TO THE CHAIR OF THE SCIENTIFIC JURY
APPOINTED BY ORDER NO. R-109-148/24.03.2026
OF PROF. DIMITAR RAYKOV, MD, DSC
RECTOR OF THE MEDICAL UNIVERSITY
"PROF. DR. PARASKEV STOYANOV" – VARNA

OPINION

By prof. Dimitar Ivanov Bulanov, MD, PhD
Dean of the Faculty of Medicine, Medical University – Sofia
Department of General and Operative Surgery, Faculty of Medicine, Medical University -Sofia
Clinic of General and Hepato-pancreatic Surgery, University Hospital "Alexandrovska", Sofia

On the dissertation entitled:

"CONTEMPORARY SURGICAL APPROACHES IN MALIGNANT DISEASES OF THE GASTROINTESTINAL TRACT – CLINICAL AND EPIDEMIOLOGICAL ASPECTS IN NORTHEASTERN BULGARIA"

Submitted for the award of the scientific degree „**Doctor of Sciences**", field of higher education 7. Health care and sport, professional field 7.1 Medicine

Author of the dissertation - **prof. Kostadin Georgiev Angelov, MD, PhD**

Institution: Department of General and Operative Surgery, Faculty of Medicine, Medical University "Prof. Dr. Paraskev Stoyanov" – Varna

I. General characteristics and comments on the procedure

The present opinion is based on Order No. R-109-148/24.03.2026 issued by Prof. Dimitar Raykov, MD, DSc, Rector of the Medical University "Prof. Dr. Paraskev Stoyanov" – Varna, by which I was appointed as a member of the Scientific Jury.

The set of materials submitted to me by the candidate in both printed and electronic format, as well as the procedure for the defense of the dissertation, are fully compliant with the requirements of the currently effective regulatory framework in the Republic of Bulgaria, namely the Academic Staff Development Act in the Republic of Bulgaria, the Implementing Regulations of the Act, and the Regulations for Academic Staff Development of the Medical University – Varna concerning the award of the scientific degree Doctor of Sciences.

At the first remote meeting of the Scientific Jury I was assigned to prepare the present opinion.

II. Brief biographical information about the candidate

Prof. Kostadin Angelov graduated from the Medical University – Sofia in 2004 with a degree in Medicine. He subsequently obtained the specialty in General Surgery at the Faculty of Medicine of MU-Sofia. He also holds a second Master's degree in Public Health and Health Management. In 2015 he completed a Master's degree in Finance at the University of National and World Economy. He worked for two years as a resident physician in the Emergency Department – Shock Room at the Center for Emergency Medical Care – Sofia Region, University Hospital "St. Anna". In 2006, after a competitive procedure, he was appointed Assistant Professor of Surgery at the Department of Surgery, Faculty of Medicine, MU-Sofia. In 2015 he was elected Associate Professor at the same department, and in 2020 he was elected Professor. Between 2013 and 2020 he served as Executive Director of the University Hospital "Alexandrovska". During the period 2020–2021 he held the position of Minister of Health of the Republic of Bulgaria. Throughout his professional career Prof. Angelov has demonstrated continuous professional development, improvement and positive growth. This progress is attributable both to his strong theoretical background and to his personal qualities. He has completed numerous courses within the framework of continuing medical education.

Prof. Angelov is an established surgeon and academic lecturer with extensive clinical and managerial experience. He successfully combines practical surgical work with scientific and teaching activities, thereby contributing to the development of medicine and healthcare management in Bulgaria.

III. Relevance and significance of the topic

The approaches to prevention, early detection, diagnosis, surgical treatment and prognosis of malignant diseases of the gastrointestinal tract remain highly relevant not only for Bulgarian but also for global oncological surgery. These malignancies are characterized by local aggressiveness, high metastatic potential, a tendency toward recurrence and metachronous metastasis following radical resections, and consequently unfavorable long-term outcomes. According to data from the National Center of Public Health and Analyses, the incidence of digestive organ cancers in Bulgaria in 2023 was 87.9 per 100,000 population, ranking third among all oncological diseases. More than 5600 new cases annually were registered during the period 2022–2023. The dissertation topic selected by Prof. Angelov is therefore extremely relevant as it addresses one of the most important challenges faced by contemporary healthcare systems. The treatment of malignant diseases of the gastrointestinal tract requires coordinated actions of interdisciplinary teams of highly qualified specialists, complex therapeutic strategies involving costly medications and high-technology diagnostic and surgical procedures, which together impose a considerable financial burden on healthcare systems.

In summary, the combination of high medical relevance, clearly defined regional necessity and scientific novelty renders the topic both timely and practically significant for healthcare in Northeastern Bulgaria and for the country as a whole.

IV. Characteristics of the dissertation research

The dissertation submitted by Prof. Angelov comprises 263 standard pages and is illustrated with 61 tables and 29 figures. The bibliography includes more than one thousand references and two electronic appendices. The study is interdisciplinary and analytically structured. The literature review has a strong analytical character and occupies a significant portion of the dissertation. The author demonstrates excellent knowledge of the problems related to malignant diseases of the gastrointestinal tract.

Methodology of the study

The dissertation includes two complementary research components:

Part 1. Systematic review of scientific publications

A documentary method was applied, consisting of an analysis of specialized medical literature conducted in accordance with the international standards PRISMA 2020 (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) and the Cochrane Collaboration. The PICOS framework (Population, Intervention, Comparison, Outcomes, Study design) was used to evaluate the results. The search included the MEDLINE database, the resources of the Central Medical Library of the Medical University – Sofia, and national peer-reviewed scientific journals for the period January 2000 – 2025. A total of 796 publications were identified. After applying inclusion and exclusion criteria, 303 studies were selected for qualitative synthesis. Fundamental and laboratory studies, studies without surgical relevance, case series with fewer than 10 patients, and editorial articles were excluded. The workflow passed through five consecutive stages: preliminary definition of PICOS criteria, screening of titles and abstracts, in-depth extraction of numerical results and methodological details, and assessment of risk of bias.

Part 2. Clinical-epidemiological study

A retrospective observational single-center study based on electronic medical records was conducted. The study center was University Hospital "St. Marina" – Varna, Department of General and Operative Surgery, the largest diagnostic and treatment institution in Northeastern Bulgaria with 1292 hospital beds. The analyzed period covered 2013–2023 (10 years) and included more than 2000 electronic medical records of hospitalized patients over 18 years of age. The analyzed parameters included - demographic characteristics (sex and age in four age groups), clinical pathways at admission and discharge, ICD diagnostic codes, hospital mortality, comorbidities, histological diagnosis, type of admission (elective/emergency), length of hospital stay, TNM staging, ECOG performance status.

The statistical methods applied included descriptive and variation analysis, frequency analysis with one- and two-dimensional distribution tables, calculation of means, standard deviation, median and 95% confidence intervals at significance level $\alpha = 0.05$, as well as sensitivity analysis. The statistical software Jamovi and Microsoft Excel 2016 were used.

The study was conducted in accordance with the Declaration of Helsinki and the Guidelines for Good Clinical Practice. Due to the retrospective nature of the study and the use of depersonalized data only (sex and age), approval from a local ethics committee was not required.

Statistical analysis includes descriptive statistics, frequency analysis, confidence intervals, and sensitivity analysis using Jamovi and Microsoft Excel.

Characterization and evaluation of the results of the dissertation

The results of the epidemiological study conducted in our country demonstrate that malignant neoplasms of the gastrointestinal tract represent a significant public health problem. Bulgaria is one of only two countries in the European Union where cancer mortality increased during the period 2011–2021. Colorectal carcinoma ranks third among oncological diseases in terms of incidence, with approximately 5,086 new cases annually, and represents the second leading cause of cancer-related mortality. Pancreatic cancer is the fifth most frequent cause of death from malignant disease despite its relatively lower incidence. Five-year survival remains low for most tumor localizations—approximately 51% for colorectal carcinoma, around 12% for gastric cancer, and below 6% for esophageal and liver cancers. A key problem is the diagnosis at advanced stages: only 21% of gastric cancer cases are detected at an early stage, 17% in pancreatic cancer, and merely 10% in liver cancer. The proportion of cases with unspecified stage is particularly high in liver cancer (50%) and esophageal cancer (36%), reflecting substantial diagnostic challenges.

The author identifies "contradictory and opposing trends" in the national data—decreasing incidence against a background of increasing mortality. This is a methodologically concerning observation, which most likely reflects underreporting and incomplete data registration following the closure of the National Cancer Registry, rather than a true epidemiological phenomenon.

The clinical study covers an 11-year period (2013–2023) and analyzes 2,103 patients hospitalized at the University Hospital "St. Marina" in Varna. Among the analyzed patients, men predominate significantly—58.9% compared to 41.1% women. The mean age is 67.66 years (median 69 years). The dominant age group is 66–75 years (40.4%), followed by 46–65 years (33.9%). More than 62% of patients are older than 66 years, while only 3.7% are under 45 years of age. Patients were admitted through 74 different clinical pathways, the most common being Clinical Pathway No. 175 (major and complex surgical procedures on the small and large intestines), accounting for 29.62% of all admissions. The leading diagnosis at hospitalization is rectal cancer (C20) with 15.22%, followed by sigmoid colon cancer (C18.7) with 9.03%. At discharge these two diagnoses remain in the leading positions with 19.42% and 15.04%, respectively. It is noteworthy that a complete match between the clinical pathway at admission and that at discharge is observed in only 56.97% of patients. Hospital mortality for the studied period is 8.1% (170 deaths among 2,103 admitted patients). At least one comorbidity is present in 91.87% of patients, with an average of 3.11 comorbid conditions per patient. The most common comorbidity is hypertensive heart disease without heart failure (55.02%), followed by type II diabetes mellitus (16.93%), anemia associated with malignant neoplasms (15.94%), and secondary malignant neoplasm of the liver (13.20%). The type of admission and hospital stay indicate that 64.6% of patients were admitted electively, while 35.4% were hospitalized with varying degrees of urgency, with 27.5% admitted as emergency cases within six hours of the

registration of the need for hospitalization. The average hospital stay is 10.65 days (median 9 days, mode 7 days), without a significant difference between sexes. The longest hospital stay is observed among patients over 75 years of age (mean 11.29 days). TNM staging data are available for 70% of patients during the period 2016–2023 (data for 2013–2015 were not collected). A very large dispersion is observed—567 different TNM configurations, of which 79% are unique. The most frequent configuration is T3NxM0 (3.65%). According to the T criterion, the majority of patients are classified as T3 (55.3%), followed by T4 (25.2%), T2 (14.9%), and T1 (3.9%), indicating that most cases are diagnosed at a locally advanced stage. These data are a clear indicator, on the one hand, of clinical heterogeneity of cases and, on the other hand, of the lack of standardized and widely accepted coding according to the TNM system. The mixing of clinical (cTNM) and pathological (pTNM) staging within a single formulation without distinction is methodologically questionable. Among patients with available staging data (50.3% of the sample), the distribution is as follows: stage III — 35.9%, stage II — 25.4%, stage IV — 24.5%, stage IB — 10.7%, stage IA — 3.0%, and stage 0 — only six patients. These findings confirm the alarming trend toward late diagnosis—nearly 60% of staged patients are in stage III or IV at the time of hospitalization. G-grading is documented in only 4.56% of patients, with moderately differentiated G2 carcinoma predominating (79.17%), followed by poorly differentiated G3 carcinoma (13.54%). ECOG performance status is available for 50.8% of patients. Among them, the majority present with symptomatic disease (77.3%), only 7.6% are asymptomatic with normal performance status, and 12.9% exhibit disabling tumor manifestations.

Scientific contributions

Prof. Angelov has successfully substantiated his claims regarding the scientific contributions of the present research. The contributions of the dissertation may be grouped into four main directions:

✓ Scientific-theoretical and methodological contributions

The dissertation is distinguished by exceptional methodological innovativeness and scientific boldness. For the first time in Bulgaria—and, to the best of current knowledge, also for the first time in international surgical research practice—the methodological toolkit of Health Technology Assessment (HTA) has been applied to retrospective data derived from real-world clinical practice in relation to oncological diseases of the gastrointestinal tract. This represents a conceptual breakthrough, as this approach has traditionally been employed in the evaluation of medicinal products and medical devices rather than clinical and epidemiological datasets, whose assessment is methodologically far more complex. Particularly noteworthy is the author's contribution in developing a modified version of the PICOS instrument—designated *"a'modo Angelov"*—specifically adapted for the evaluation of surgical interventions in oncological diseases of the gastrointestinal tract. The standard five elements of the instrument have been expanded to include tumor type, TNM classification, ECOG performance status, and the type of surgical procedure (radical/palliative). This modification is not merely formal; rather, it reflects the author's profound understanding that without these additional dimensions, the evaluation of

the clinical effectiveness of surgical interventions is fundamentally impossible. The proposed instrument has the potential to become a methodological standard for future systematic analyses in surgical oncology. Equally significant is the systematic review of the scientific literature conducted in accordance with the recommendations of the Cochrane Collaboration and the PRISMA 2020 standard, covering a 25-year period and including 303 studies. The developed two-stage data extraction process, with a clear distinction between CORE and DEEP selection, represents an original authorial protocol that may be applied in future scientific investigations.

✓ Epidemiological contributions

The dissertation fills a substantial gap in Bulgarian medical science. For the first time, a comprehensive epidemiological study of malignant diseases of the gastrointestinal tract has been conducted on the basis of a systematic analysis of data from the European Cancer Information System (ECIS) and IARC/GLOBOCAN, integrated with national data from the National Center of Public Health and Analyses (NCPHA) and the National Cancer Registry. The result is a unique large-scale representation of the epidemiological profile of these diseases in Bulgaria - by anatomical localization, stage, sex, and age - for which no comparable investigation has previously existed. Of particular value is the study's documentation and analysis of the alarming inconsistencies within national epidemiological data - namely, increasing mortality in the context of apparently decreasing incidence. Although concerning, this finding is of considerable importance for health policy and reflects the author's analytical depth.

✓ Clinical and applied contributions

The study of a clinical cohort comprising 2,103 patients over an 11-year period at the St. Marina University Hospital, Varna, is unprecedented in scale and duration within the context of clinical and epidemiological research concerning oncological surgical pathology in Bulgaria. The analysis based on 15 clinical and administrative criteria provides comprehensive information derived from real-world clinical practice, including the demographic profile of patients, diagnostic behavior, surgical approaches, in-hospital mortality, comorbidity, and oncological staging. The documented high comorbidity burden among Bulgarian patients—91.87% presenting with at least one concomitant disease and a mean of 3.11 comorbidities per patient—constitutes in itself an original contribution with practical implications for the planning of perioperative management. These data partially explain why treatment outcomes in Bulgaria lag behind those reported in Western Europe and provide an important starting point for future clinical research. The identified trend toward late diagnosis—nearly 60% of staged patients being in stage III or IV at the time of hospitalization, and 34.4% of admissions being emergency cases—provides a concrete, evidence-based rationale for the immediate introduction of national screening programs.

✓ Contribution to health policy

The presented data constitute direct evidence supporting the need for a national screening program for colorectal carcinoma, the reactivation of the National Cancer Registry with the

implementation of strict standards for oncological data collection, and the imperative development of regionally adapted therapeutic protocols for Northeastern Bulgaria. In this respect, the dissertation makes a significant pioneering contribution to clinical oncology and extends beyond the framework of a conventional scientific investigation, acquiring measurable relevance for health policy. At the same time, the study exhibits methodological limitations characteristic of retrospective analyses based on administrative data. These primarily include the incompleteness of key clinical parameters (TNM, ECOG, G classification), the absence of analytical statistical approaches beyond descriptive analysis, and the limited generalizability inherent in a single-center study. These limitations do not diminish the value of the dissertation but should be explicitly considered when interpreting its conclusions.

V. Scientometric indicators

In relation to the dissertation topic, Prof. Angelov has submitted 15 full-text publications, in 10 of which he is the first author. All scientometric requirements stipulated by Bulgarian legislation and the regulations of the Medical University – Varna are fulfilled.

VI. Abstract

The abstract of the dissertation meets the required standards in terms of volume and content and adequately reflects the objectives, methodology, results and conclusions of the study.

CONCLUSION

The dissertation of Prof. Angelov contains scientific and applied contributions that represent an original authorial contribution to medical science and enrich knowledge regarding the epidemiology, prevention, diagnosis and multidisciplinary treatment of malignant diseases of the gastrointestinal tract. The presented materials, methodology, analyses and results fully comply with the requirements for a dissertation submitted for the award of the scientific degree Doctor of Sciences.

No evidence of plagiarism was identified.

Based on the above considerations, I give my highly positive evaluation of the dissertation entitled "Contemporary Surgical Approaches in Malignant Diseases of the Gastrointestinal Tract – Clinical and Epidemiological Aspects in Northeastern Bulgaria". I propose to the esteemed Scientific Jury to award the scientific degree Doctor of Sciences in the field of higher education 7. Health Care and Sport, professional field 7.1 Medicine to Prof. Kostadin Georgiev Angelov, MD, PhD, and I firmly vote "YES".

Prof. Dimitar Bulanov, MD, PhD

28.03.2026
Sofia