

Comparison of VMAT, IMRT, and 3DCRT radiotherapy techniques in the treatment of synchronous bilateral breast cancer patients

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Abstract

Purpose: Synchronous bilateral irradiation of both the mammary glands and the chest wall is a challenging task due to technical difficulties and limited evidence supporting an optimal technique for positive treatment outcomes. We analyzed and compared the dosimetry data of three radiotherapy techniques and selected the most effective one.

Methods: Three-dimensional conformal radiation treatment (3DCRT), intensity-modulated radiation therapy (IMRT), and volumetric-modulated arc therapy (VMAT) were compared during the irradiation of synchronous bilateral breast cancer. This was followed by examination of the dose distribution to the target organs (myocardium, left anterior descending artery (LADA), right coronary artery (RCA), and lungs in nine patients.

Results: Dose distribution in the lungs was optimal using VMAT, while IMRT was less effective. Doses in the lungs, myocardium, and LADA were highest with 3DCRT. The highest mean dose in the myocardium was observed with IMRT, and a similar effect was noted with RCA. VMAT is the most sparing technique for the myocardium and LADA, despite the RCA dose being slightly higher when compared with that of 3DCRT.

Conclusion: We concluded that VMAT is a very effective and satisfactory radiation technique for sparing critical organs. With VMAT, regardless of the volume and side of irradiation, a lower mean dose (D_{mean}) value was noted in organs at risk such as the myocardium, LADA, and lungs, but not the cardiac conduction system. The use of 3DCRT significantly increases the dose of ionizing radiation reaching the lungs, myocardium, and LADA, which can subsequently cause cardiovascular and lung complications.

Introduction

Synchronous bilateral breast cancer (SBBC) is commonly referred to as two or more malignant neoplasms in both the mammary glands detected up to 6 months apart [1]. SBBC of the mammary glands accounts for 1-3.5% of all cases of breast cancer [2]. SBBC staging is done for each side separately as the treatment consists of the same steps as in unilateral breast cancer treatment. Depending on the stage of the disease (on each side), treatment approaches may include breast-conserving surgery/mastectomy (with lymphadenectomy), neoadjuvant/adjuvant chemotherapy or hormone therapy, and radiation therapy. The administration of radiotherapy after breast-conserving surgery reduces the risk of local recurrence by 4–5% [3, 4].

In cases of bilateral breast cancer, dosimetric planning of radiation therapy is a particularly complex and time-consuming process. The use of tangential fields is often associated with inhomogeneous dose distribution in the planned treatment volume (PTV) and with the formation of hotspots [5–8]. The latter leads to complications such as radioepidermitis, telangiectasia, shrinkage of the mammary gland, and a subsequent decrease in the quality of life. However, the most serious danger is radiation damage to the myocardium and coronary vessels, as well as the occurrence of secondary malignant tumors, most often

in the esophagus, with unilateral radiation in the contralateral mammary gland [9, 10]. Also, in some patients, especially high dose loads on the heart and lungs were noted [5–6, 8, 11].

According to a 2000 review by the Early Breast Cancer Trialists Collaborative Group (EBCTCG), mortality among radiation-exposed patients with secondary neoplasms is higher than that from primary breast cancer. The 15-year accumulation rate of secondary malignant tumors is 16–19% in patients undergoing radiation therapy [10]. In 2013, Darby et al. investigated the consequences of radiation treatment of breast cancer in 2,168 women in Sweden and Denmark who were treated between 1958 and 2001. Of these, 963 were found to have cardiovascular issues, including myocardial infarction, ischemia with the need for myocardial revascularization, or death from myocardial ischemia [12].

The average dose to the whole heart was 6.6 Gy for left-sided cancer and 2.9 Gy for right-sided breast cancer. It was discovered that exceeding the average dose in these patients linearly increased the frequency of the above cardiac complications by 7.4% without a visible threshold. One Gray(Gy) of the standard prescribed 50 Gy is 2% of the total dose. This further demonstrates the need to consider small radiation doses, the effect of low dose bath (LDB), and the necessity for safer radiation methods. If the distance between the heart and the chest wall is minimal, or if the parasternal lymph nodes are irradiated, then the average dose to the heart can increase up to 10 Gy. The average dose to the whole heart was 4.9 Gy, with the absolute range of dose spread 0.03–27.72 Gy. This is evidence of the relevance of a comparative dosimetric analysis of modern irradiation methods.

The increase in the incidence of cardiac events begins within the first 5 years after treatment, while the factors that increase the risk of ischemic heart disease have no influence on the complication/Gy ratio. However, the absolute number of complications in those with an initial predisposition was higher. Fifty-four percent of patients with post-radiation coronary complications died from these causes. Interestingly, it was not the dose to the left descending coronary artery that correlated best with the frequency of events but the dose to the whole heart. Based on these findings, it appears radiation injuries of the main coronary arteries and myocardial structures - cardiomyocytes and the microvasculature - are jointly involved in the pathogenesis of the most severe outcomes.

Wu et al. (2017) demonstrated that in modern conditions of combined treatment, ischemic attacks in the heart, discussed at length in the literature, gave way to arrhythmias and disturbances of intracardiac impulse conduction in a substantial number of cases. Modern post-radiation arrhythmias were discovered to be as life-threatening as post-radiation myocardial infarction was in the past [13]. The significance of radiation damage to the cardiac conduction system has rarely been discussed to date. Consequently, in our study, we will address this knowledge gap by studying radiation exposure to different cardiac regions: coronaries, different parts of the myocardium, and the conducting system.

Patients And Methods

This was an open-label, prospective and comparative study focused on the treatment of synchronous bilateral breast cancer, the radiation dose distribution over the PTV, and the dose distribution to organs at

risk (OARs). Nine patients at the European Medical Center (EMC) Radiation Therapy Department, from 2015 to 2019, participated in the study.

The main research question was: What is the most effective and safest radiotherapy technique in the treatment of patients with SBBC?

All patients underwent standard examinations including diagnostic mammography, a biopsy and estrogen/progesterone receptor (ER/PR) and *ERBB2* (*HER2* or *HER2/neu* status) determination. All nine patients underwent surgery and neoadjuvant chemotherapy/hormone therapy as recommended in the National Comprehensive Cancer Network (NCCN) guidelines. All patients had indications for adjuvant radiotherapy and were assessed by a multidisciplinary team comprising chemotherapy oncologists, oncological surgeons, and radiation therapists at the initial referral. Patient median age was 62 years (range: 43–73). The detailed patient characteristics of disease stage and the scope of surgery is shown in Table 1.

All patients underwent computed tomography on Brilliance CT Big Bore Philips (Philips, Amsterdam, Netherlands). Scans were performed without contrast enhancement with the patient in the supine position with arms raised above the head at an angle of 120° to the median body axis using QUEST™ Breastboard RT-4543 (Qfix, Avondale, PA, USA). CT scans were performed with unlabored breathing on the area between the lower jawbone and the diaphragm. CT sections were 1 mm thick. Treatment plans were created using the computer planning system Eclipse (v. 11.0) by Varian Medical Systems (Plato Alto, USA). Linear accelerators were used for administering therapy (TrueBeam (v. 1.6), Varian Medical System) with energy beams of 6 and 10 MeV. Three-dimensional conformal radiation treatment (3DCRT), intensity-modulated radiation therapy (IMRT), and volumetric-modulated arc therapy (VMAT) plans were generated and compared dosimetrically using the same set of structures. These linear accelerators have similar identical therapeutic characteristics and are equally suitable for research purposes.

We investigated external irradiation with three techniques of radiation therapy: 3DCRT, IMRT, and VMAT. Initial dosimetry planning was based on the experience and intuition of a medical physicist and radiotherapist and approved at a medical conference. For research purposes, the other two exposure methods/dosimetry plans were simulated using the planning system. Comparative assessment of the plans was made using dose-volume histograms and cross-sectional analysis of dose distribution in PTV, OARs, and irradiated volume (IV). A uniform basis for comparison was the use of the same contours for all three variants of the plan in one patient.

Radiotherapy was planned according to the Radiation Therapy Oncology Group (RTOG) recommendations for outlining PTV with consideration of critical organs. The criteria for adopting a PTV dose distribution plan were: $V(95\% \text{ of prescription dose} - 50 \text{ Gy}) \geq 95\% \text{ of volume} (\geq 47,5 \text{ Gy})$. A dose deviation of up to $V(90\% \text{ of prescription dose}) > 90\% \text{ of volume}$ was considered acceptable in especially difficult cases. Figures 1–3 show the variations of dosimetry plans for SBBC radiation therapy, as well as examples of comparative dose-volume histograms (DVH) for different treatments.

The sinoatrial, atrioventricular nodes, and Bundle branch were not visible on CT scans; therefore, their locations were estimated based on descriptions in Tonkov's manual on normal anatomy [14] and Sinelnikov's anatomical [15]. The preliminary studies of Saremi et al. (2009), Malik (2015), Stefenson et al. (2017), and Stefenson et al. (2018) were used to determine the components of the cardiac conduction system on computed tomograms [16–19]. We then conducted a training session to identify visualized cardiac structures related to the conduction system on cardiac-coronary angiograms.

Results

3DCRT, IMRT and VMAT techniques in modern technical and computational performance (on linear accelerators "TrueBeam" or "Trilogy" according to the plans calculated in the Eclipse v.15.5 system) can provide at least V (95% of prescription dose) \geq 95% of volume. The greatest differences between the techniques are in the distribution of absorbed doses outside the PTV and in individual OARs.

In the literature on radiation therapy for bilateral breast cancer, doses outside of the PTV are usually considered separately for the right and left lung [20]. We studied this in more detail and recorded the mean dose (D_{mean}; in ICRU (International Commission on Radiation Units and Measurements)), the volume of the lungs (both received a relatively large dose of 40 Gy), and the volume that fell into the LDB region (between 20 and 4 Gy). When studying the distribution of low doses of ionizing radiation outside the treated volume, we focused on their most carcinogenic interval - from 2 to 10 Gy (4–20%) of the prescribed total dose. The indicated dose range was chosen based on previously reported ranges in studies of radiation-induced secondary malignant diseases arising after the treatment of the primary tumor [21–29].

The data presented in Table 2 show that the choice of irradiation method in SBBC is not clear and depends on many individual factors, but mainly on which is the most affected side (i.e., left or right), the size and stage on this side, and the size and shape of general (bilateral) PTV. These parameters are decisive and will determine the choice between 3DCRT, IMRT and VMAT. Although there is an opinion that the IMRT and VMAT methods are preferable for use in SBBC, it is not known to what extent their use allows one to achieve optimal dose distribution in PTV and to reduce the total dose in OARs compared to 3DCRT [30–34]. We studied the dose loads on the myocardium, LADA, right coronary artery, and the lungs using 3DCRT, IMRT, and VMAT techniques. Furthermore, we irradiated patients with SBBC whose disease was synchronous at the beginning of treatment.

The VMAT technique shows the lowest dose load on the lung, myocardium, and LADA as compared to 3DCRT and IMRT.

Discussion

Based on the results obtained as well as the literature data, VMAT was found to be the most appropriate method in many treatment situations. However, this cannot be applied universally, and each case must be

considered individually in order to get the best outcome. If we evaluate the effect of LDB, then VMAT has the largest impact. It is also higher in IMRT than in 3DCRT and, according to a study by Hall et al. (2003) is accompanied by almost twice the frequency of secondary radiation-induced cancers in successfully treated patients [27]. However, these aspects for VMAT require further investigation. Additionally, if we consider the data obtained for the first time on the dose load on the cardiac conduction system, we have yet to study the role of VMAT in the occurrence of post-radiation arrhythmias.

An overwhelming majority of scientists agree that radiation treatment of left-sided breast cancer is associated with a higher risk of heart complications than treatment of right-sided tumors. Rehammar et al. (2017) reported that this association is especially true if we focus on ischemic complications or all cardiac complications [35]; however, this difference is practically nullified if arrhythmias and conduction disturbances can be distinguished from each other. In this case, the ratio between the left and right side in the localization of cancer will be 32:26, but in ischemia it will remain at the level widely described in the literature – 32:19. As mentioned earlier, the VMAT method is not universal. It has the highest LDB and, thus, gives the greatest dose load on the cardiac conduction system and on the contralateral lung. In addition to studying absorbed doses in different parts of the heart, we studied the features of the propagation of low doses of ionizing radiation at a distance from the target.

Many researchers, demonstrating the dose load on the left coronary artery, calculate it according to representations from static images of topometric CT scans, where the artery occupies a position corresponding to the moment in time when the CT scan occurred. Mobility is not taken into consideration. We specifically studied Internal target volume (ITV) using coronary angiograms. This revealed that the difference of their position depending on the phase of the cardiac cycle, can reach 1-1.5 cm. The data are presented in Figs. 4–6. Then, we analyzed the change in dose load on the LAD artery when shifted in the ventro-dorsal direction by at least 1 cm. It was found the range of 5–10% doses shifted to 10–20% and, overall, the dose load increased by 25–30% when compared to those established by static CT-cuts. If this is correlated with the data obtained on absorbed doses in individual volumes of the myocardium, then the dose, instead of those indicated in Table 2 (4.49–27.32 Gy), will become 5.82–35.41 Gy. Of course, the dose will depend on how long a particular section of the artery has been in a particular isodose area. However, the results obtained more closely represent true radiation dose absorbed by the coronary arteries. Coronary angiograms are not performed for radiotherapeutic purposes; therefore, it is impossible to assess the physiological mobility of blood vessels in three directions as is customary in radiation therapy. It should be noted, however, that the order of the numbers is quite indicative. If we extrapolate the displacements that we have discovered into the planning system, this changes the concept of the absorbed dose, which has not been described in the literature so far. The displacement of the LAD artery towards the target is particularly dangerous.

Our study of the dose load on the cardiac conduction system is, to the best of our knowledge, the first experiment in the history of radiotherapy. The importance of obtaining such knowledge is clear from the side effects of radiation therapy for breast cancer in the cited literature. This should be especially important when treating patients with heart disease, and doctors do not have any information about this

at the time. We tried to delineate in our patients the most functionally important part of the cardiac conduction system: the atrioventricular node, the sinoauricular node and bundle bunch. Our sample size was small since in the conditions of native CT scans, the anatomical structures of the heart, acting as landmarks, are visualized indistinctly when searching for them or are not differentiated due to the lack of contrast and artifacts from respiratory movements and heartbeat.

Previously, we tried to estimate the dose load on the cardiac conduction system in 24 patients with unilateral disease in whom we were able to develop the corresponding Planning organ at risk volume (PRV) with the highest reliability on topometric CT scans [36–38]. We found that, regardless of the side and volume of irradiation, the lowest average doses to the conducting system were obtained using the 3DCRT method. IMRT and VMAT performed less effectively, mainly due to the effect of LDB. We identified that, even with the most advanced irradiation methods in the context of the dose to the conduction system, LDB is not as low a dose as expected. The data obtained are presented in Figs. 7 and 8. We have shown that the greater the side effects of ionizing radiation during radiation treatment of breast cancer on the main elements of the cardiac conduction system, the larger the clinical target volume (CTV). The sinoauricular node receives the highest doses with right-sided irradiation (according to Dmean, up to 33.6% of the prescribed dose for irradiation of the right breast and all areas of regional metastasis), the atrioventricular node and especially the bundle bunch receive from 12–22.4% of the prescribed dose, with a similar left-sided exposure from 12–17.6%. However, these data are subject to large individual fluctuations and, in practice, require separate monitoring during dosimetric planning for each patient individually. In addition, the effect of the LDB must also be taken into account.

We concluded that VMAT is the best treatment for SBBC with any irradiation volume as it shows the lowest dose load on the lung, myocardium, and LADA as compared to 3DCRT and IMRT. IMRT is generally intermediate between VMAT and 3DCRT in terms of effectiveness in the irradiation of mammary glands or mammary glands with lymphatic drainage areas. In contrast, IMRT showed the least effective results in relation to the myocardium and LADA with post-mastectomy irradiation. Our study showed that the highest dose load on the myocardium and LADA in patients with SBBC was achieved with 3DCRT. However, this technique is not recommended for use in the treatment of patients with concomitant cardiovascular disease. IMRT gives better indicators of conformity and homogeneity when more beams are used, but this is accompanied by a pronounced increase in LDB, which is almost absent in 3DCRT.

Summary

VMAT is a very effective method that provides satisfactory sparing of critical organs. With VMAT, regardless of the volume and side of irradiation, lower dose distribution in the critical organs (myocardium, LADA, lungs) was noted. IMRT generally takes an intermediate position between VMAT and 3DCRT methods in the irradiation of mammary glands or mammary glands with lymphatic drainage areas. However, IMRT showed the least effective All authors contributed equally result in relation to the myocardium and LADA with post-mastectomy irradiation. When using the 3DCRT technique, the dose of ionizing radiation entering the lungs and myocardium with LADA significantly increases, which can

subsequently cause cardiovascular and lung complications. We do not recommend using this method in the treatment of patients with SBBC, especially in young patients and patients with concomitant heart diseases. If it is not possible to use another method of radiation therapy, we recommend referring these patients to other clinics. In modern radiotherapy of breast cancer, the absorbed dose in the volume at risk of the cardiac conduction system should be assessed, especially in the sinoatrial node with right-sided irradiation, and in the atrioventricular node, and bundle branch with left-sided irradiation.

Declarations

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Competing Interests

The authors have no relevant financial or non-financial interests to disclose.

Author Contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Salim Nidal, Alexandr Stolbovoy, Kristina Tumanova and Daria Shonus. The first draft of the manuscript was written by Alexander Stolbovoy and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Data Availability

Available upon request.

Ethics Approval

This is an observational study. The XYZ Research Ethics Committee has confirmed that no ethical approval is required.

Consent to Participate

Informed consent was obtained from all individual participants included in the study.

Consent to Publish

The authors affirm that human research participants provided informed consent for publication of all images in Figures.

References

1. Alongi F, Ricchetti F, Fiorentino A, Gori S (2014) Postoperative breast radiotherapy after neoadjuvant chemotherapy: which uncertainties still remain? *Tumori* 100(5):212-213. <https://doi.org/10.1700/1660.18196>
2. Padmanabhan N, Subramanyan A, Radhakrishna S (2015) Synchronous bilateral breast cancers. *J Clin Diagn Res* 9:5–8. doi: 10.7860/JCDR/2015/14880.6511
3. Darby S, McGale P, Correa C. et al. (2011) Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10,801 women in 17 randomized trials. *Lancet* 378:1707–1716. doi: 10.1016/S0140-6736(11)61629-2
4. Fung M, Schultz D, Solin L (1997) Early-stage bilateral breast cancer treated with breast-conserving surgery and definitive irradiation: the University of Pennsylvania experience. *Int J Radiat Oncol Biol Phys*. 38:959–967. doi: 10.1016/s0360-3016(97)00133-8
5. Fisher J, Scott C, Stevens R. et al. (2000) Randomized phase III study comparing Best Supportive Care to Biafine as a prophylactic agent for radiation-induced skin toxicity for women undergoing breast irradiation: Radiation Therapy Oncology Group (RTOG) 9713. *Int J Radiat Oncol Biol Phys* 48:1307–1310. doi: 10.1016/s0360-3016(00)00782-3
6. Mukesh M, Harris E, Collette S. et al. (2013) Normal tissue complication probability (NTCP) parameters for breast fibrosis: pooled results from two randomized trials. *Radiother Oncol* 108:293–298. doi: 10.1016/j.radonc.2013.07.006
7. Poortmans P, Marsiglia H, De Las Heras M, et al. (2013) Clinical and technological transition in breast cancer. *Rep Pract Oncol Radiother* 18(6):345–52. doi: 10.1016/j.rpor.2013.08.002
8. Feng M, Moran J, Koelling T. et al. (2011) Development and validation of a heart atlas to study cardiac exposure to radiation following treatment for breast cancer. *Int J Radiat Oncol Biol Phys* 79(1):10–8. doi: 10.1016/j.ijrobp.2009.10.058
9. doi: 10.1016/j.ijrobp.2009.10.058
10. Early Breast Cancer Trialists' Collaborative Group. (2000) Favorable and unfavorable effects on long term survival of radiotherapy for early breast cancer: an overview of the randomized trials. *Lancet* 355:1757-1770. [https://doi.org/10.1016/S0140-6736\(00\)02263-7](https://doi.org/10.1016/S0140-6736(00)02263-7).
11. EBCTCG (Early Breast Cancer Trialists' Collaborative Group), McGale P, Taylor C, Correa C. et al. (2014) Effect of radiotherapy after mastectomy and axillary surgery on 10-year recurrence and 20-

- year breast cancer mortality: meta-analysis of individual patient data for 8135 women in 22 randomized trials. *Lancet* 383:2127-2135. doi: 10.1016/S0140-6736(14)60488-8
12. Back M, Guerrieri M, Wratten C, Steigler A. (2004) Impact of radiation therapy on acute toxicity in breast conservation therapy for early breast cancer. *Clin Oncol* 16:12–16. doi: 10.1016/j.clon.2003.08.005
 13. S. Darby, M. Ewertz, P. McGale et al. (2013) Risk of Ischemic Heart Disease in Women after Radiotherapy for Breast Cancer. *N Engl J Med* 368:987-998. doi: 10.1056/NEJMoa1209825/
 14. Wu S, Tam M, Vega R. et al. (2017) The effect of breast irradiation on cardiac disease in women enrolled on BCIRG-001 at 10 year follow-up *Int J Radiat Oncol Biol Phys* 99:541-548 doi: 10.1016/j.ijrobp.2017.06.018
 15. Тонков В. Сосудистая система.(1953) Учебник нормальной анатомии человека. Издание 5.
 16. Синельников Р. (1942) Атлас анатомии человека. Учебное пособие. Том 3.
 17. Malik S, Kwan D, Shah A, Hsu J. (2015) The right atrium: gateway to the heart–anatomic and pathologic imaging findings. *Radiographics* 35(1):14-31. doi: 10.1148/rg.351130010
 18. Saremi F, Torrone M, Yshar N. (2009) Cardiac conduction system: delineation of anatomic landmarks with multidetector CT. *Indian pacing and electrophysiology journal* 9:318-333.
 19. Stephenson R, Atkinson A,, Kottas P. et al. (2017) High resolution 3-Dimensional imaging of the human cardiac conduction system from microanatomy to mathematical modeling. *Sci. Rep* 7(7188):1-13. doi: 10.1038/s41598-017-07694-8
 20. Stephenson R, Jones C, Guerrero R, et al. (2018). High-Resolution Contrast-Enhanced Micro-Computed Tomography to Identify the Cardiac Conduction System in Congenitally Malformed Hearts. *JACC: Cardiovascular Imaging* 11(11):1706-1712. doi: 10.1016/j.jcmg.2018.05.016
 21. Kim S, Lee M, Youn S. (2018) Radiation therapy of synchronous bilateral breast carcinoma (SBBC) using multiple techniques. *Med. Dosim* 43(1):55–68. doi: 10.1016/j.meddos.2017.08.003
 22. De Gonzalez B, Curtis R, Gilbert E. et al. (2010) Second solid cancers after radiotherapy for breast cancer in SEER cancer registries. *Br J Cancer* 102(1):220-226. doi: 10.1038/sj.bjc.6605435
 23. Huang Y, Huang T, Lin F. et al. (2017) Radiation Therapy for Invasive Breast Cancer Increases the Risk of Second Primary Lung Cancer: A Nationwide Population-Based Cohort Analysis. *Journal of Thoracic Oncology* 12(5):782-790. doi: 10.1016/j.jtho.2017.01.021
 24. Journy N, Mansouri I, Allodji R. et al. (2019) Volume effects of radiotherapy on the risk of second primary cancers: A systematic review of clinical and epidemiological studies. *Radiotherapy and oncology* 131:150–159. doi: 10.1016/j.radonc.2018.09.017
 25. Xie L, Lin C, Zhang H, Bao X. (2018) Second malignancy in young early-stage breast cancer patients with modern radiotherapy: A long-term population-based study (A STROBE-compliant study). *Medicine* 97(17):1-8. doi: 10.1097/MD.00000000000010593

26. Zhang W, Becciolini A, Biggeri A. et al. (2011) Second malignancies in breast cancer patients following radiotherapy: a study in Florence, Italy. *Breast Cancer Res* 4(13):1-9. doi: 10.1186/bcr2860
27. Rehman J, Taylor R, Isa M. et al. (2015) Evaluations of secondary cancer risk in spine radiotherapy using 3DCRT, IMRT, and VMAT: A phantom study. *Medical Dosimetry* 40(1):70–75. doi: 10.1016/j.meddos.2014.10.003
28. Hall E, Wu C. (2003) Radiation-induced second cancers: the impact of 3D-CRT and IMRT. *Int J Radiat. Oncol. Biol. Phys* 56(1):83–88. doi: 10.1016/s0360-3016(03)00073-7
29. Hall E, Kaplan H. (2004) The crooked shall be made straight; dose-response relationships for carcinogenesis. *Int. J. Radiat. Biol* 80(5):327–337. doi: 10.1080/09553000410001695895
30. Xu X, Bednarz B, Paganetti H. et al. (2008) A review of dosimetry studies on external beam radiation treatment with respect to second cancer induction/ *Phys. Med. Biol* 53(13):193–241. doi: 10.1088/0031-9155/53/13/R01
31. Fiorentino A, Mazzola R, Ricchetti F. et al. (2015) Intensity modulated radiation therapy with simultaneous integrated boost in early breast cancer irradiation. Report of feasibility and preliminary toxicity. *Cancer Radiother* 19(5):289–294. doi: 10.1016/j.canrad.2015.02.013
32. Franco P, Migliaccio F, Torielli P et al. (2015) Bilateral breast radiation delivered with static angle tomotherapy (TomoDirect): clinical feasibility and dosimetric results of a single patient. *Tumori* 01(1):4-8. doi: 10.5301/tj.5000264
33. Mcdonald M, Godette K, Butker E et al. (2008) Long-term outcomes of IMRT for breast cancer: a single-institution cohort analysis. *Int J Radiat Oncol Biol Phys* 72:1031–1040. doi: 10.1016/j.ijrobp.2008.02.053
34. Scorsetti M, Alongi F, Fogliata A. et al. (2012) Phase I–II study of hypofractionated simultaneous integrated boost using volumetric modulated arc therapy for adjuvant radiation therapy in breast cancer patients: a report of feasibility and early toxicity results in the first 50 treatments. *Radiat Oncol* 7:145. doi: 10.1186/1748-717X-7-145
35. Seppälä J, Heikkilä J, Myllyoja K. et al. (2017) Volumetric modulated arc therapy for synchronous bilateral whole breast irradiation – A case study. *Radiol Med* 122(6):464-471. doi: 10.1007/s11547-017-0741-y. doi: 10.1186/s13014-021-01763-z
36. Rehammar J, Jensen M, McGale P. et al. (2017) Risk of heart disease in relation to radiotherapy and chemotherapy with anthracyclines among 19,464 breast cancer patients in Denmark, 1977-2005. *Radiother Oncol* 123(2):299-305. doi: 10.1016/j.radonc.2017.03.012. DOI: 10.1016/j.radonc.2017.03.012
37. Салим Н, Столбовой А, Котляров П, Лагкуева И, Шонус Д. (2020) Проводящая система сердца как новый критический орган в радиотерапии рака молочной железы. *Вестник Российского научного центра рентгенорадиологии* 20(2):162-178.
38. Салим Н, Столбовой А, Котляров П, Лагкуева И, Шонус Д. (2020) Оконтуривание проводящей системы сердца в радиотерапии. / В книге: «Белые ночи 2020». Тезисы VI Петербургского

международного онкологического форума. - 2020. - С. 378. https://forum-onco.ru/upload/unsorted/forum_tezis_2020.pdf.

39. Салим Н, Столбовой А, Лагкуева И, Шонус Д. (2020) Дозная нагрузка на проводящую систему сердца при лучевом лечении рака молочной железы. Белые ночи 2020». Тезисы VI Петербургского международного онкологического форума. - 2020. - С. 380. https://forum-onco.ru/upload/unsorted/forum_tezis_2020.pdf.

Tables

Table 1. Clinical characteristics of the patients with SBBC

Patient's characteristics				
Nº	Age	Staging right/left breast	Surgery type	PTV (planning target volume)
1	56 y.o	T1N1cM0 T2N2bM0	lumpectomy +ALND lumpectomy +ALND	mammary glands on both sides + I-III levels of axillary Lns, supraclavicular Lns, parasternal Lns
2	61 y.o	T3N2aM0 TisN0M0	mastectomy lumpectomy	chest wall on the right + I-III levels of axillary Lns, supraclavicular Lns, parasternal Lns breast on the left
3	43 y.o	T2N1M0 T1N1M0	mastectomy mastectomy	chest wall on both sides + + I-III levels of axillary Lns on the left; I-III levels of axillary Lns, supraclavicular Lns on the right
4	68 y.o	T1cN0M0 T1cN0M0	lumpectomy +ALND lumpectomy +ALND	mammary glands on both sides + I-III levels of axillary Lns on both sides
5	58 y.o	TisN0M0 T1cN0M0	lumpectomy lumpectomy +ALND	mammary glands on both sides
6	64 y.o	T2N0M0 T1cN2aM0	lumpectomy +ALND lumpectomy +ALND	mammary glands on both sides + I-II levels of axillary Lns on both sides
7	61 y.o	T1cN1aM0 T1bN0M0	lumpectomy +ALND lumpectomy +ALND	mammary glands on both sides + I-II levels of axillary Lns on both sides
8	58 y.o	T1N0M0 T1N0M0	lumpectomy +ALND lumpectomy +ALND	mammary glands on both sides

9	73 y.o	T1cN1aM0	mastectomy	chest wall on both sides + I-III levels of axillary Lns, supraclavicular Lns, parasternal Lns on both sides
		T1cN0M0	mastectomy	

ALND - axillary lymph node dissection; LNs - lymph nodes.

Table 2. Comparison of the dose absorbed by at-risk organs under irradiation using 3DCRT, IMRT, and VMAT techniques up to total dose 50 Gy with bilateral PTV in all patients.

Number of patients	PTV	Organ at risk	Dosimetric parameters	Parameter value			
				3DCRT	IMRT	VMAT	
1	Chest Wall + levels I-III axillary LNs, supraclavicular LNs, parasternal LNs on the right	Left lung	Dmean (Gy)	18,77	15,28	10,42	
			V4Gy (%)	69,20	84,70	74,40	
		Right lung	Dmean (Gy)	18,83	15,28	10,24	
			V4Gy (%)	65,20	88,40	67,60	
		Myocardium	Dmean (Gy)	6,86	8,38	5,07	
			V4Gy (%)	13,80	24,80	7,80	
	LAD artery	Dmean (Gy)	13,77	18,21	10,22		
		V4Gy (%)	8,80	0,00	0,00		
	RCA	Dmean (Gy)	3,91	7,34	5,30		
		V4Gy (%)	0,00	0,00	0,00		
	2	Mammary gland + levels I-II axillary LNs on the right	Left lung	Dmean (Gy)	10,86	9,25	6,71
				V4Gy (%)	38,30	69,60	56,30
Right lung			Dmean (Gy)	9,93	9,64	7,36	
			V4Gy (%)	37,00	66,70	53,80	
Myocardium			Dmean (Gy)	4,59	5,90	3,80	
			V4Gy (%)	8,20	8,40	0,70	
LAD artery		Dmean (Gy)	13,91	9,64	9,45		
		V4Gy (%)	0,00	0,00	0,00		
RCA		Dmean (Gy)	3,29	5,39	5,04		
		V4Gy (%)	0,00	0,00	0,00		
3, 5		Mammary gland + levels I-III axillary LNs on the right	Left lung	Dmean (Gy)	16,94	16,00	7,28
				V4Gy (%)	57,65	94,90	54,90
	Mammary gland + levels I-III axillary LNs on the left						

		Right lung	Dmean (Gy)	19,37	15,56	8,29
			V4Gy (%)	59,80	83,60	61,65
		Myocardium	Dmean (Gy)	10,86	8,54	4,04
			V4Gy (%)	25,80	20,10	2,45
		LAD artery	Dmean (Gy)	27,32	12,55	5,88
			V4Gy (%)	37,90	0,00	0,00
		RCA	Dmean (Gy)	2,92	10,57	4,59
			V4Gy (%)	0,00	0,00	0,00
4,6	Mammary glands on both sides	Left lung	Dmean (Gy)	11,68	9,13	6,33
			V4Gy (%)	41,75	67,40	61,30
		Right lung	Dmean (Gy)	9,68	8,64	7,46
			V4Gy (%)	40,20	63,10	60,75
		Myocardium	Dmean (Gy)	6,92	7,45	4,82
			V4Gy (%)	14,75	19,30	3,15
		LAD artery	Dmean (Gy)	9,21	7,36	5,52
			V4Gy (%)	5,10	0,00	0,00
		RCA	Dmean (Gy)	2,29	7,86	6,10
			V4Gy (%)	0,00	0,00	0,00
7	Mammary gland + levels I-III axillary LNs, parasternal LNs on the right	Left lung	Dmean (Gy)	21,49	14,20	11,40
			V4Gy (%)	76,60	91,80	83,10
	Mammary gland + levels I-III axillary LNs, parasternal LNs on the left	Right lung	Dmean (Gy)	20,88	15,64	12,17
			V4Gy (%)	77,30	96,50	90,40
		Myocardium	Dmean (Gy)	7,89	8,08	7,96

		V4Gy (%)	19,00	15,50	22,00	
		LAD artery	Dmean (Gy)	24,65	10,76	8,57
			V4Gy (%)	35,38	0,00	0,00
		RCA	Dmean (Gy)	3,23	9,70	8,68
			V4Gy (%)	0,00	0,00	0,00
8	Mammary gland + levels I-III axillary LNs, supraclavicular LNs on the right	Left lung	Dmean (Gy)	18,22	12,76	8,43
			V4Gy (%)	56,20	89,40	47,50
	Mammary gland + levels I-III axillary LNs on the left	Right lung	Dmean (Gy)	16,75	14,61	8,13
			V4Gy (%)	64,40	95,70	48,60
		Myocardium	Dmean (Gy)	8,77	8,81	3,61
			V4Gy (%)	18,80	30,80	5,40
		LAD artery	Dmean (Gy)	11,13	10,89	4,49
			V4Gy (%)	5,00	0,00	0,00
		RCA	Dmean (Gy)	3,21	10,35	3,61
			V4Gy (%)	0,00	0,00	0,00
9	Chest Wall + levels I-III axillary LNs, supraclavicular LNs, parasternal LNs on the right	Left lung	Dmean (Gy)	12,16	9,06	7,14
			V4Gy (%)	48,90	75,30	70,00
	Left mammary gland	Right lung	Dmean (Gy)	17,85	13,77	11,06
			V4Gy (%)	62,10	87,80	58,20
		Myocardium	Dmean (Gy)	3,61	7,15	4,41
			V4Gy (%)	4,00	18,90	4,60
		LAD artery	Dmean (Gy)	6,70	9,60	6,18
			V4Gy (%)	0,00	0,00	0,00
		RCA	Dmean (Gy)	3,58	10,27	4,27

		V4Gy (%)	0,00	0,00	0,00
All patients	Left lung	Dmean (Gy)	15,73	12,24	8,24
		V4Gy (%)	55,51	81,87	63,93
	Right lung	Dmean (Gy)	16,19	13,31	9,24
		V4Gy (%)	58,00	83,11	63,00
	Myocardium	Dmean (Gy)	7,07	7,76	4,82
		V4Gy (%)	14,91	19,69	6,59
	LAD artery	Dmean (Gy)	15,24	11,29	7,19
		V4Gy (%)	13,17	0,00	0,00
	RCA	Dmean (Gy)	3,21	8,78	5,37
		V4Gy (%)	0,00	0,00	0,00

Dmean is the standard term of the 83rd ICRU Report for PRV: the sum of doses received by each of its voxels divided by the number of voxels.

Figures

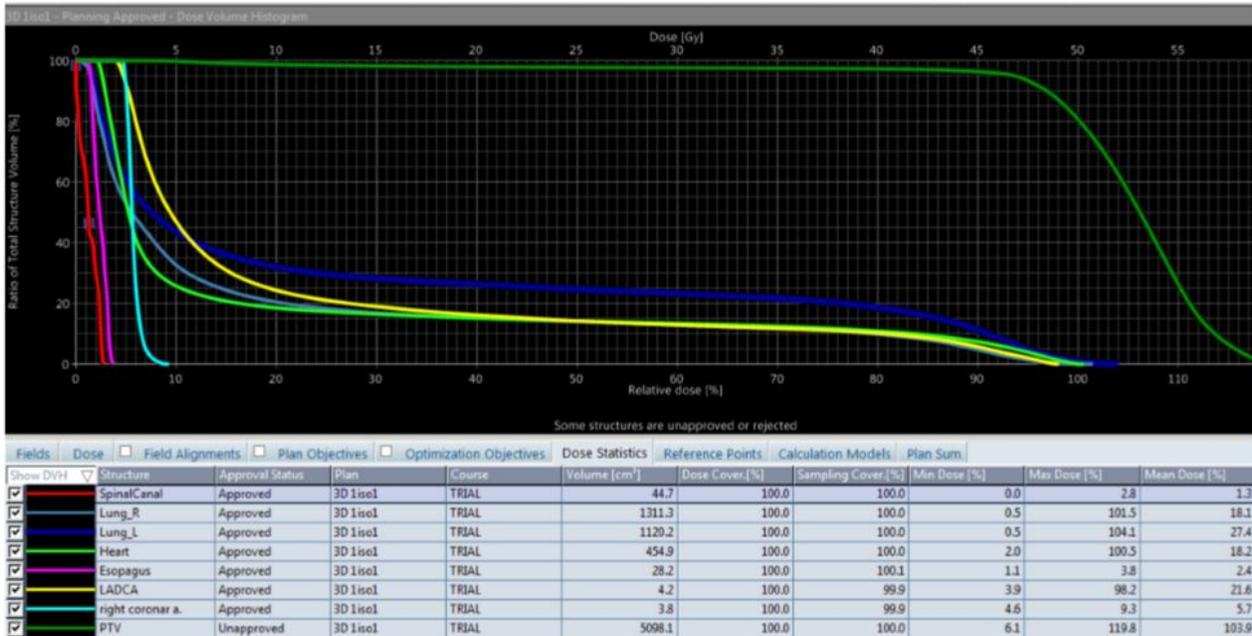
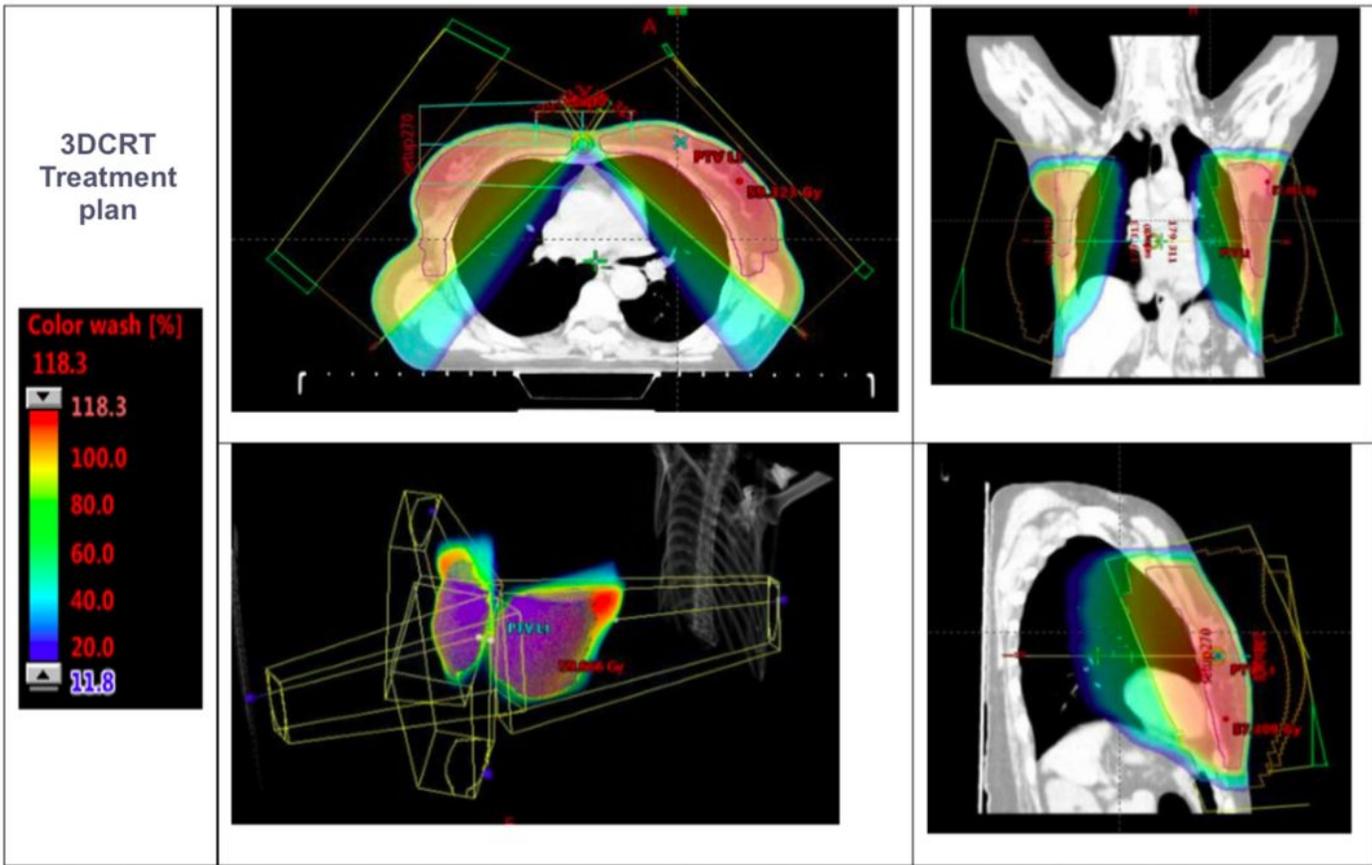


Figure 1

Examples of the prescribed dose distribution in 3DCRT. Treatment plan and DVH.

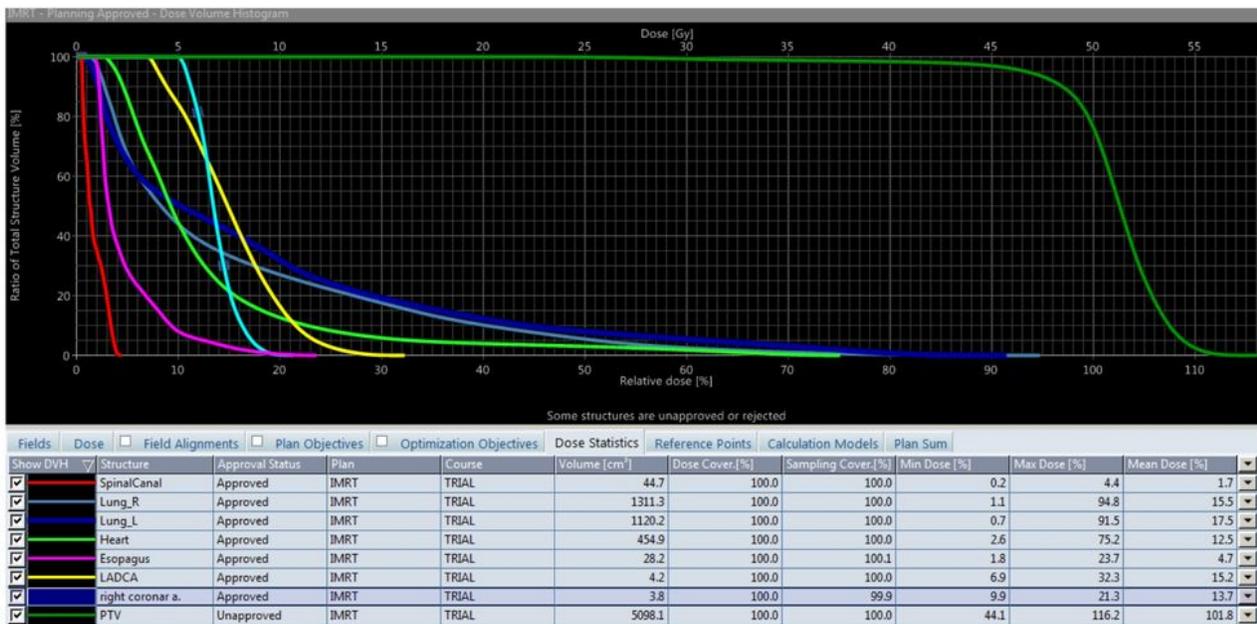
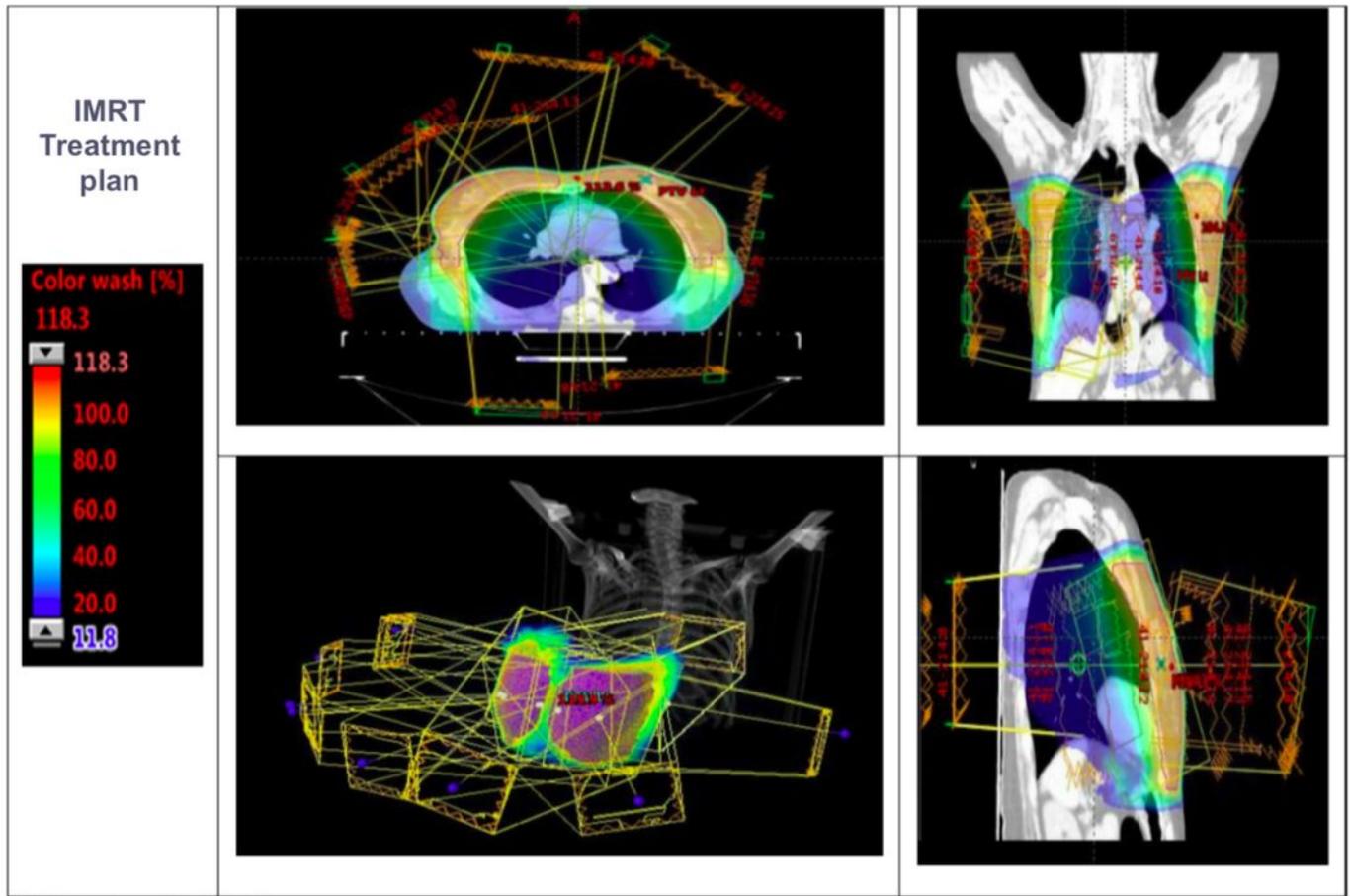


Figure 2

Examples of the prescribed dose distribution in IMRT. Treatment plan and DVH.

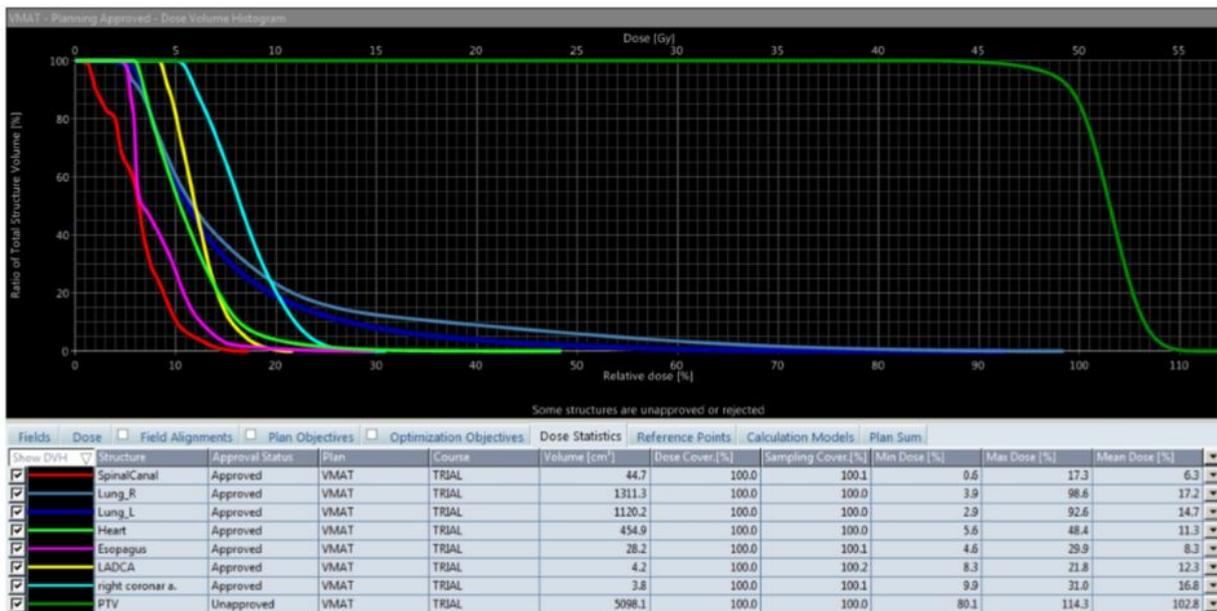
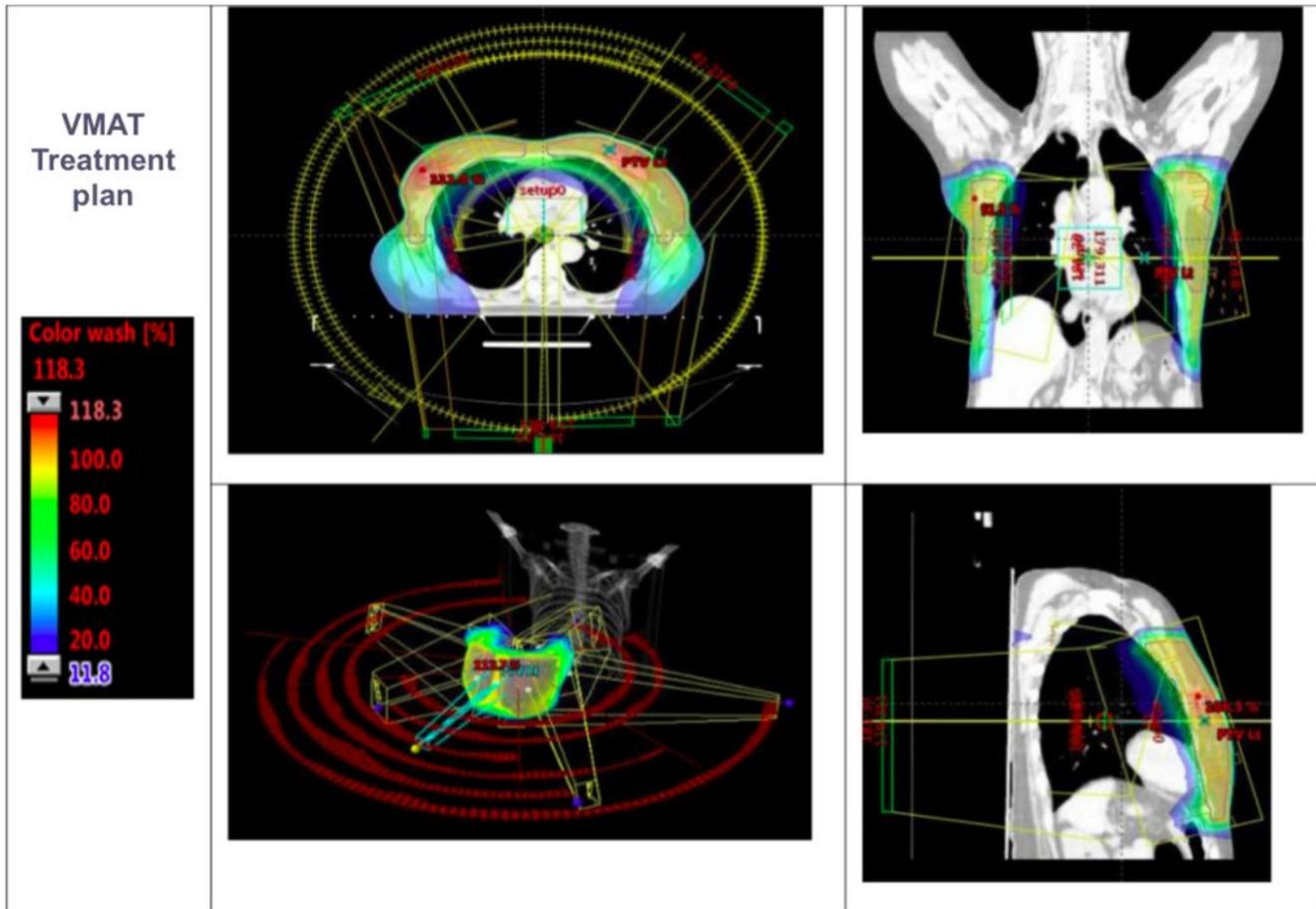


Figure 3

Examples of the prescribed dose distribution in VMAT. Treatment plan and DVH.

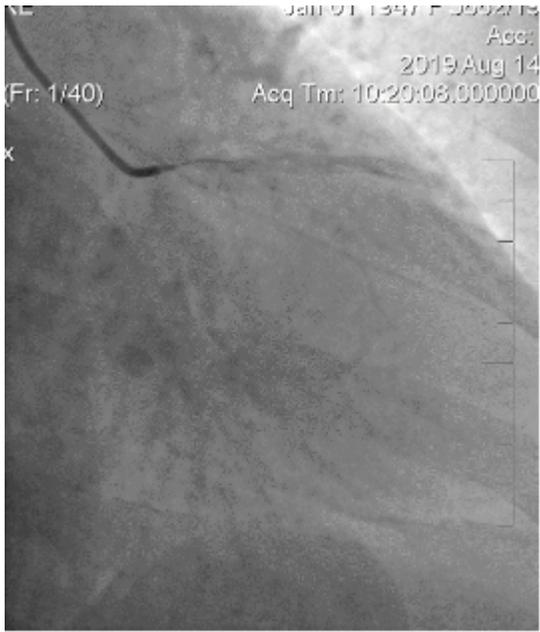


Figure 4

Coronary angiogram. Right: the catheter is in the orifice of the left coronary artery trunk, beginning to fill the trunk and anterior branch of the left coronary artery with contrast agent. Left: the trunk of the left coronary artery and its anterior branch (running horizontally) are contrasted, and the anterior circumflex artery extends downward from them. The pictures were taken at different phases of the cardiac cycle. The difference in the position of the arteries in systole and diastole in the cranio-caudal direction is approximately 1.5 cm.



Figure 5

Contrasting the right coronary artery in different phases of the cardiac cycle. Systolic-diastolic displacement in the transverse direction of about 1.5 cm.

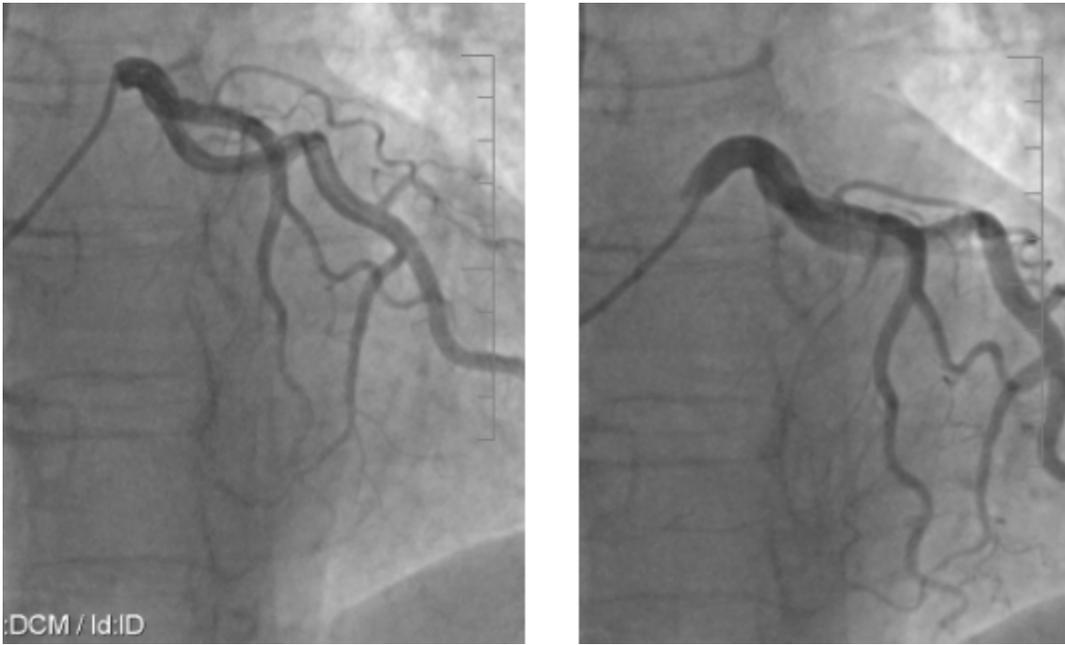


Figure 6

Left coronary arteries. The X-ray tube is rotated at an angle of 48° ; it is possible to roughly estimate the dorso-ventral displacement of the arteries in systole and diastole - it is about 1.5 cm.

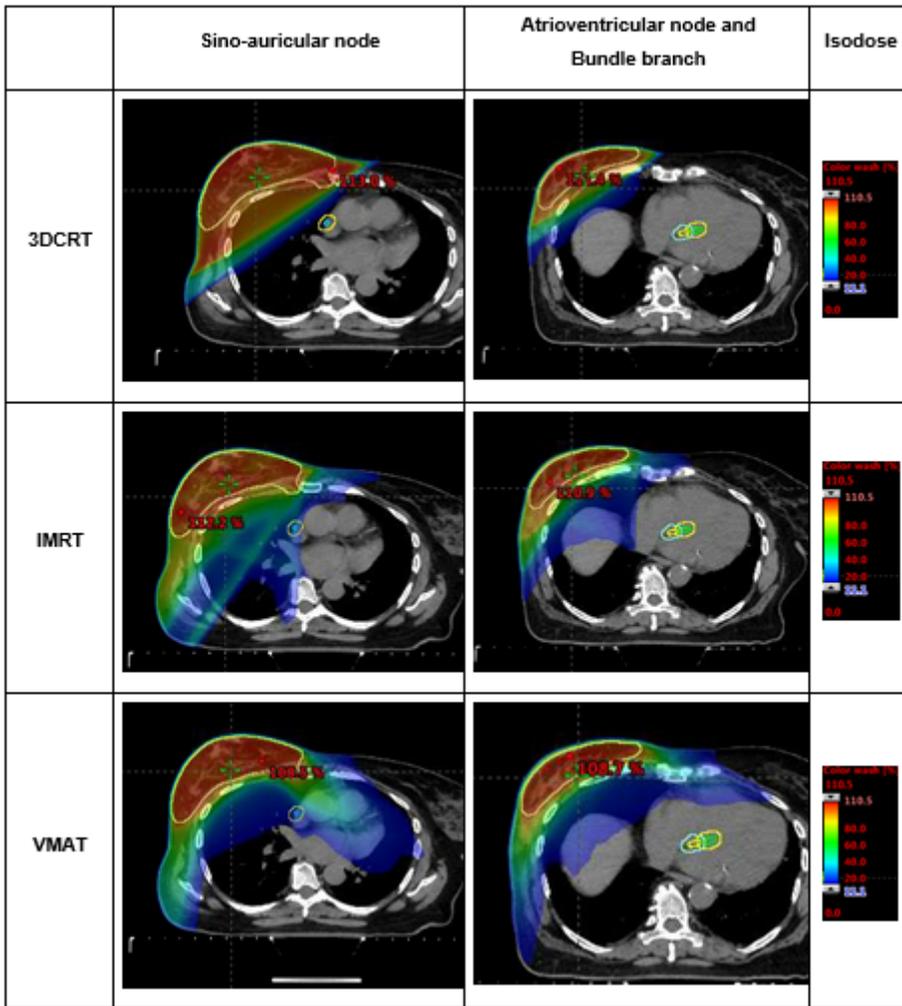


Figure 7

Dose distribution on the main elements of the cardiac conduction system during radiation treatment of right breast cancer.

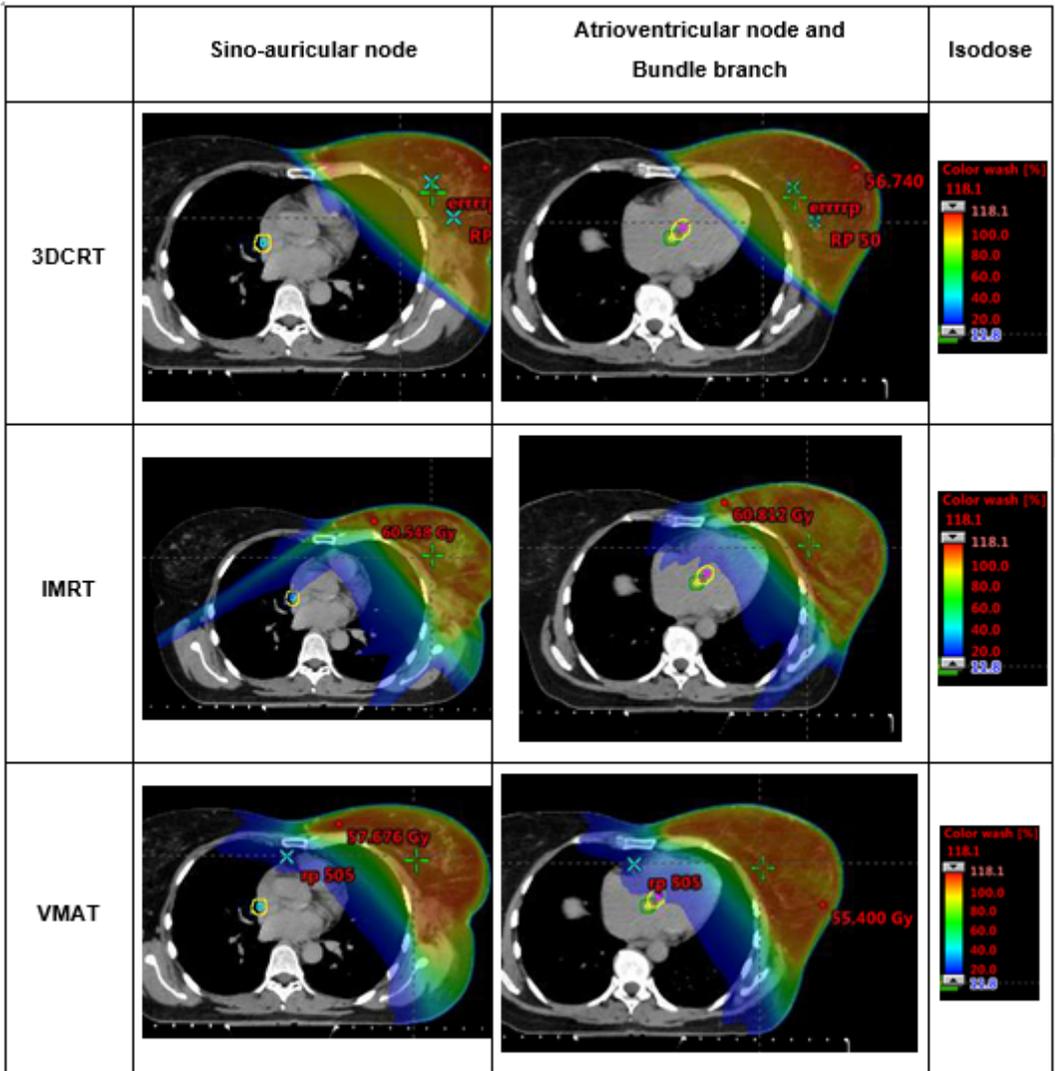


Figure 8

Dose distribution on the main elements of the cardiac conduction system during radiation treatment of left breast cancer.