**To the Chairman of the Scientific Jury**

**Prof. Dr Boyan Balev, MD**

**appointed by Order**

**of the Rector of Medical University- Varna**

**Review**

of the dissertation submitted for educational and scientific degree “**Doctor**"

Higher education field: Health and Sport

Professional field: 7.1 Medicine

Doctoral Program: Medical Radiology and Roentgenology

Scientific specialty: 03.01.28 Medical Radiology and Roentgenology

Nuclear Medicine and Radiotherapy

**Doctoral student:** Albena Dimitrova Botushanova

**Type of Doctoral Program:** Self-Directed Learning

**Department:** Imaging Diagnostics and Radiotherapy, Department of Nuclear Medicine- Prof. Dr Paraskev Stoyanov Medical University- Varna

**Title:** Nuclear Medicine Methods for Evaluation of Abnormal Parathyroid Glands in Patients with Primary and Secondary Hyperparathyroidism

**Supervisor:** Ass Prof Dr Borislav Chaushev, MD

Reviewer: **Prof. Dr Marianna Petrova Yaneva, MD**

Specialties: Medical Radiology- Nuclear Medicine and Radiotherapy, Oncology

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1. General presentation of the procedure and the doctoral student

The presented set of paper/electronic materials **is** in compliance with Art. 115 (1) of the Procedure for Acquisition of Academic and Scientific Degree of “Doctor” at Medical University- Varna; Regulations of MU-Varna including all required documents:

* Application to the Rector of Medical University- Varna to open a procedure for dissertation defense
* Curriculum vitae in EU format signed by the doctoral student
* Notary certified copy of higher education diploma
* Order for enrollment in a doctoral program; order for entitlement to thesis defense
* Order for a passed doctoral minimum exam
* Minutes of a departamental committee meeting for preliminary discussion of the dissertation and decision to open a procedure and to appoint the members of the Scientific Jury
* Dissertation
* Dissertation abstract
* List of scientific publications on the dissertation topic
* Copies of the scientific publications
* List of contributions to scientific forums

**REVIEW**

**By Prof. Dr Marianna Petrova Yaneva, MD**

Dr Albena Dimitrova Botushanova was born on 5.06.1966 in Haskovo. She graduated from Georgi Dimitrov High School- Plovdiv in 1984. In 1992 she was awarded higher education in Medicine by the Faculty of Medicine, Medical University- Plovdiv. Since February 1995, she has been working as a resident doctor at the Laboratory of Radiobiology, Clinic of Radiotherapy, Section of Nuclear Medicine, St George University Hospital. In 1998, she was awarded a degree in Radiobiology. Until 2000, she worked at the Immunological Laboratory, Section of Nuclear Medicine. Since 2000, she has been working as a resident doctor at the Section of Nuclear Medicine. In 2002 she received a degree in Nuclear Medicine. At present she is working at the Department of Nuclear Medicine which is divided into two units in St. George University Hospital. Unit 1- scintigraphy scans with gamma camera and Unit 2- nuclear medicine tests with PET/CT scanner.

She is a member of the Bulgarian Society of Nuclear Medicine and of the Union of Scientists.

She completed trainings at the European School of Nuclear Medicine- Varna in 2008 and in 2012.

She holds a Certificate of training for hybrid PET/CT scan held in Erlangen, Germany, in 2015.

Since 2015, she has been part of the academic staff as Lecturer in Radiobiology at Medical College-Plovdiv and since 2016 as Lecturer at Medical University- Plovdiv.

In 2018 she received a Master’s degree in Health Management.

Dr Botushanova is an ambitious and established specialist with a strong interest in scientific and clinical developments. She is detail-oriented and responsible towards her work.

Topicality of the Dissertation

Until recently considered rare disease, primary hyperparathyroidism (PHPT) is due to excessive production of parathyroid hormone (PTH) from one or more abnormal parathyroid glands and causes the development of hypercalcemia. In recent years, with the introduction of routine serum calcium measurements, it has been found that its incidence is approximately 42 per 100 000 persons and most of the cases are asymptomatic. Primary hyperparathyroidism (PHPT) occurs 2 to 3 times more frequently in women, with the incidence increasing with age and reaching 4 per 1000 persons in women older than 60. The classic symptoms of primary hyperparathyroidism such as: nephrocalcinosis, nephrolithiasis and osteitis fibrosa cystica are rarely present nowadays. Most patients with PHPT have no symptoms, making detected changes of the blood values of calcium, phosphorus and PTH to be the main reason for diagnosis. In more than 85-90% of the patients, the cause of PHPT is the presence of solitary parathyroid adenoma, and in the rest 10-15% it is due to primary hyperplasia of the parathyroid glands.

Imaging diagnostics of parathyroid glands is of paramount importance in the diagnostic and differential diagnostic process. The standard surgical approach for primary hyperparathyroidism is the bilateral cervical exploration with the removal of each gland which shows changes macroscopically. In this respect, the preoperative scintigraphy of parathyroid glands with 99mTc – sestamibi or 99mTc – tetrofosmin to detect hyperfunctioning parathyroid glands, especially for those with ectopic location, as well as with recurrence of the disease, is of major importance. The scintigraphy localization of hyperfunctioning parathyroid glands is of paramount importance for minimizing surgical intervention to reduce the risk of complications. Especially problematic are the abnormally located parathyroid glands that are difficult to access or inaccessible for examination by ultrasound scan of the neck. In secondary hyperparathyroidism, as a result of negative calcium balance due to other co-morbid conditions, most patients are in a severe general condition and have limited diagnostic and therapeutic options. In these cases, the localization of hyperplastic parathyroid glands and the exclusion of their mediastinal location are of utmost importance for the therapy approach.

The dissertation, dedicated to the application of nuclear medicine methods for visualization of abnormal hyperfunctioning glands, is very topical and relevant. The subject of the dissertation is valuable for both clinicians and surgeons- especially in case of doubt about the ectopic location of the parathyroid glands.

**Structure of the Dissertation:**

Dr Botushanova’s dissertation titled: “Nuclear Medicine Methods for Evaluation of Abnormal Parathyroid Glands in Patients with Primary and Secondary Hyperparathyroidism" consists of 117 pages and is structured as follows: literature review- 35 pages, aim and related objectives- 3 pages, material and methods- 7 pages, results and discussion- 49 pages, conclusions- 3 pages, contributions- 1 page and references- 9 pages. It is properly structured in terms of the required components. There is a purposeful literature review of the subject, including 104 sources, 4 of which from Bulgarian authors, and the rest 100 from authors from all over the world. The etiological forms of primary and secondary hyperparathyroidism, their clinical, hormonal and biochemical features and diagnostic methods are presented.

The emphasis is placed on the techniques of nuclear medicine methods and used radiopharmaceuticals, detailed analysis of the knowledge and applicability of these methods and their evolution. Dr Botushanova has a deep knowledge of the problem, both historically and as contemporary achievements. She is able to creatively assess the literature material a proof of which is the professionally presented and discussed literature review. The doctoral student has an essential personal contribution to the dissertation study. The credit for the concept of the dissertation, the organization of the work, its implementation, results and formulated contributions, is attributed to her.

The lack of comparative assessments of known nuclear medicine methods and the lack of summarized data for Bulgaria are noted. The advantages of the SPECT technique with improved resolution are outlined. In the Nuclear Medicine Standard of Bulgaria there is no protocol for nuclear medicine examination of parathyroid glands. The aim and the eight objectives of the dissertation are derived from these data and accurately and clearly correspond to the subject: To determine the diagnostic possibilities of the nuclear medicine methods for visualization of abnormal hyperfunctioning parathyroid glands in patients with primary and secondary hyperparathyroidism.

The approach used in the study and in its individual stages, as well as the selection of patients with inclusion and exclusion criteria, is in line with the aim of the project and the resulting objectives. The methodology is precisely described and demonstrates high competence and self-participation of the doctoral student.

A total of 94 patients with proven hyperparathyroidism were studied- 78 of them with primary and 17 with secondary hyperparathyroidism. 46 patients with PHPT and 6 patients with SHPT were examined with radiopharmaceutical Sestamibi. 32 patients with PHPT and 10 patients with SHPT were examined with the second radiopharmaceutical Tetrofosmin. Two types of techniques are studied- single-isotope dual-phase and dual-isotope subtraction techniques, with the use of radiopharmaceuticals Sestamibi and Tetrofosmin.

The results are obtained from a sample of sufficient size and ensure reliability of the methodology. The dissertation is illustrated with 33 figures and 4 tables.

The eleven conclusions summarize the results and the most important aspects of the research. The sensitivity in the application of the two radiopharmaceuticals is determined. The advantages and disadvantages of the two methods (dual-phase and subtraction) are presented. The role of the early SPECT technique as well as the possibility to increase the diagnostic sensitivity of the two techniques when combined with the SPECT technique, is outlined. Positive scintigraphy findings are correlated with biochemical parameters and echographic volumes of parathyroid glands. Risks for false negative and false positive results are analyzed. The contribution of the study to the determination of the surgical approach after the examination is outlined.

The discussion of the results and the conclusions drawn represent the doctoral student as an experienced professional in the field of nuclear medicine.

Based on the research, the results obtained and the eleven detailed and clinically oriented conclusions, the dissertation proposes a diagnostic algorithm for nuclear medicine examinations in patients with primary and secondary hyperparathyroidism as well as protocols for the examination of abnormal hyperfunctioning parathyroid glands in patients with primary and secondary hyperparathyroidism. They are extremely valuable for the clinical practice and should be widely used.

The contributions of the dissertation are synthesized and are valuable both in clinical and methodological aspect.

Dr Albena Botushanova’s dissertation titled: “Nuclear Medicine Methods for Evaluation of Abnormal Parathyroid Glands in Patients with Primary and Secondary Hyperparathyroidism" is an important contribution to our country.

For the first time in Bulgaria a comprehensive study on the application of the nuclear medicine methods for the diagnosis of abnormal parathyroid glands is presented and there are important methodical contributions.

 The doctoral student has applied four thematically related publications, including 1 in Folia medicine, 1 in Endocrynology and 2 in the scientific journals of the Union of Scientists in Bulgaria. She has three contributions to scientific forums with research related papers – one in an international and two in national scientific forums. In 6 of the seven publications and papers, Dr Botushanova is the first author.

In 2012, she was awarded the first prize for the presentation of original results on Science and Youth Competition of Medical University- Plovdiv.

In conclusion, I believe that the submitted dissertation has all the qualities required for awarding Dr Albena Botushanova with the academic and scientific degree “Doctor”.

**Dissertation abstract**

The dissertation abstract fulfils the current requirements and has a very good visualization. It presents the essence of the main components of the research. It reflects all the results achieved in the dissertation, and contains reasonably formulated conclusions and contributions.

**Conclusion**

The dissertation ***contains scientific and applied research results, which represent an original contribution to science*** and **meet all** the requirements of the Law on the Development of the Academic Staff in the Republic of Bulgaria, the Regulations for the implementation of the Law on the Development of the Academic Staff in the Republic of Bulgaria, and the Regulations of Medical University - Varna. The presented materials and the dissertation results are in **full** compliance with the specific requirements adopted in connection with the Regulations of Medical University - Varna for the application of the Law on the Development of the Academic Staff in the Republic of Bulgaria.

The dissertation **demonstrates** Dr Albena Dimitrova Botushanova’s in-depth theoretical knowledge and professional skills in the field of Medical Radiology - Nuclear Medicine, and her qualities and ability to carry out and interpret scientific researches.

Given the above, I convincingly give my ***POSITIVE evaluation*** of the study presented with the reviewed dissertation, abstract, achieved results, conclusions and contributions, and ***I propose to the honorable Scientific Jury to award*** Dr. Albena Dimitrova Botushanova ***with the academic and scientific degree "Doctor"*** in the Doctoral Program of Medical Radiology and Roentgenology.

Reviewer:

07.02.2019 Prof. Dr Marianna Yaneva, MD