OPINION

For a dissertation for the acquisition of the educational and scientific degree "doctor" in the field of higher education 7: "Healthcare and Sports", professional field 7.1 "Medicine" and specialty "Cardiology"

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Topic: "Cardiotoxicity in traditional and modern antineoplastic regimens"

Scientific supervisor:

Assoc. Prof. Dr. Atanas Angelov Atanasov, MD, Head of the First Department of Internal Medicine, Medical University "Prof. Dr. Paraskev Stoyanov", Varna.

Prepared by: Prof. Dr. Yoto Trifonov Yotov, MD, cardiologist, professor at the Education Sector of Cardiology, First Department of Internal Medicine, Medical University "Prof. Dr. Paraskev Stoyanov", Varna.

By order No. P109-101/28.01.2025 of the Rector of the Medical University, Varna, based on a decision of the Faculty Council of the Faculty of Medicine under protocol No. 33/ 20.01.2025. I am elected as a member of the Scientific Jury for the public defense of the thesis of Dr. Svetoslava Elefterova Slavcheva. At the first meeting of the Scientific Jury, I was elected as the Chairman of the Jury and I was assigned to prepare an opinion on the procedure for acquiring the educational and scientific degree "Doctor".

Brief data on the professional development and qualifications of the doctoral student:

Dr. Svetoslava Elefterova Slavcheva graduated Medicine in 1999 at the Medical University "Prof. Dr. Paraskev Stoyanov", Varna, after which she worked as a physician at the Central Emergency Unit-Varna, Provadia branch. She was successively a doctor in the Emergency Department for adults and a cardiologist at the First Cardiology Clinic with ICU of the University Hospital "St. Marina", Varna. From 2019 to 2023 she was an assistant professor, and from 2023 until now as a lecturer at the First Department of Internal Medicine, Medical University "Prof. Dr. Paraskev Stoyanov", Varna.

In 2009, she was certified as specialist in Internal Medicine, and in 2014 – in Cardiology. Dr. Slavcheva has acquired professional qualifications in echocardiography - fundamental and expert level.

Significance of the topic: Cardio-oncology is a rapidly developing cardiology subspecialty that studies all aspects of the relationship between malignant and cardiovascular diseases. Antitumor therapy, which is in most cases combined, can lead to various adverse effects on the cardiovascular system – myocardial dysfunction and HF, coronary artery disease, valvular involvement, rhythm disorders, arterial hypertension, thromboembolic complications, peripheral vascular damage and stroke, pulmonary hypertension and pericardial involvement. Modern science provides us with information about the cellular and molecular mechanisms underlying early-onset cardiotoxic effects. Apart from the systolic damage, pathophysiological mechanisms also clarify potential disorders in diastolic myocardial function. Changes in the RV structure and function in oncological patients are associated with increased mortality, worsening of HF functional class, and the occurrence of multiorgan dysfunction. The accumulated clinical data on the significance of right ventricular dysfunction are based on small and heterogeneous populations, and the results do not provide unambiguous information. The clinical significance of right ventricular damage is unclear and its prognostic value is still

unknown. The need for further studies on functional changes in the RV under the influence of OT justified the present study.

Structure of the thesis: It is written on a total of 222 pages. The dissertation is well balanced in 9 chapters and includes an introduction, literature review, aim and objectives, material, methods, own results and discussion, conclusions, imference, scientific contributions, publications and reports in scientific forums, reference literature. It is illustrated with 41 tables and 83 figures. The bibliography includes a total of 262 titles, of which 4 are in Cyrillic by Bulgarian authors. The abstract includes 32 of the figures and 25 of the tables.

Literature review: This section is structured with several foci. It begins with an overview of the development of cardio-oncology with a historical review and of current issues. The next section defines cardiac dysfunction associated with oncological therapy, examining the potential and mechanisms for cardiac involvement of different chemotherapeutic agents and radiotherapy.

A separate section of the literature review is dedicated to the anatomy and function of the right ventricle, as well as to right ventricular damage during antitumor therapy. Methods for echocardiographic assessment of the RV in normal and during treatment with antitumor agents are examined in detail. Parameters of systolic and diastolic function are defined using common and modern methods in normal and pathological conditions.

The review also examines the changes in left ventricular diastolic function during the treatment of oncological diseases using different methods. In conclusion, it is emphasized that detailed knowledge of the specific mechanisms of cardiac damage in different antitumor therapies is essential for the early detection of cardiac dysfunction. Due to the small number of studies on the importance of the RV in the process of cardiac involvement as a result of antitumor therapy, the prognostic significance of RV damage is not clear. The state of scientific research on the development of LV diastolic dysfunction in oncological patients is similar. These gaps in the available evidence are a significant reason for their more detailed study in the present work, seeking an easily applicable and sufficiently informative algorithm for echographic assessment of cardiac disorders in various methods of antitumor treatment.

Aim and objectives: the main aim of the project is: to prospectively study the change in right ventricular systolic and diastolic function under different chemotherapy regimens and to propose an easy-to-use algorithm for echocardiographic assessment of the right ventricle. It is well formulated, but does not include the studied LV parameters that are indicated in the tasks. The 5 tasks related to it are a logical continuation of the literature review and of the main aim and are clearly and precisely defined. However, they are broader than the defined aim. The tasks reflect the individual steps – methods of obtaining information, an analytical approach to generalizing the obtained results and defining a useful algorithm for practice for early prediction of myocardial damage and risk stratification of patients.

Methods and subjects: For the purposes of the dissertation, a total of 60 patients over the age of 18 with neoplasms of the mammary gland, gastrointestinal tract and female genital system, who were to undergo systemic antitumor therapy after signing an informed consent, were studied. Clear exclusion criteria were indicated. The patients were followed up at baseline (before starting chemotherapy or target therapy) at the 1st, 3rd, 6th, 9th, 12th and 18th months. The methods of examination using clinical signs, laboratory parameters (hsTnT), ECG and echocardiography were described. The statistical methods used to analyze the results obtained were elaborated in detail and were fully adequate to get relevant conclusions.

Results: The presented data show that in all treated patients there is a decrease in LV systolic function, with 10% already having suppressed pump function, confirmed by both low EF and myocardial systolic longitudinal motion velocities. These systolic velocities decrease over time and this decrease is maintained up to 18 months of observation. There is a moderate positive correlation between LV myocardial tissue velocities and LV EF, more significant for the septal component. Systolic dysfunction was observed most often during treatment with anthracyclines, radiotherapy and on average after 6 months of observation. Protective cardiological therapy was started in 5/6 of them.

Diastolic LV dysfunction was observed in 12% of patients during the entire observation period. At the 6th and 12th months of antitumor systemic treatment, the probability of developing diastolic LV dysfunction increases, with the relative risk exceeding 6 times.

Similar negative dynamics are observed in the parameters of the RV after antitumor therapy. The RV shortening fraction decreases by an average of 15% from the baseline to the end of follow-up, and S' of the lateral wall of the RV is lower by 0.87 cm/s at the 12th month. Although insignificant, there is a decrease in TAPSE, with this indicator reaching a pathological value ≤16 mm in 25 patients. RV dysfunction related to antitumor therapy has occurred in 7 patients or 11.7 % of the population. No significant deterioration of the right ventricle diastolic function was detected in the study population from the beginning of therapy at any stage of follow-up.

The temporal relationships between changes in LV and RV, as well as the factors for the occurrence of various cardiac disorders, were analyzed. As a result of the results, a practical algorithm for the assessment of patients undergoing oncological treatment was created.

The discussion is in the chapters after the individual parts of the results. As a recommendation, it is good to have the discussion part into a separate chapter.

Conclusions: The conclusions drawn are complete and summarize the presented results in detail. They meet the goals and objectives set by the author of the thesis, with the exception of conclusion 5. Their number – 7, is sufficient and reflects the significance of the obtained results.

I fully agree with the original and confirmatory **contributions made by the PhD candidate. There is a discussion of the potential limitations of the work which is one positive benefit.**

In connection with the developed thesis, 2 full-text **publications have been made** in a medical journal, referenced in the international database, as well as 5 presentations at high-rated scientific forums.

The abstract meets the requirements of the Academic Staff Development Act.

I could find any missing documentation submitted by Dr. Svetoslava Elefterova Slavcheva, and they fulfil the legal requirements of the of the Academic Staff Development Act and its Regulations, as well as the Regulations for the Development of the Academic Staff at Medical University-Varna.

Conclusion: The dissertation work of Dr. Svetoslava Elefterova Slavcheva treats an extremely important interdisciplinary problem in cardiology and oncology – the development of cardiac changes in different modes of antitumor treatment, the solution of which is crucial for their early diagnosis and for improving the prognosis and quality of life of patients. The presence of cardiac dysfunction also determines a change in the method of drug treatment. The aim has been achieved, the tasks set have been fulfilled. The conclusions are sufficiently

accurate and comprehensive, clearly formulated. Contributions have not only scientific but also practical value, especially the developed algorithm. The submitted publications and scientific communications meet the requirements.

Under these circumstances, I believe that the dissertation work of Dr. Svetoslava Elefterova Slavcheva meets all the requirements for awarding the scientific and educational degree "Doctor" and I strongly recommend that the esteemed jury vote positively.

11.03.2025
Varna

Prepared the opinion:

(Prof. Dr. Yoto Yotov, MD)