



REVIEW

From Assoc. Prof. Milko Bozhidarov Mirchev, MD, PhD
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Regarding the procedure for the academic position "associate professor" in the field of education in "Health and Sports", professional direction "Medicine" and scientific specialty "Pathology" requested by the Department "Anatomy, histology and embryology, pathology, forensic medicine and deontology", Medical faculty, University "Prof. A. Zlatarov" - Burgas.

The competition for associate professor requested by the Department "Anatomy, histology and embryology, pathology, forensic medicine and deontology", Medical faculty, University "Prof. A. Zlatarov" - Burgas was published in the "State Gazette" no. 43 from 17.05.2024

The scientific jury for the competition was appointed by the Rector's order No. РД-237/15.07.2024 from University "Prof. A. Zlatarov" - Burgas.

The candidate for the competition for associate professor is Dr. Nedyalka Todorova Zgurova, MD, specialist in pathology, chief assistant in the Department "Anatomy, histology and embryology, pathology, forensic medicine and deontology", Medical faculty, University "Prof. A. Zlatarov" – Burgas. Dr. Zgurova has submitted a complete set of documents in due time that meet the requirements for the Academic development in the Republic of Bulgaria and the Regulations for the Terms and Conditions for Acquiring Scientific Degrees and Holding Academic Positions at the University "Prof. A. Zlatarov" – Burgas.

I. Analysis of the candidate's career profile:

Dr. Zgurova was born in 1989. She completed her medical education in 2011 at the Medical University "Prof. Dr. Paraskev Stoyanov", Varna. She began her teaching career as an assistant and chief assistant at the Department of General and Clinical Pathology, Forensic Medicine and Deontology, MU "Prof. Dr. Paraskev Stoyanov" - Varna from 2013 to 2022. Meanwhile, she worked at the Provadia Center for Emergency Medical Assistance. From 2022, she leads the Histopathology Laboratory at the "Doctors for Us Burgas" Medical Center and the Department of General and Clinical Pathology, Saint Ivan Rilski Medical Center - Razgrad. In 2020, she successfully defended her thesis named "Comparative morphological and immunohistochemical analysis of benign and malignant epithelial tumors of the colon" and was awarded the educational and scientific degree "doctor" in the specialty "Pathology and cytopathology" (Diploma No. 396 of 29.12. 2020). Dr. Zgurova is board-certified as a General and Clinical Pathologist since 2017. She is a member of the Bulgarian Society of Pathology. She is interested in the field of gastrointestinal pathology, brain tumors, hemopathies, etc. She has the following professional experience: over 8 years as a clinician, over 7 years as a pathologist and over 10 years as an assistant.

As a teacher, the candidate participates in the training of medical students, dental students, medical interns and specialists, as well as medical assistants. Her academic employment report shows 248 hours of academic workload for 2017/2018, 258 hours for 2020/2021 and 158 hours for 6 months for 2021/2022 (with a minimum of 220 hours/year according to MU-Varna regulations). From 2018 to 2020, Dr. Zgurova used maternity leave.

II. General description of the presented materials:

Dr. Zgurova submits for review 5 full-text publications in peer-reviewed journals, 10 full-text publications in non-refereed journals with scientific review or published in edited collective volumes and 1 monographic work. Of the publications, 5 are in Bulgarian and 10 in English.

III. Evaluation of the candidate`s scientific works for overall academic development:

The candidate presents 15 publications - 2 reviews, 6 originals and 7 case-reports. They encompass the following areas: chronic myeloproliferative neoplasia, basal cell carcinoma, colorectal adenocarcinoma, cytological examination of the neck, implantology, clinical cases. Basocellular carcinoma is the topic in the two review articles, with risk factors and histological features being thoroughly explained. Sunlight, nitrosamines, exposure to certain toxins, radiotherapy, etc. are indicated as the basis of risk factors, and for each risk factor the corresponding mechanism of carcinogenesis is described. A significant histological diversity of the mentioned carcinoma is present, which is related to the risk of local invasion, recurrence and metastatic potential. In two of the original articles, Dr. Zgurova addressed the role of angiogenesis in chronic myeloproliferative neoplasia. A correlation was established between increased microvessel density, bone marrow fibrosis and the presence of JAK2V617F mutations. The latter occur mainly in polycythemia vera and primary myelofibrosis and can be used as a prognostic factor. Another two articles discuss APC and BRAF expression in patients with colorectal carcinoma. No correlation was found between the expression of the two proteins and the indicated clinical-morphological characteristics, but there was a correlation with the frequency of lymph node invasion. The role of fine-needle aspiration biopsy in neck processes has been investigated in 2 publications. More than 130 patients with various pathologies were examined, including lesions of the parotid, submandibular gland and lymph nodes. It turns out that this is the first study of its kind in Bulgaria, showing a high diagnostic accuracy, especially with regard to malignant processes. The method allows a reduction in unnecessary surgical interventions with a low frequency of complications, being particularly suitable in childhood. The following case-reports are presented: 1. a case of liver abscess due to retrograde intestinal bacterial contamination of the bile ducts at choledochoduodenal anastomosis, proven histologically; 2. 27 autopsy cases of patients with proven COVID 19 infection. The changes in the lungs and their dynamics over time are described. There is an increase in lung volume at the beginning and a decrease subsequently, diffuse alveolar damage with hyaline

membranes and multinucleation, endotheliitis, pneumocyte hyperplasia, metaplasia and fibrosis of the squamous epithelium of the respiratory tract - changes due to the characteristic viral tropism towards epithelial cells and endothelium; 3. rare cases of arrhythmogenic right ventricular hyperplasia and schwannoma in childhood. The latter was interpreted as an adrenal cyst with normal hormonal status, but due to MRI suspicion of a mass in the area of the right adrenal gland, a laparoscopic resection was performed; 4. a study of the expression of gastric mucins: MUC1, MUC5AC and MUC6 in gastric carcinoma proves that the process of neoplastic transformation in the stomach is associated with a reduction of gastric mucins: MUC5AC and MUC6, and an increased expression of MUC1 in tumor tissue, which is probably involved in the transformation of gastric epithelial cells; 5. treatment of verapamil poisoning with lipid emulsions in experimental animals. The idea is interesting because of the lack of a specific antidote to the mentioned antihypertensive medication. Treated experimental animals show preserved structure of the myocardium, lung and liver parenchyma compared to untreated ones, which could find practical application; 6. Implantology is a new and not particularly researched field. Through the description of a clinical case, the formation of new natural bone in the case of vertical bone deficiency in the distal parts of the upper jaw is shown. A synthetic bone restorative material was used with subsequent placement of an implant by creating an original methodology. The individual stages of recovery are biopsially proven by means of Goldner's Masson trichrome staining, which allows the differentiation of mature mineralized bone tissue from newly formed unmineralized bone (osteoid).

In conclusion, the articles reflect the author's wide range of research interests, including diseases of hematopoiesis, colorectal carcinoma, parotid and submandibular salivary glands, gastric carcinoma, implantology, etc. Some of the studies are original and include methods implemented for the first time in our country.

IV. Evaluation of the monography:

The candidate's monograph - "Colorectal carcinoma - risk and prognostic factors", issued in 2024 consists of 168 pages, divided into twelve sections.

In the introduction, the mechanisms of colorectal carcinogenesis are reviewed. In the "Epidemiology" section, several interesting facts are indicated: the frequency of CRC will increase even in highly developed countries, for Bulgaria the mortality rate in men is higher compared to the average for Europe, with the capital and large regional cities being the most affected, and the weakest Vidin and Kardzhali. Attention is drawn to the classification of CRC according to etiology: sporadic, familial and hereditary, and genetic disorders are described in detail. Risk factors for CRC are discussed in a separate chapter. In addition to the known ones - from the environment and lifestyle, inflammatory bowel diseases, diabetes mellitus, cholecystectomy, the histological variants of polyps are examined in detail. The progression of CRC from adenomas is clear, depending on their size, villous structure and degree of dysplasia. More interesting, however, is the relationship between hyperplastic polyps and CRC, which until recently was considered almost impossible. Today it is known that they are part of the so-called "Serrated" neoplasias of the colon, which are associated to a greater extent with CRC. In the section "Phases of carcinogenesis" the step-by-step formation of tumors is presented by going through initiation, promotion, conversion and progression with the corresponding participation of tumor suppressors and oncogenes, and a new group is also mentioned - the so-called Mutator genes. The pathways of colorectal carcinogenesis were examined in detail, including chromosomal instability, microsatellite instability and the phenotype of methylated CpG islands. Three generalizing pathways have also been proposed: serrated pathway, defective microenvironment, and de novo. It has been rightly emphasized that, in addition to genomic and epigenomic instability, genes involved in various signal transduction pathways are damaged in colorectal carcinogenesis, which are discussed in detail in a separate chapter. Traditional morphologic variants of CRC and staging according to the TNM classification are also presented, and everything mentioned so far is then summarized and considered as a potential prognostic marker. The most essential part of the monograph is the chapter

"Prognostic Markers". It includes clinical, pathological and molecular ones, which emphasizes the heterogeneity of colorectal carcinoma. The Pathological Markers section discusses the discovery and development of the Dukes and TNM classifications, the latter of which is still generally accepted today. The role of lymph node metastases for the subsequent behavior was separately considered, including minimal number of resected nodes, use of molecular markers, relationship with depth of infiltration, neural vascular invasion, sentinel lymph nodes, etc. Tumor budding, tumor necrosis, the presence of an inflammatory response, micrometastases are mentioned - each with a different prognostic significance. Special attention is paid to molecular predictive and prognostic markers. KRAS and NRAS oncogenes are widely studied because tumors with mutations have resistance to anti-EGFR therapy and worse prognosis. The same applies to the presence of a BRAFV600E mutation. The presence of MSI and methylated CpG island phenotype are also associated with worse prognosis and resistance to adjuvant chemotherapy.

In conclusion, the monograph "Colorectal carcinoma - risk and prognostic factors" shows the heterogeneity of CRC, the wide variety of pathologo-anatomical and molecular-biological markers, and the presence of many unexplored areas. It is a useful guide for any specialist wishing to obtain additional information in a practical and scientific aspect.

V. Citations of the applicant's publication activity:

Dr. Zgurova submits 4 publications for evaluation, all of which are in English. The provided reference shows the presence of 33 citations, of which 7 are in the Web of Science database, 18 are in other freely available online sources and 8 are in Bulgarian sources from the central medical library collection. The cited articles examine the relationship between JAK2V617F mutations and angiogenesis in patients with myeloproliferative neoplasms, rate of bone regeneration in vertical bone deficiency in the distal parts of the maxilla, COVID-19 associated complications, malignant schwannoma resembling an adrenal cyst.

VI. Evaluation of the candidate's educational and teaching activity:

Dr. Zgurova is involved in the training of medical students grades III and IV, as well as dentistry students II grade, having over 10 years of experience as an assistant. Her involvement in organizing practical training and lectures is evident from the provided reference. With the norm for non-qualified teachers of 220 hours per academic year according to the rules of the Medical University, Varna, Dr. Zgurova presents a workload above the minimum (between 242 and 258 hours/year), which indicates an active teaching and learning activity. Dr. Zgurova participated in 3 scientific projects concerning simulation models, three-dimensional visualization and in situ relationships of glial and tumor cells.

VII. Critical notes and recommendations:

In the articles concerning the expression of BRAF and APC proteins in patients with colorectal carcinoma and polyps, a more detailed presentation of the data in a tabular form and of the results of the regression analysis is appropriate.

VIII. General assessment of the applicant's compliance with the mandatory conditions and the mandatory quantitative criteria and scientometric indicators:

7. Health and sports. Professional direction 7.1 medicine

Group of indicators	Content	Minimum required points for "Associate Professor"	Actual points by groups of indicators for "associate professor" of Dr. Nedyalka Zgurova
A	Indicator 1	50	50
Б	Indicator 2	-	0
B	Indicators 3 and 4	100	100
Г	Sum of indicators 5 to 9	200	245,35
Д	Sum of indicators 10 to 12	100	235
E	Sum of indicators 13 to 22	60	55
	Total score	510	685,35

According to the applicant's self-assessment report provided, the latter meets and exceeds the minimum quantitative criteria and scientometric indicators necessary for holding the academic position "Associate Professor".

IX. Conclusion:

The candidate MEETS the mandatory and specific conditions and scientometric criteria for occupying the academic position of "ASSOCIATE PROFESSOR".

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