

TO

**THE CHAIRMAN OF THE A SCIENTIFIC JURY,
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OF PROF. DIMITAR RAYKOV, MD, PhD, D.Sc.,
RECTOR
MEDICAL UNIVERSITY**

“PROF. DR. P. STOYANOV”– VARNA

P E E R R E V I E W

By Prof. Veselina Metodieva Parvanova, MD, PhD

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. Candidate: Teodora Stoyanova Gugleva, MD,
for the acquisition of the educational and scientific degree "PhD"**

The area of higher education: Healthcare and Sports,

Professional Direction: Medicine (Code 7.1)

Scientific Specialty: Medical radiology and roentgenology speciality (including use of radioactive isotopes)

Ph.D tutor

Prof. Elitsa Petkova Encheva-Mitsova, MD, PhD

The dissertation of Gugleva, MD is dedicated to a relevant problem in the science and practice of radiotherapy: the application of a deep inspiration breath-hold technique (DIBH) with automatic active breathing device in radiotherapy of left breast to reduce cardiac and pulmonary toxicity. The final purpose of breast cancer radiotherapy is not only achieving high therapeutic outcomes but also reporting low acute and long-term late toxicity. The introduction of this technique for the first time in Bulgaria, raises numerous questions, which are explored and answered in Ph.D. Candidate's dissertation.

The dissertation thesis is written on 132 pages, illustrated with 16 tables and 44 figures. It follows the standard structure: Introduction – 2 pages; Literature Review – 36 pages; Aim and Tasks – 1 page; Material and Methods – 23 pages; Results – 30 pages; Discussion – 11 pages; Conclusions – 3 pages; Contributions of the Dissertation – 2 pages. Additionally, the dissertation includes a Title page, List of Abbreviations and Table of Contents (6 pages in total) and a bibliography - 18 pages - consisting of 178 references (3 in Bulgarian and 175 in English).

The dissertation comply with the regulations in accordance with the Law on the Development of the Academic Staff in the Republic of Bulgaria.

The literature review is written on 36 pages and is based on 178 sources. The state of the issue - the application of a breath-holding technique with automatic active breathing device for left breast cancer radiotherapy and the study of cardiac and pulmonary toxicity - is systematically and critically presented. This demonstrates the Ph.D. candidate's analytical capabilities. The section is well-structured, analyzing the epidemiological, staging, and anatomical specifics of breast cancer. Therapeutic strategies are presented in details by stages, focus on radiotherapy following breast-conserving surgery, mastectomy - with or without breast reconstruction, depending on the extent of axillary dissection, and the administration of neoadjuvant systemic treatment. The pathophysiological mechanisms of cardiotoxicity during breast cancer radiotherapy, their clinical significance, and the importance of individual risk factors, are discussed. Methods for limiting cardiac and pulmonary toxicity, both radiobiological and radiotherapeutic, are examined. These include decreasing of heart dose by reducing irradiated volumes and various fractionation schemes. Physical-technical methods in three-dimensional planning are reviewed - intensity-modulated radiotherapy (IMRT), volumetric-modulated arc therapy (VMAT), helical tomotherapy, and proton therapy. Specifically, methods for heart separation from the chest wall and lung toxicities during left breast irradiation, such as the "prone breast" technique and deep inspiration breath hold (DIBH) - whether voluntary (vDIBH) or through active automatic device controlled breath-hold (mDIBH) - are critically analyzed. The detailed literature review leads Gugleva, MD to formulate the aim of dissertation, evident in its title: to investigating the irradiation technique with deep inspiration breath hold and automatic active breathing device (mDIBH), and to reduce cardiac and pulmonary toxicity when applying intensity modulated radiotherapy (IMRT/VMAT) compared to free-breathing (IMRT) in patients with left-

sided breast cancer, with and without indications for irradiation of intramammary lymph nodes (IMLN), around the lateral edge of the sternal bone.

To achieve the aim, 13 tasks have been formulated: 1. Selection of patients with left-sided breast cancer for the control group – 30 in number, as a representative sample of the total group, for which patients two dosimetric plans are calculated: with IMRT technique during free breathing and with IMRT / VMAT during mDIBH. 2. Obtainning two localization computed tomography (CT) scans with free breathing and with mDIBH in 30 patients, contouring of organs at risk and target volumes. 3. Development of individual dosimetric plans with IMRT/VMAT treatment techniques for free breathing and mDIBH for the control group of 30 patients, who are irradiated with mDIBH; 4. Assessment of doses in organs at risk (OR); 5. Comparative analysis of doses in OR of the two dosimetric plans in the control group; 6. Assessment of statistical significance (advantage) of mDIBH technique versus free breathing technique. 7. Introduction of anatomical indicators on localization CT scans that determine the change in anatomy during breath hold compared to free breathing; 8. Measurement and analysis of the studied indicators under task 7. and the studied toxicity; 9. Selection of 70 patients for implementation of mDIBH; 10. Tolerability study of implementation of mDIBH; 11. Assessment of cardiac and pulmonary toxicity during the follow-up period; 12. Analysis of additional factors smoking, hypertension, diabetes mellitus; 13. Recommendations for application of mDIBH for left-sided breast cancer are reported.

The clinical data: The scientific study includes a total of 100 participants with left-sided breast cancer, divided into two groups: a control group and a target group. All of the participants had indications for adjuvant radiotherapy (without contraindications) with DIBH with automatic active breathing device in the Radiotherapy Clinic of University Hospital "St. Marina," Varna, from April 2017 to July 2022. Information about previous and accompanying diseases, risk factors, and hereditary oncological burden was also provided, after informed consent to participate in the study.

The control group includes 30 patients with left-sided breast cancer and two individual dosimetric plans: one plan on CT images in DIBH with automatic active breathing device, used for patient treatment, and the second one plan on CT images in free breathing. The dose coverage of target volume in both plans is the same and differences in the doses in OR were analyzed between free-breathing treatment and DIBH with automatic active breathing device.

The target group includes 100 patients as 30 of whom are used for the control group. All patients have no contraindications and all of them are treated with DIBH with automatic active breathing device.

For clear presentation, when publishing the results of the dissertation, it is recommended to present all 100 patients in the study, i.e., the target group, in table with criteria of patients, cancer and treatment methods, the presentation of these criterias: median age, other patients diseases, tumor characteristics by T, N, tumor locations, histological type (in situ, invasive ductal, invasive lobular, and others), immunophenotype, treatment provided (surgical – 50% breast-conserving surgery and 50% mastectomy), systemic treatment, radiotherapy with prescribed dose, boost, irradiation of regional lymph nodes.

The present study of the control group, which constitutes a sample of the target group, with median age of the patients $56.9 \text{ years} \pm 10.14$ (25-78 years) versus $54 \text{ years} \pm 10.6$ (25-78 years), with metastatic involvement of regional lymph nodes 56% vs. 61%, provides grounds for the significance of the sample when performing statistical analysis.

I associate the mentioned weaknesses in the presentation of the clinical data with the complexity topic, which fits a radiation oncologist with longer experience, but this also sets high expectations for Gugleva, MD in the future and her development as a radiation oncologist and researcher in oncology direction at all.

A part of the dissertation that is excellently presented and reflects the youth of the Ph.D. candidate presents the radiotherapy method: description of the automatic active breathing device (ABC system), training the patients with the breath hold system, performing localization CT, contouring organs at risk, target volumes, dose prescription, dosimetric planning, constraints for doses in OR, used in the clinic for evaluating dosimetric plans; measuring criteria on localization CT scans that determine anatomical changes with breath-hold compared to free breathing, irradiation with a linear accelerator using DIBH with automatic active breathing device, etc.

The average follow-up time for the patients is 33.73 ± 18.15 (4-68) months, with the largest number of patients (26%) for the period of 31-45 months, indicate to the higher objectivity of the results, as well as the use of modern software products for statistical data processing, such as Jamovi Version 2.3 and SPSS v23; A Language and environment for statistical computing Version 4.1., Graphical presented with Microsoft Excel for Windows 10.

The results are presented on 30 pages, and their description corresponds to the set tasks, but the characteristic attempt by the author to present all the results from the statistical analysis, rather than only the significant ones that lead to the corresponding conclusion, is apparent.

In the **Discussion** chapter, presented on 11 pages, could be recognized the Ph.D. candidate's ability to synthesize and select own results and critically compare them with those of other authors. This shows the Ph.D. candidate's growth during the preparation of the dissertation and the formulation of the corresponding conclusions.

Conclusions 1 to 6 suggest that using the technique DIBH with automatic active breathing device leads to 100% tolerance or completion of the treatment course without interruption and 100% reproducibility in delivering the prescribed dose by eliminating chest movements with the same amount inhaled air volume, the possibility of reducing the safety margin from CTV to PTV. Conclusions 4, 5, and 6 indicate no influence of age on the application of the technique, reporting an average breath-hold time of 29.7 seconds, with 67% of patients allowing breath-hold close to 30-34 seconds, and the inhaled air volume was 1.6-2 liters in 79%.

Conclusion 7, which is significant for clinical practice, points to the advantage of using the technique with VMAT in left breast cancer, achieving optimal dose coverage of PTV. Conclusions 8 to 10 indicate a statistically significant reduction in the dose to the heart, left ventricle, and LAD, and to the lung dose, when comparing DIBH and automatic active breathing device with free breathing treatment in the control group. During the average follow-up period of 33.7 months, no cardiac or pulmonary toxicity was observed, highlighting the advantage of the applied technique. The formulation of the conclusions could be improved, and the listed points in conclusions 8, 9, and 11 could be avoided. Conclusion 10 and 19 are awaiting future confirmation when applying both techniques in separate groups of patients with left-sided breast carcinoma.

Based on these conclusions, **11 contributions** have been formulated, which are of an original, scientific-applied nature: Introduction of the technique - DIBH with automatic active breathing device - for the first time in radiotherapy practice in our country, with analysis and reporting the reduction of doses in the ipsilateral lung and heart in left breast cancer; The advantages of VMAT technique are reported and a higher likelihood of reducing cardiac and pulmonary toxicity in left breast cancer radiotherapy while dose coverage of target volumes is the same, as well as the implementation of IGRT verification of target volume and organ-at-risk position with the use of DIBH with automatic active breathing device; Precise contouring of the heart, left

ventricle, and LAD has been performed for evaluating the doses received by them, with a detailed assessment of doses in the heart, left ventricle, and LAD for 100 patients with left breast cancer; The advantage of the radiation technique with automatic active breathing device in deep inspiration and left-sided breast cancer for reducing doses in the heart, its structures, and the lungs, and consequently reducing cardiac and pulmonary toxicity during the study period, compared to free-breathing radiation, with simultaneous use of VMAT and IGRT, is demonstrated; This contribution is also observed in irradiation of the IMLN; A significant scientific-applied contribution to radiotherapy practice is contribution 11: a protocol for adjuvant radiotherapy using DIBH for left-sided breast cancer is reported.

The accumulated experience of the young researcher, Gugleva, MD, with the active participation of her Ph.D. tutor, gives them reason to share it with the scientific community. In connection with the dissertation, 3 publications and 1 scientific communication have been made in the country.

The issue addressed in Dr. Gugleva's dissertation is highly relevant, with practical contributions and is unique and labor-intensive in its execution, not only for the young Ph.D. candidate but also for the entire clinic team and the Ph.D. tutor. The presented 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", is suitable for a dissertation defense, with significant results reflected in conclusions and contributions of both theoretical and applied nature.

Dr. Gugleva meets evaluation criteria for the defense of the educational and scientific degree " Ph. D ". The dissertation meets the criteria of the Academic Staff Development Act and presents the young candidate as a successful future researcher in the direction of breast cancer and radiation therapy in general.

I confidently recommend that the esteemed scientific jury vote positively for the award of the educational and scientific degree " Ph. D " in the scientific specialty of Medical Radiology and Radiography (including the use of radioactive isotopes) for Teodora Stoyanova Gugleva, MD.

January 27, 2025

Peer Reviewer:

Prof. Veselina Metodieva Ivanova, MD, PhD

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