, which shows the importance of the scientific works and their adequate realization in appropriate scientific publications.

Thematic areas and contributions

On the basis of the presented scientific works published in the period 2005-2022, including the author's abstract of a dissertation work, monograph, full-text publications and summaries of participation in scientific forums, it is evident that the author works and builds his professional development directed in the field of nuclear oncology and radionuclide therapy.

Radionuclide therapy:

Dr. Dancheva's dissertation work (A 1) is the first and essentially the only scientific work in the field of radionuclide therapy in Bulgaria outside of radiation therapy. The design of the dissertation studies was in line with the then ongoing pan-European studies (the results of which also came out later), which shows the topicality of the topic. The results of the study, as well as the later results of the TRAPEZE study, did not show an effect on overall survival, which did not allow for a more permanent presence of radionuclide therapy with osteotropic radiopharmaceuticals in treatment recommendations outside the palliative regime, but in purely scientific terms demonstrated the innate talent of Dr. Dancheva to structure and conduct scientific trials in a statistically sustainable design and in accordance with the much later published recommendations for conducting such type of studies.

Diagnostic nuclear medicine:

Nuclear oncology: The leading and original scientific contributions, ascertainable from the articles presented in the competition and participation in scientific forums of Dr. Zhivka Dancheva, are mainly related to the long-term and extensive experience with 18F-FDG PET/CT and 68Ga-PSMA. The studies with 18F-FDG PET/CT concern several main topics - malignant melanoma, head and neck carcinomas, breast carcinoma, multiple myeloma and two publications related to conducting the study in the conditions of the Covid-19 pandemic. Regarding prostate carcinoma, the author presented 6 publications and one presentation at a national urology conference, where he demonstrated extensive research and his own results and experience.

Malignant Melanoma: The scientific works presented show a sustained and detailed interest of Dr. Dancheva directed and specifically to patients with malignant melanoma, which is the subject of the monographic work. The topic of the application of nuclear medicine diagnostic methods in skin melanoma is extremely topical. The monograph is a summary of the world and Bulgarian experience in the staging, follow-up and reporting of the effect of the treatment of skin melanoma, with an emphasis on Nuclear Medicine, both from the point of view of lymphoscintigraphy, as the gold standard for nodal staging in early melanoma, as well as hybrid positron -emission tomography with computed tomography (18F-FDG PET/CT) in advanced disease. A teaching-methodical contribution is the recommendations for the methodology of sentinel lymphoscintigraphy, the recommendations and contraindications for its implementation. In recent years, new therapeutic options and medications, and their therapeutic and side effects, have required new knowledge from nuclear medicine physicians in evaluating the effect of treatment. Evidence-based literature, global and national guidelines are presented and summarized. The demonstration of personal results from over 500 patients can be defined as an original contribution, defining in several chapters the role of 18F-FDG PET/CT, in staging, the strengths and weaknesses of the methodology in relation to different types of metastatic lesions, the evaluation of the effect of treatment and follow-up of high-risk groups of patients. An essential scientific-applied contribution is the recommendations presented in two of the chapters (Chapters 6 and 7), which concern the application of 18F-FDG PET/CT for staging and follow-up of high-risk patients, and which are based on both the literature review and of own results. The most frequent adverse side effects of immunotherapy detectable with 18F-FDG PET/CT are discussed and presented in detail, and its role in the early, subclinical detection of the latter, which is of practical importance in the need for treatment correction, is summarized.

Dr. Dancheva's extremely thorough work with patients with malignant melanoma makes her an undisputed expert and reference specialist for the country regarding the application of positron emission tomography in these patients.

Head and Neck Tumors: Five of the reports presented addressed several aspects of the application of 18F-FDG PET/CT in head and neck carcinomas, including a proprietary patient cohort study. In D7.2, D7.12 and D.17, the role of 18F-FDG PET/CT in detecting synchronous occult carcinomas, which are common in head and neck carcinomas and are often the reason for the short duration of the patient's life, which necessitates their early detection. D7.13 compared the role of clinical examination and endoscopy and that of 18F-FDG PET/CT in the detection of local recurrence after radical treatment. The role of 18F-FDG PET/CT is highlighted and supported by a study of sensitivity, specificity, negative and positive predictive accuracy, demonstrating the advantage of the method in suspected recurrence over physical examination/endoscopy. A major applied contribution is the study of three patients with head and neck carcinoma after radiotherapy reported in D7.22. This report highlights an important point in the evaluation of the effect of treatment in this type of tumors, namely the delayed manifestation of the full metabolic response to the given treatment. According to the results and literature review, almost half of patients with nasopharyngeal carcinoma do not have a complete clinical response (cCR) 3-4 months after

radiotherapy, and in fact achieve a cCR by 6-9 months, without cCR delay being a prognostic factor.

Hematological neoplasms:

Multiple myeloma is addressed in two of the publications G7.3 and G7.7. In the first, the role of 18F-FDG PET/CT in the staging of bony lesions was compared to that of MRI and radiographs. It is established that 18F-FDG PET/CT is better for staging than other imaging methods (MRI, X-ray and CT).

In G7.7, a case of a patient with prostate carcinoma and synchronous extramedullary multiple myeloma with multiple osteolytic PSMA negative bone lesions is presented. The main contribution has a scientific-applied nature, emphasizing the accumulation of knowledge and experience with 68Ga-PSMA PET/CT in patients with various malignant diseases. The degree of uptake of the marker is not reliable for distinguishing between them and PC lesions, which is of great clinical importance.

One publication beyond the minimum scientometric requirements was also presented, including a literature review and a clinical case of a patient with diffuse B large cell NHL. The role of 18F-FDG PET/CT for staging, monitoring response to treatment, and detecting relapse is highlighted. Presenting a clinical case of a patient with generalized diffuse large B-cell lymphoma (DLBCL) with multiple extranodal lesions detected with 18F-FDG PET/CT, which appears to be a more effective technique than CE-CT for evaluating extranodal involvement and should be combined in DLBCL monitoring.

Breast Cancer: Dr. Dancheva is part of a multidisciplinary, multi-institutional team working on practical guidelines for the management of men with breast cancer. Four of the publications addressed different aspects of breast carcinoma, with 3 of them discussing different aspects of the treatment of men with stage IV breast cancer (G7.4, G7.5, G7.6, G8.4). The contribution of two of the publications (G7.4, G7.5) is regarding the endocrine treatment of men with metastatic breast cancer, encouraging the application of this type of treatment in Bulgaria with a view to better survival in this high-risk group of patients. The second study (G7.5) is particularly large, including 520 patients diagnosed between 2002 and 2013 in Bulgaria. The results represent a significant clinically-applied and innovative contribution, highlighting the great role of endocrine treatment of men with ER+ BC, which is currently not well represented in clinical practice in Bulgaria. The results show that aET delays the time to progression in men with BC and should be used routinely in all ER+ men with BC.

The third publication (G7.6) is related to the surgical treatment of breast carcinoma in men, and an international multicenter study was conducted including 391 male breast cancer patients from Bulgaria and Serbia. The main contribution consists in summarizing data from the application of breast surgery in men at different stages, emphasizing the wide application of the latter in patients at a locally advanced stage.

In D8.4, an overview of the problems associated with breast carcinoma in young women, summarized as 'the different disease', is presented. The latter is determined, on the one hand, by the often aggressive biological factors, and on the other, in terms of psychosocial difficulties and those related to family planning.

Prostate carcinoma: A significant number of articles – 7 of those participating in the competition are on the diagnosis of prostate carcinoma (Г7.7, Г7.9, Г7.16, Г7.19, Г7.20, Г7.21, Г8.5 and one entry in a scientific forum.) The major contributions of these articles include revealing that PSMA is not prostate-specific, as was believed at the beginning of the PSMA diagnostic era. It is possible to identify benign formations and processes with pathological expression of PSMA in the pancreas (G7.7). Similar is the thesis of the participation in a scientific forum (item 8 of the List of participations in national and international scientific forums), where it is established that false positive lesions are often found, mainly in bones. This should be considered in patients with low-risk carcinomas and a normal PSA value.

Two of the articles (D7.9 and D8.5) are on the sensitivity of PSMA-PET/CT in low PSA values, below 0.2 ng/ml. The articles contribute to the correct understanding and interpretation of the results, given that there is a significant relationship between the PSA level and the ability of PSMA to reveal metastatic lesions. The article summarizes that low and normal PSA values should be thought of as false positives. The sensitivity of the method according to the PSA value was determined, finding that local recurrence was associated with higher PSA values, while bone metastases and lymph nodes could also be detected at lower PSA levels. Also of practical importance is the report on the efficacy of 68Ga PSMA PET/CT in patients with ISUP grade 5 high-risk prostate carcinoma. The topic is controversial because of the existing literature regarding loss of PSMA expression in patients with poorly differentiated tumors. The research is on three groups: 1) with biochemical relapse (BCR) after radical therapy; 2) with biochemical progression (including PSA <0.2 ng/ml) after radical prostatectomy (RP); 3) with primary PC referred for staging. The results indicate that 68Ga-PSMA PET/CT is an excellent imaging modality for PC detection in ISUP grade 5 patients with BPH and for PC staging. A relatively high frequency of false-negative findings (mainly bone lesions) was found, which requires special attention when interpreting the results. In a large cohort (133 patients), the role of 68Ga PSMA PET/CT in the detection of BPH after radical treatment was studied (G7.19). The results show that the method is an excellent tool for detecting recurrent PC after radical treatment, even with low aPSA levels, and that the aPSA value at the time of examination is the main predictor of PSMA positive findings. Another aspect of 68Ga PSMA PET/CT, namely the relationship between iPSA and the likelihood of metastatic disease, is discussed in D7.20. The detection of locoregional nodal and distant metastatic spread of PCa was found to be positively associated with iPSA levels, ISUP grade and EAU risk groups. Another report highlighted the role of PSMA-PET for accurate staging of patients compared to conventional imaging methods (D7.21). It was concluded that the method was superior to conventional staging in detecting nodal and distant metastases in staging patients with intermediate and high-risk PC. Again, detection of locoregional nodal and distant metastatic spread of PC was found to be positively correlated with PSA levels and ISUP grade.

Nuclear medicine diagnostics outside of oncology: In addition to the application of 18-F FDG PET/CT in oncological diseases, among the publications there is also the application of the methodology in inflammatory diseases, and in three of the publications it demonstrates cases of patients with chronic tonsillitis (see D7.1), infective endocarditis of prosthetic heart valves (G7.15) and sarcoidosis (G7.14).

TEACHING AND LEARNING ACTIVITY

In the presented academic reference, a teaching experience of 6 years and 9 months has been declared, in the position of "chief assistant" at the Department of Imaging Diagnostics, Interventional Radiology and Radiotherapy, effective from 06/20216. Apart from the formal reference for time served, it should be noted that Dr. Dancheva has a teaching activity in the specialty of Medicine - Bulgarian language training, specialty - Medicine - English language training and at a medical college - specialty X-ray laboratory technician. She also carried out non-standard (according to the tbz that time valid legislation) teaching activity as a doctoral student. Dr. Dancheva is also a lecturer on some of the topics within the theoretical training in the specialty Nuclear Medicine (basic course).

GUILD AND EXPERT ACTIVITY

From 2023, Dr. Zhivka Dancheva was elected as a deputy national delegate representing Bulgaria in the European Association of Nuclear Medicine (EANM), which is a recognition of her positions in the national plan and the commitment to the development of the Nuclear Medicine specialty.

PERSONAL IMPRESSIONS OF THE CANDIDATE

Dr. Zhivka Dancheva is an undisputed expert in the field of Nuclear Medicine, especially when it comes to positron emission tomography. She is one of the pioneers of hybrid imaging in the country, part of the team that introduced the PET CT method for the first time in the country. Part of the team that run the country's second radiochemical laboratory for the synthesis of gallium radiopharmaceuticals (second application in the country of 68 Ga PSMA and first application of 68 Ga - DOTA). Part of the team that commissioned the first cyclotron complex in the country. A specific expertise that is not reflected in scientific activity, but is invaluable for patients, is working with children. Dr. Dancheva has a leading role in the country in terms of nuclear medicine diagnostics for children with oncohematological diseases and has established herself as a leader in this field. Striving for perfectionism and professional uncompromisingness is also notable. Exceptional talent in modeling and designing research theses and studies. Work with patients is also highly professional and rests on the rules of good medical practice and the recommendations of evidence-based medicine. Very collegial, honest and direct in her professional contacts. A good teacher of students and specialists (it is easy to recognize the professional stzle of the colleagues she taught). A fascinating lecturer.

CRITICAL NOTES AND RECOMMENDATIONS - NA

In conclusion, the candidacy of Dr. Zhivka Dancheva Mezan fully meets the state and institutional requirements for occupying the academic position "Associate Professor". Its

scientometric indicators exceed the mandatory requirements. The scientific activity of the candidate is diverse, but they show specific directions in which maximum expertise is sought (and achieved). The candidate's scientific achievements have been realized both independently or in compact institutional author collectives, as well as within the framework of multi-institutional scientific projects. Dr. Dancheva's scientific and practical work makes her a recognizable and reference specialist in Nuclear Medicine. Apart from the purely scientometric data and required documentary attributes, Dr. Dancheva also realized a corresponding professional and career development, fully corresponding to the expected occupation of AD Associate Professor. In his work with students, specialists and doctoral students, the candidate also demonstrates commitment to learning and teaching activities, which should be an integral part of the content of AD Docent.

Fully convinced and with great respect and professional respect, I recommend to the Scientific Jury to award Dr. Zhivka Dancheva Mezan, PhD, the academic position of "Associate Professor" in the scientific specialty "Nuclear Medicine" for the needs of the Department of Imaging, Interventional Radiology and Radiotherapy, Medical University - Varna and Nuclear Medicine Clinic at "Sveta Marina" UMBAL - Varna.

24/7/2023 Assoc. Dr. Pavel Bochev

A handwritten signature in blue ink, appearing to be 'Pavel Bochev', is written over the printed name.