Peer Review

By Prof. Tatiana Dimitrova Hadjieva, MD, PhD, DSc,

Radiotherapy Department, UH "St. Ivan Rilski," Sofia,
Accredited in professional direction 7.1
Appointed by Order No. R-109-466 from 06.12.2024, as an external member of the Scientific Jury, by Decision of the Scientific Jury in accordance with Protocol No. 1/18.12.2024 to prepare peer reviews in Bulgarian and English

To
Teodora Stoyanova Gugleva, MD,

Author of a dissertation thesis for the acquisition of the educational and scientific degree "PhD" in the area of higher education 7. Healthcare and Sports, Professional Direction 7.1 Medicine, Scientific Specialty "Medical radiology and Roentgenology speciality (including use of radioactive isotopes)

Title of the dissertation thesis:
"Investigating the role of deep inspiration breath-hold technique (DIBH) with automatic active breathing device in radiotherapy of left breast to reduce cardiac and pulmonary toxicity"

Ph.D tutor

Prof. Elitsa Petkova Encheva-Mitsova, MD, PhD

Varna, 2025

The dissertation thesis was discussed, approved, and forward for defence by the Departmental Council of the Department of "Nuclear Medicine, Metabolic Therapy and Radiotherapy", Faculty of Medicine, at the Medical University "Prof. Dr. Paraskev Stoyanov" – Varna.

1. General Overview of the Procedure and Documents:

The submitted documents comply with the regulations for obtaining a Doctor of Science degree, in accordance with the Law on the Development of the Academic Staff in the Republic of Bulgaria (dated 19.07.2022) and the Rules for the Development of Academic Staff at the Medical University- Varna (dated 08.07.2024).

2. Relevance of the Dissertation Topic, Aim and Tasks

Radiotherapy (RT) is a rapidly evolving specialty in Bulgaria and worldwide, driven by the modernization of the armamentarium. Use of intensity-modulated RT (IMRT) enables the delivery of high cancericit doses while minimizing exposure to surrounding healthy tissues. A notable advance in this direction is RT for left-sided breast cancer using the deep inspiration breath-hold (DIBH) technique, that reduces radiation doses to cardiac structures and lungs. In Bulgaria, equipment for active breathing control during irradiation is uniquely available at the Radiotherapy Clinic of University Hospital "St. Marina," Varna, installed under the guidance of the Ph.D. Advisor, Prof. Elitsa Encheva, MD, Ph.D., Head of the Radiotherapy Department.

The dissertation aims to standardize this methodology and provide guidelines for its implementation in other Bulgarian RT centers if such a new equipment will be available. The tasks include detailed studies of the anatomical target volumes and organs at risk (OARs) — heart and lung, along with a precise definition of tolerance doses for various volumes according to standards for postoperative breast cancer RT. This leads to presumsion of late cardiac and pulmonary toxicity preduction that is especially relevant for left-sided location cancer.

3. Dissertation structure:

The dissertation thesis is written on 132 pages, illustrated with 16 tables and 44 figures. The literature review includes 178 references, of which 3 in Bulgarian and 175 in English. The structure includes the following chapters: "Introduction" – 2 pages, "Literature Review" – 36 pages, "Aim and tasks" – 2 pages, "Materials and Methods" – 22 pages, "Results" – 30 pages, "Discussion" – 10 pages, "Conclusions" – 3 pages, "Contributions of the Dissertation" – 2 pages.

Three publications in Bulgarian journals of Dr Gugleva as the first author are presented.

The dissertation thesis is well-balanced between sections, in accordance with the Law on the Development of the Academic Staff in the Republic of Bulgaria.

4. Rationale:

The Ph.D. candidate demonstrates a deep understanding of issue, having worked in the Radiotherapy Clinic since 2016. The review thoroughly examines the risks to normal organs during postoperative RT for left-sided breast cancer, especially

with techniques involving larger volumes of intramammary lymph nodes. It justifies the need for an irradiation technique that further minimize doses to OARs. The review also describes the risks of late pulmonary and cardiac toxicity associated with various indications for postoperative RT, explores the mechanisms of their development, and discusses strategies for dose reduction to eliminate this toxicity.

In Bulgaria, the application of RT for left-sided breast cancer using the deep inspiration breath-hold technique with the ABC system (Active Breathing Coordinator, Elekta VersaHD) and VMAT irradiation technique has not been studied before. The only licensed ABC system in Bulgaria has been installed at the Radiotherapy Clinic of University Hospital "St. Marina," Varna, since 2015. Due to its complexity and need for staff training, the new practice was initiated in 2017. Before applying such dose-limiting techniques, RT was routinely performed under free breathing, strictly adhering to tolerance doses for OARs. These tolerance dose requirements are standardized and widely applied in RT globally, including in Bulgaria.

Developing individualized dose reduction strategies for each patient is in concordance with the ALARA (As Low As Reasonably Achievable) principle in RT and the medical principle "" *Primum non nocere* "".

Described rationale justifies the aim and tasks of the dissertation thesis to conduct a comparative study with the standard 'free breathing' technique to highlight the advantages of the ABC system and its routine application. The lack of randomized studies, with small number of cases reported so far, will help expand the global database. For Bulgaria, it will demonstrate the further extent of dose reduction in OARs and will serve as a reference center for it routine implementation.

5. Materials and Methods:

In the control group of 30 patients, individual dosimetric plans were compared under free breathing and during deep inspiration breath-hold using the ABC system. The detailed dosimetric plans for 70 patients were also analyzed. On 22 pages, the equipment details and the characteristics of 100 patients are described. Dissertation thesis also includes the contouring of left anterior descending coronary artery, a practice not routinely performed in all Bulgarian RT clinics, making it a training resource for young specialists.

6. Results and Conclusions:

The results are presented in details on 23 pages, corresponding to tasks 1-13, some of which can be combined. The results are presented in 11 figures and 8 tables. They have been statistically processed using linear regression and correlation analysis, and are thoroughly and precisely executed, providing reliable data for the conclusions.

The conclusions 1-18 are also written spaciously and are summarized by me as follows:

1. The irradiation technique with deep inspiration breath-hold (DIBH) with automatic active breathing based device in patients with left-sided breast cancer is fully tolerable and reproducible – all patients complete the full course of radiotherapy.
2. The irradiation technique with DIBH-ABC combined with daily CT verifications (IGRT) allows the reduction of the safety margin to 5mm from CTV to PTV with 95% coverage of the prescribed dose, 90% of the PTV volume – 98% of the dose, 105% up to 5%, and 107% of the dose – up to 2% of the PTV volume.
3. The average breath-hold time was 29.7 seconds (20-40 seconds); 67% of patients tolerating the breath-hold, making the method feasible, regardless of age. The inhailed air volume ranged from 1.1 to 3.4L; 79% of patients held 1.6-2L.
4. Numerous details have been obtained showing statistically significant reductions in cardiac dose parameters – mean dose, V25Gy, V5Gy, mean and maximum dose to LAD, as well as dose reductions in both lungs – all compared to free-breathing irradiation. The total lung volume most strongly affects left cardiac ventricle volume , while the central lung distance affects volume of LAD and V25 of the heart.
5. A statistically significant trend has been established showing higher doses in the OAR in the mastectomy group compared to the quadrantectomy group, and in cohort with regional lymph nodes irradiation, especially in RT of intramammary lymph nodes.
6. A detailed statistical increase in the dose in OARs has been established in left-sided irradiation with simultaneous integrated boost, compared to sequential boost in left-sided irradiation, across all heart and lung parameters studied.
7. No statistically significant correlation was found between smoking and the volume of inhailed air in breath-hold in liters, or the breath-hold time, which supports the methodology even for smokers.

7. Publications Related to the Dissertation Thesis:

The candidate has three scientific publications in Bulgarian as the first author, related to the dissertation.

The dissertation summary aligns with the dissertation's structure and conclusions.

Summary of Contributions:

1. **Scientific-Theoretical Contribution:**

For the first time in Bulgaria, the advantage of the irradiation technique DIBH with automatic active breathing device is being studied, compared to free-breathing

irradiation based on a very detailed assessment of the reduced doses in the heart, left ventricle, and LAD in 100 patients. That is provided for various indications and irradiation volumes, after mastectomy and quadrantectomy, including irradiation of the regional and ipsilateral intramammary lymph nodes. Provided detailed information will serve for global dosimetric database inclusion about this technique.

8. Scientific and Applied Contributions:

1. For the first time in Bulgarian radiotherapy practice, a routine DIBH-ABC technique combined with IMRT has been introduced for women with left-sided breast cancer, controlled with daily CT verifications (IGRT).
2. A detailed contouring of the heart, left ventricle, LAD, and other organs at risk (OARs) is presented using the described technique, compared with the volumes under free breathing, which has didactic value for specialists in training.
3. Correlation coefficients based on detailed dosimetric data are presented about cardiac structures dose reduction with the volume of hold air and chest wall, movement , which underlines the technique.advantage.
4. Despite the required extended time for patient training, the applied technique is believed to contribute to long-term improvement of women with left-sided breast cancer quality of life, given the predominant patients younger age and expected long-term survival.
5. The further doses reduction compared to standard tolerant doses for cardiac structures and lung is a presumption to expect a decrease in late cardiac and pulmonary toxicity, which will be explored in the long-term aspect.
6. A concluding protocol has been proposed on the technique implementation in left-sided breast cancer patients.

A main remark to thesis description could be made. The conclusions and contributions described are somewhat verbose, thus reduces the perception and understanding of the large amount of quantitative data. Undoubtedly, once the results are published in global literature sources, they will contribute to the dosimetric database, accumulated over years for each new method and will provide additional benefit regarding side effects limitation after left-sided breast cancer radiotherapy.

The dissertation will continued with detailed research on the late radiation toxicity to the heart and lungs, which will require numerous specialized clinical investigations during the follow-up of these patients. This will further accomplish the detailed dosimetric data obtained.

9. **Personal Contribution of the Ph.D. Candidate:**

Teodora Gugleva, MD has contoured the volumes for treatment, treatment planning and treated the patient in both groups, processed and structured the results

and conclusions, leading to the formulation of the scientific-theoretical and scientific-practical contributions, which I consider to be her personal achievement.

10. Biographical Data

Teodora Stoyanova Gugleva, MD, graduated from the Medical University of Varna in 2014. Since 2016, she has been working as a resident at the Radiotherapy Clinic of University Hospital "St. Marina," Varna. In 2018, she became a full-time Ph.D. student and then in 2020 - assistant professor at the Department of „Nuclear Medicine, Metabolic Therapy, and Radiotherapy" at the Medical University "Prof. Dr. Paraskev Stoyanov". In 2021, she passed the state board axamination and became a specialist in "Radiotherapy".

Conclusion:

The documents presented by Teodora Gugleva, MD meet the requirements set forth in the Law on the Development of Academic Staff in the Republic of Bulgaria (2022) and the Rules for the Development of Academic Staff at the Medical University of Varna (2024). The quality of the dissertation thesis reflects a multi-layered study as well as routine introduction of a new technique for sparing normal tissue in left-sided breast cancer radiotherapy, which is innovative for Bulgaria. The generated numerous dosimetric data for dose reduction in OARs were excellently processed with various statistical methods. All this leads to contributions with both scientific-theoretical and scientific-practical value, published in 3 articles. This gives me arguments for my positive review, and I recommend to the esteemed scientific jury to award Teodora Gugleva, MD with the educational and scientific degree "Ph.D." in the scientific specialty "Medical Radiology and Roentgenology, including the use of radioactive isotopes in Oncology" (code 03.01.46)

29.01.2025 Prof. Tatiana Dimitrova Hadjieva, MD, PhD, Dsc