To the Chairman
of the Scientific Jury,
appointed by Order
№R-109-101/28.01.2025
of the Rector of the Medical University – Varna

REVIEW

by Prof. Borislav Georgiev Georgiev
Head of the Cardiology Clinic at the National Heart Hospital,
member of the Scientific Jury for awarding the scientific and educational degree Philosophy Doctor,
appointed by Order № R-109-101/28.01.2025 of the Rector of the Medical University – Varna

Regarding: The thesis presented by Dr. Svetoslava Elefterova Slavcheva, a full-time doctoral student at the Medical University – Varna. Thesis subject: *Cardiotoxicity in Conventional and Contemporary Cancer Treatment Protocols,*
research supervisor Assoc. Prof. Atanas Angelov, MD, PhD;
Field of higher education 7. Healthcare and Sports, Professional field 7.1. Medicine, Doctoral program 03.01.47 in Cardiology.

The documentation submitted by Dr. Svetoslava Elefterova Slavcheva – thesis, thesis summary, and additional paperwork comply with the requirements for obtaining the educational and scientific degree of Philosophy Doctor and the Rules and Regulations of the Medical University – Varna. I find no omissions in the submitted documentation.

I confirm that I do not have any conflicting interests in relation to the candidate.

All submitted documentation is precisely arranged and filed.

There is no evidence of plagiarism.

Brief biographical data

Dr. Svetoslava Elefterova Slavcheva was born in 1972 in Varna. She graduated in medicine from the Medical University "Prof. Dr. Paraskev Stoyanov" – Varna in 1999. In 2009, she acquired a speciality in Internal Medicine, and in 2014 –in Cardiology. Since February 2019, she has been a full-time doctoral student at the First Department of Internal Medicine with a research supervisor Assoc. Prof. Atanas Angelov. Since 2019, she has been an assistant professor in cardiology. In 2023, she became a lecturer at the First Department of Internal Diseases, Educational Section Cardiology, at the Medical University "Prof. Dr. P. Stoyanov".

Dr. Slavcheva is a member of the European Society of Cardiology (ESC), European Association of Cardiovascular Imaging (EACVI), Heart Failure Association of the ESC (HFA), ESC Council of Cardio-Oncology, International Cardio-Oncology Society (IC-OS), and Bulgarian Society of Cardiology (BSC). She speaks English, Portuguese, and Russian.

Significance of the subject

The focus of the thesis is of great relevance, especially considering the global developments that are steering the future of cardiology, particularly in the intersection of cardiology and oncology.

With the introduction of new therapies in cancer treatment, attention is focused on organ toxicity of antitumor agents. Algorithms for monitoring toxicity to the cardiovascular system have been developed. Developing integrated algorithms that are easy to implement and tailored to practical requirements is essential. Echocardiographic diagnostics is in the daily practice of the cardio-oncologist, but not all investigated parameters are well studied in the context of cardiotoxicity. The subject's significance is also confirmed by the ESC position paper published in 2024 on "The Right Ventricular in Cancer Patients." Regrettably, there are few teams in our country focusing on this topic. It would be beneficial for the author to familiarise herself with their work, which is not clearly reflected in the referenced sources.

Thesis structure

Dr. Svetoslava Elefterova Slavcheva's thesis is presented on 222 pages; it is structured according to requirements and contains a literature review, aims and objectives of the study, materials and methods, results and discussion, conclusions, summary, contributions, and bibliography. The thesis material is illustrated with 41 tables and 83 figures.

The Literature review is presented on 55 pages and is organised in several key points: cardio-oncology – introduction and historical facts; definition of cardiac dysfunction related to oncological therapy; systemic antitumor therapy associated with the development of cardiac dysfunction; right ventricle and right ventricular damage resulting from antitumor therapy; left ventricular diastolic dysfunction during antitumor therapy and conclusion from the literature review. The review demonstrates the author's good awareness regarding cardiotoxicity from the application of antitumor therapy, and non-invasive assessment of these effects with special attention paid to the right ventricular function and right ventricular damage.

An increasing number of scientists are studying the changes in the right ventricle, but clinical data are based on small and heterogeneous populations. These results do not provide unambiguous evidence. There is no clarity about the clinical significance of right ventricular damage. Its prognostic value and whether it can justify the inclusion of preventive treatment are still unknown. There is also little clinical evidence regarding left ventricular diastolic dysfunction.

Based on the literature review, Dr. Svetoslava Slavcheva logically derives the importance of conducting her research.

The Bibliography contains 262 sources, of which 4 are in Cyrillic and are 258 in Latin. All references are properly documented.

The aim of Dr. Svetoslava Slavcheva's research is to investigate the change in the **right ventricular** systolic and diastolic function under various chemotherapeutic therapies and to propose an easy-to-apply algorithm for the echocardiographic assessment of the right ventricle.

To achieve this aim, she sets the following **tasks**:

1. To dynamically monitor the echocardiographic parameters for LV systolic and diastolic function through 2D echocardiography and tissue Doppler in patients on different systemic antitumor therapies.

2. To dynamically assess the echocardiographic parameters for RV systolic and diastolic function through 2D echocardiography and tissue Doppler in patients on different systemic antitumor therapies.

3. To establish a correlation between changes in the echocardiographic parameters for right and left ventricular function and deviations in the biochemical markers of myocardial injury.

4. To analyse temporal, correlational, and predictive associations between echocardiographic indicators for LV and RV and clinical factors.

5. To develop an algorithm for early prediction of myocardial injury and risk stratification of patients.

Methodological approach: A total of 60 patients with a mean age of 53 years were prospectively studied, the youngest patient being 31 years old and the oldest 74 years old. Regarding the oncological disease, the majority of patients, 83.3% (n = 50), were diagnosed with breast cancer, while the remaining 10 patients (16.7%) had gastrointestinal tract neoplasms – colon cancer, pancreatic cancer, or stomach cancer. Anthracyclines (epirubicin) were administered to 50% of the patients, with a mean equivalent cumulative dose (ECD) of doxorubicin 128 (SD 36) mg/m2. Targeted therapy was applied in 29 (48%) of patients, primarily HER2-targeted therapy with trastuzumab and trastuzumab modifications (n=24, 40%). In 11 (n=18%) patients, trastuzumab was administered in combination with Pertuzumab, and in 9 (15%) patients, trastuzumab was administered sequentially to anthracyclines. On average, the duration of trastuzumab treatment lasted 447 days from the initiation of monitoring. Six patients were treated with other targeted medications: bevacizumab, lapatinib, and ribociclib. A total of 45% of the population received radiotherapy as part of their breast cancer treatment, with nearly half receiving it in the left-sided breast. Due to the higher risk of developing cardiomyopathy associated with the combined administration of trastuzumab and anthracyclines, an evaluation was carried out among patients undergoing this combined therapy.

The following statistical methods were used to conduct the research: descriptive statistics for determining (depending on the type and distribution of variables) the mean value, median, standard deviation (SD), interquartile range (IQR) and proportions; Paired t-test for comparing correlating variables between two-time intervals; correlation analysis for correlation between variables and intraclass correlation analysis and Bland-Altman test for assessing the variability of echocardiographic examinations; linear and logistic generalised mixed effect regression univariate and multivariate analysis using generalized estimating equations(GEE) for monitoring and comparing related variables over time and for assessing the impact of factors on the variable; ROC analysis. The program "R" – version 4.3.2 (31/10/2023) was used.

The author analyses the demographic and clinical indicators of the studied population, baseline echocardiographic parameters, and other baseline indicators from clinical follow-up.

Results in response to the set tasks initially include monitoring of left ventricular function (left ventricular ejection fraction, LV systolic tissue velocities, left ventricular systolic dysfunction and MAPSE monitoring; LV diastolic function, LV myocardial performance index (LVMPI). Right ventricular parameters were monitored – right ventricular fractional area change (RVFAC), RV systolic tissue velocity (S' RV), and TAPSE. RV diastolic function, right ventricular myocardial performance index (RVMPI), and determination of right ventricular dysfunction were assessed. The correlations between echocardiographic indicators of left and right ventricular function with biochemical markers of myocardial injury were analysed, as well as the correlation between RV and LV indicators – temporal relationships between functional echocardiographic indicators for LV and RV, correlational dependencies between functional echocardiographic indicators for LV and RV, predictive interactions between echocardiographic indicators for LV and RV and clinical factors. Ultimately, an algorithm was developed for the early prediction of myocardial injury and risk stratification of patients.

Results: The results obtained by Dr. Svetoslava Slavcheva are meticulously presented and well-illustrated.

Although the group is heterogeneous in terms of cancer disease and applied therapy, the patients are consolidated into one cohort for echocardiographic and other analyses (ECG, arterial pressure, heart rate).

The results include left ventricular analysis, which is not specified in the study objectives but makes the echocardiographic examination more valuable. Particularly valuable are the data comparing changes in left and right ventricles.

Since the subject is relatively new to cardio-oncology, echocardiographic assessment of right ventricular function during chemo (and radiation) therapy is very relevant. The credibility of the evidence in the thesis would be strengthened through the study of larger cohorts, due to the prevalence of oncological diseases, and analysis of uniform cohorts (only one type of carcinoma, only one type of chemotherapy).

An algorithm is proposed for evaluating and monitoring cardiac function during and after oncological therapy, incorporating all cardio-oncology guidelines established in 2022. An integral part of the assessment is patient risk stratification, which combines anamnestic, laboratory, and echocardiographic data for cardiovascular risk factors, cardiovascular diseases, and baseline functional status of LV, RV, and heart valves. When it is impossible to conduct a quality assessment of deformation indicators, systolic and diastolic parameters from tissue Doppler of mitral and tricuspid annulus (S', e' and combined parameter E/e' for LV and RV) are proposed as mandatory elements of cardiac function assessment. The proposed algorithm for evaluating RV and LV function includes S'RV, e'RV, septal, lateral and mean S'LV, E/e' of LV and RV, along with LVEF and RVFAC at each follow-up stage. The algorithm is well illustrated in the presented figure. The author summarizes the most important findings in 15 points.

Discussion of results is presented in a separate chapter and compares the author's results with publications on the subject. Whenever applicable and when relevant studies are available, the author compares her research with results from published (small) patient cohorts. Due to the small and heterogeneous group, it is challenging to make valid comparisons and precise conclusions in various contexts. Particularly valuable in the discussion is the in-depth analysis of publications on right ventricular function and comparisons with the thesis results. The comparisons between results for changes in right and left ventricles are important as they show trends that need to be explored more deeply due to contradictory results in the literature as well.

It is acknowledged that the diagnostic algorithms in cardio-oncology differ according to applied therapies and their cardiotoxicity. In that context, the proposed unified algorithm could serve as a solid base for standalone algorithms in subsequent larger-scale studies.

Dr. Svetoslava Slavcheva is critical of the obtained results, which she details in the limitations of her study. The study was conducted in a small population; the population is represented mainly by female patients without significant cardiovascular comorbidities. The follow-up duration is 18 months, therefore there is no information about longer-term cardiac function disorders. Only 70% of the population was followed for 12 or more months. Therefore, the results for acute early functional disorders carry more weight. Direct comparison between indicators for longitudinal systolic function of LV and RV, systolic tissue velocities, and longitudinal strain was not performed. Therefore, the study does not establish the relative change of these parameters over time. The dynamics of the monitored parameters are a result of the oncological therapy but also reflect the impact of cardioprotective treatment conducted in nearly half of the population.

Conclusions: Dr. Svetoslava Slavcheva presents 7 conclusions. They are derived from the set tasks and conducted research.

1. Conventional echocardiographic indicators can detect early deviations within the first 1–3 months in LV systolic and diastolic function as a result of the oncologic therapy (OT).
2. Right ventricular conventional functional echocardiographic indicators show statistically significant deviations in the first 1–3 months from the start of OT.
3. Systolic tissue velocity S'RV is a more suitable parameter compared to RVFAC for monitoring right ventricular function, due to early deviation and low variability.
4. Oncologic therapy affects the systolic and diastolic function of RV, which can be asymptomatic and not accompanied by LV damage.
5. hsTnT testing can help diagnose myocardial injury induced by OT.
6. Early changes in right ventricular conventional parameters, and their functional and predictive value provide compelling reasons to keep track of them in patients undergoing OT.
7. Correlational and prognostic relationships between echocardiographic indicators from tissue Doppler for RV and LV justify their routine monitoring during OT.

Contributions: There are 9 contributions, divided into two groups – **original** (5) and confirmatory (4).

Original contributions:

1. For the first time in Bulgaria, changes in RV systolic function were monitored through conventional echocardiographic indicators for 18 months in a cohort on systemic OT.
2. Assessment of RV diastolic function was performed during and after OT for 18 months.
3. For the first time in Bulgaria, changes in LV function, both systolic and diastolic, were monitored through conventional echocardiographic indicators in a population on systemic OT for 18 months.
4. For the first time in Bulgaria, the predictive value of various echocardiographic indicators for the onset of cardiac dysfunction (left and right ventricular) was studied within 18 months after starting OT.
5. A follow-up of patients undergoing oncologic therapy was conducted for the first time at the Medical University – Varna and St. Marina University Hospital, laying the groundwork for both theoretical and practical future collaboration between oncologists and cardiologists.

Confirmatory contributions:

1. Deviations in echocardiographic systolic conventional indicators of RV were found, comparable with scientific data, due to the OT.
2. Deviations in echocardiographic diastolic conventional indicators of RV were found due to OT.
3. The frequency of RV dysfunction was established in a cohort undergoing OT.
4. Systolic and diastolic LV disorders influenced by ongoing oncologic therapy were established; they correspond with scientific data.

The thesis summary is presented in both Bulgarian and English languages, the Bulgarian version contains 88 pages, and the English version – 93 pages, and mirrors the content of the thesis. It meets all requirements.

Publications: Thesis-related publications presented by the author – 2 publications in journals and 5 presentations at scientific forums.

Conclusion: I find Dr. Svetoslava Elefterova Slavcheva's research on *Cardiotoxicity in Conventional and Contemporary Cancer Treatment Protocols* to be both scientifically valuable and significant for application in clinical practice. I believe that the thesis meets the requirements for awarding the educational and scientific degree Philosophy Doctor stated by the Development of Academic Staff in the Republic of Bulgaria Act (DASRBA) and the Rules and Regulations for Development of the Academic Staff at the Medical University-Varna. Considering the outlined value of the thesis research, I confidently recommend to the members of the esteemed Scientific Jury to vote positively and award Dr. Svetoslava Elefterova Slavcheva the educational and scientific degree of Philosophy Doctor.

23/02/2025
Sofia

Prepare

Заличено на основание чл. 5, §1, б. „В“ от Регламент (ЕС) 2016/679

Prof. Borislav Georgiev Georgiev, MD, PhD