

**To: The Chairman of the Scientific Jury,  
Appointed by Order No. P-109-466/06.12.24  
By Prof. Albena Georgieva Kerekovska, MD, PhD  
Vice-Rector for Academic Affairs at  
Medical University  
"Prof. Dr. Paraskev Stoyanov," Varna**

## **S T A T E M E N T**

**From: Prof. Elitsa Petkova Encheva-Mitsova, MD, PhD**  
Department of Nuclear medicine, Methabolic therapy and Radiotherapy  
Head of the Educational Sector "Radiotherapy"  
Medical University "Prof. Dr. Paraskev Stoyanov" – Varna  
Head of the Radiotherapy Clinic, University Hospital "St. Marina" – Varna

**In reference to:** Defense of the PhD thesis of **Teodora Stoyanova Gugleva, MD** with title of the 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 "*, with PhD tutor Prof. Elitsa Petkova Encheva-Mitsova, MD, PhD at the Department of Nuclear Medicine, Methabolic therapy and Radiotherapy for obtaining the educational and scientific degree "PhD" in the area of higher education 7. Healthcare and Sports, in the professional direction 7.1. "Medicine", and the PhD program "Medical Radiology and Roentgenology speciality (including the use of radioactive isotopes)

### **Information about the Procedure**

By Order No. P-109-466/06.12.24, of Prof. Albena Kerekovska, MD, PhD – Vice-Rector for Academic Affairs at Medical University "Prof. Dr. Paraskev Stoyanov" – Varna, I was appointed as a member of the scientific jury and participate with a statement.

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

### **Biographical Data of the PhD student**

Dr. Teodora Stoyanova Gugleva was born on January 3, 1988, in Varna. She 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 PhD. 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 examination and became a specialist in "Radiotherapy".

### **Structure of the PhD thesis**

The PhD thesis of Dr. Teodora Gugleva, is written on 132 pages, structured according to standard requirements, including the following chapters: Introduction– 2 pages; Literature Review of the topic– 36 pages; Aim and tasks– 2 pages; Materials and Methods – 22 pages; Results– 30 pages; Discussion – 10 pages; Conclusions – 3 pages; Contributions of PhD thesis – 2 pages. The PhD thesis contains 16 tables and is illustrated with 44 figures. The references list includes 178 papers, of which 3 in Bulgarian and 175 in English.

### **Evaluation of the Relevance of the Topic**

The topic of the PhD thesis is highly relevant, considering that breast cancer (BC) is the most common oncological disease among women worldwide, including in Bulgaria. It aligns with global trends in preserving the quality of life of oncology patients. With the advancement of diagnostic and therapeutic oncology methods, the number of cancer survivors is increasing. Radiotherapy (RT) is an integral part of comprehensive cancer treatment, typically applied adjuvantly. It contributes to improving overall survival and reducing the risk of recurrence in breast cancer. However, its benefits are limited by the risk of developing late cardiac and pulmonary toxicity, which is more commonly observed in left-sided breast cancer.

The improved survival rates and the challenges associated with late toxicity in breast cancer patients necessitate the development of irradiation techniques that minimize doses to organs at risk while ensuring delivery of the required total tumor dose. One of them is irradiation in Deep Inspiration Breath Hold (DIBH), using the Active Breathing Coordinator (ABC, Elekta Versa HD) system. This technique is based on the principle that during deep inspiration, the heart moves away from the target volume, respectively reducing radiation exposure to the heart and cardiac structures.

The ABC DIBH radiotherapy technique has demonstrated a 40–71% reduction in radiation dose to the heart and left anterior descending (LAD) artery. Additionally, it is highly reproducible and yields optimal results, as it eliminates chest movement, ensures a constant volume of inhaled air in the lungs, and thereby enhances precision.

The European Society of Cardiology recommends that radiotherapy techniques should be aimed at reducing radiation dose to the heart, specifically advocating for DIBH techniques.

This PhD thesis is the first study in Bulgaria to investigate the application ABC DIBH irradiation technique in patients with left-sided breast cancer, in combination with VMAT (Volumetric Modulated Arc Therapy), IGRT (Image-Guided Radiotherapy) to limit radiation dose to the heart and lungs and respectively reduce late radiation-induced toxicity.



## **Evaluation of the Literature Review of the topic**

The literature review is in-depth, comprehensive, and its structure aligns with the stated aim and tasks. It thoroughly examines the indications for radiotherapy application in breast cancer patients, target volume contouring, and dose prescription. Detailed data on cardiac and pulmonary toxicity associated with irradiation of left-sided breast cancer and current methods for its limitation and prevention are presented. This demonstrates Dr. Gugleva's extensive knowledge in the field and her ability to interpret the available literature. The scientific background of the PhD thesis topic is well established.

## **Aim and Tasks**

Thirteen main tasks are clearly and precisely formulated, logically following and corresponding to the defined aim.

## **Materials and Methods**

The materials and methods are appropriately selected to achieve the PhD thesis aim and objectives. The study includes 100 patients with left-sided breast cancer, with indication for adjuvant radiotherapy, treated at the Radiotherapy Clinic of University Hospital "St. Marina," Varna, between April 2017 and July 2022. Two groups were defined for the study: a control group and a target group. The control group consists of 30 women with left-sided breast cancer, for each of whom two individualized dosimetric plans with identical irradiation techniques (IMRT/VMAT) were compared—one performed under free breathing and the other under deep inspiration breath-hold (DIBH) using the ABC system. Using the same normalization and achieving similar target volume coverage, doses of organs at risk were assessed and compared between the free-breathing technique and the ABC DIBH technique.

The control group is part of the target group, which consists of a total of 100 women. Detailed clinical data for each patient are provided, along with dosimetric plan data on radiation doses received by cardiac structures and the lungs, and an assessment of cardiac and pulmonary toxicity during the follow-up period.

A detailed description of the ABC DIBH irradiation technique is presented, along with recommended standardized contouring protocols for organs at risk and target volumes. The indications for irradiation of intramammary lymph nodes are emphasized, and their contouring within the target volume is described.

Appropriate modern statistical methods were applied for data analysis.

## **Results and Discussion**

The results obtained after the statistical analysis of the data are adequately and systematically presented over 30 pages, illustrated with extended tables and graphs. The patients in the control group were well-selected, and individual dosimetric treatment plans at similar target coverage were created and compared for each of them using VMAT, IGRT techniques under free breathing and deep inspiration breath-hold (DIBH) with the ABC system. In the absence of statistically significant differences in PTV coverage (95%), the DIBH

technique with the ABC system achieved a statistically significant reduction in the dose to the heart, left ventricle (LV), left anterior descending artery (LAD), and the lungs, compared to free breathing irradiation. The average heart dose was statistically significantly reduced from 12.12 Gy to 8.65 Gy, V25 heart reduced from 7.37% to 1.66%, V5 Gy LV (the volume of LV receiving 5 Gy) was 15.67% lower, V20 Gy LV (the volume of LV receiving 20 Gy) decreased by 7.05%, the average LAD dose reduced statistically significantly from 20.27 Gy to 13.87 Gy, the maximum LAD dose (Dmax-LAD) decreased statistically significantly from 40.86 Gy to 30.82 Gy, the V20 Gy LAD (the volume of LAD receiving 20 Gy) decreased from 42.6% to 18.1%, the V5 Gy in both lungs statistically decreased from 50.47% to 44.59% ( $t=2.106$ ,  $p=0.040$ ), the mean dose to the contralateral lung decreased statistically significantly from 4.55 Gy to 3.93 Gy ( $t=2.216$ ,  $p=0.031$ ), the mean dose to the ipsilateral lung decreased statistically significantly from 16.76 Gy to 14.85 Gy ( $t=2.558$ ,  $p=0.049$ ), the V20 Gy of the ipsilateral lung decreased statistically significantly from 30.99% to 27.28%. The reported statistically significant differences favoring ABC DIBH irradiation result in a reduction in late toxicity—leading to reduced cardiac mortality and morbidity and simultaneously a decrease in the frequency of local recurrences. During a mean follow-up period of  $33.73 \pm 18.15$  months (range 4-68 months), no late cardiac or pulmonary toxicity was observed in any of the study participants. The applied statistical analyses support these findings.

It is observed that both the dose to the heart and the lungs are directly dependent on the maximum cardiac distance, and with increasing the total lung volume and central lung distance the dose to the heart is reduced. A statistically significant trend ( $\chi^2=4.46$ ,  $p=0.035$ ) was found between irradiating the regional lymph nodes and dose delivery to organs at risk. A moderate positive correlation was observed between the dose to organs at risk and irradiation of the intramammary lymph nodes (IMLN).

The discussion is thorough and consistent, comparing the extensive results of Dr. Gugleva's PhD thesis work with the current scientific knowledge on the subject. The achieved results are in concordance with those reported in the literature and contribute to the global research knowledge in that field. The discussion clearly demonstrates that the author has a detailed understanding of the studied subject, with profound clinical approach and excellent professional background. Future work in this research field is planned.

## Conclusions

The 18 main conclusions are clearly and precisely formulated, optimally reflecting the results achieved in the tasks and objectifying the aim of the PhD thesis. The conclusions indicate that irradiation in left-sided breast cancer patients with active breathing coordinator (ABC) DIBH technique is well-tolerated, reproducible, not dependent on patient age, and allows precise dose delivery by eliminating chest wall motion and ensuring reproducible lung air inspiration volume.

A key conclusion is that combining irradiation with active breathing coordinator (ABC) DIBH technique with daily CT verifications (IGRT) in left-sided breast cancer patients allows



for reducing the margin from CTV to PTV to 5mm for all patients without misses in the target volume using the VMAT technique. Additionally, VMAT irradiation achieves optimal coverage, with 95% of the PTV volume receiving at least 95% of the prescribed dose. The essence of the conclusions is that with comparable 95% PTV coverage ( $t=-0.722$ ,  $p=0.473$ ), irradiation in left-sided breast cancer patients with active breathing coordinator (ABC) DIBH technique achieves statistically significant reductions in dose to the heart, left ventricle, LAD, and lungs compared to free-breathing irradiation, as demonstrated in the results. The next conclusion logically follows: during the mean follow-up period of  $33.73 \pm 18.15$  months, no late cardiac or pulmonary toxicity was observed among the patients. An expected conclusion is the positive moderate correlation between the dose to organs at risk and the irradiation of IMLN, but this was not associated with higher cardiac or pulmonary toxicity. This study demonstrates that irradiating intramammary lymph nodes is both feasible and safe when using modern radiotherapy equipment for treatment of left-sided breast cancer. An interesting conclusion is that smoking has no statistically significant influence on inhaled air volume (Spearman's  $\rho = 0.093$ ,  $p = 0.358$ ) or breath-hold duration (Spearman's  $\rho = -0.093$ ,  $p = 0.355$ ) in the patients.

### Contributions

The contributions presented in the PhD thesis reflect the objective achievements of Dr. Theodora Gugleva. The contributions in the PhD have an original, scientific-theoretical, and applied scientific character. The formulated contributions are based on the author's own data from the scientific study. The most important of them are:

1. For the first time in Bulgaria, adjuvant radiotherapy with active breathing coordinator (ABC) DIBH technique was applied in women with left-sided breast cancer using VMAT and IGRT.
2. For the first time in Bulgaria, detailed contouring of the heart, left ventricle (LV), and LAD is presented for evaluation of the radiation doses received by these structures in patients with left-sided breast cancer during irradiation with ABC DIBH technique and under free breathing.
3. For the first time in Bulgaria, a detailed evaluation of the doses to the heart, left ventricle, and LAD is reported for 100 patients who underwent adjuvant radiotherapy for left-sided breast cancer.
4. For the first time in Bulgaria, the advantage of active breathing coordinator (ABC) DIBH technique irradiation was proven to reduce the doses to the heart, its structures, and the lungs, respectively reducing cardiac and pulmonary toxicity compared to free-breathing irradiation, with simultaneous use of VMAT and IGRT. This contribution is also observed when intramammary lymph nodes (IMLN) irradiation is indicated.
5. Despite the extended time for patient training and irradiation, for the first time in Bulgaria it was demonstrated that active breathing coordinator (ABC) DIBH technique irradiation improves the long-term quality of life of women with left-sided breast cancer, given the predominance of younger patients and the expected long-term survival.

6. For the first time in Bulgaria, a protocol developed for adjuvant radiotherapy in left-sided breast cancer with active breathing coordinator (ABC) DIBH irradiation technique is reported.

### **Publication Activity**

In relation with the PhD thesis, the PhD student has presented 3 full-text publications as the first author. She has also participated in a national scientific forum with a oral presentation.

### **Abstract of the PhD thesis**

The abstract of the PhD thesis accurately reproduces the content of the PhD thesis and is composed according to the requirements. It is presented over 65 pages and includes 36 figures and 15 tables.

### **Personal Impressions**

I have known Dr. Gugleva for 8 years. She possesses the necessary theoretical knowledge and professional skills as a radiation oncologist and demonstrates the qualities and abilities required for conducting independent scientific research, representing her as a promising young medical doctor and scientist.

### **Conclusion**

The PhD thesis of Dr. Theodora Stoyanova Gugleva is of high scientific and practical value on a significant topic in radiotherapy practice. It demonstrates that irradiation of patients with left-sided breast cancer patients with active breathing coordinator (ABC) DIBH technique in combination with VMAT and IGRT, leads to reduced doses to the heart and lungs, compared to free-breathing irradiation, and consequently limits the late toxicity induced by the irradiation. The PhD thesis is relevant, systematic, and comprehensive.

I consider that the presented PhD thesis, abstract of the PhD thesis and published scientific papers meet the scientometric criteria of the Law for the Development of Academic Staff in the Republic of Bulgaria and the Regulations for the Development of Academic Staff of Medical University Varna for awarding the educational and scientific degree "PhD".

As a PhD tutor and member of the Scientific Jury, I give my positive assessment and recommend to the honored members of the Scientific Jury to award Dr. Theodora Stoyanova Gugleva the educational and scientific degree "PhD".

**Varna, 24.01.2025**

**Written by**

Prof. Elitsa Encheva-Mitsova, MD, PhD

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