TURKISH JOURNAL of ONCOLOGY

Turk J Oncol 2022;37(Supp 1):35–43
doi: 10.5505/tjo.2022.S1006

REVIEW

Breast Cancer Radiotherapy-induced Cardiotoxicity

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SUMMARY

In the multimodality treatment of breast cancer, adjuvant radiotherapy (RT) has an important role in achieving local control and increasing survival. Cardiac toxicity due to breast RT, especially left-sided breast RT, is rare but clearly recognizable. As overall survival rates are steadily increasing, long-term toxicities also become increasingly important in terms of late cardiac events, possibly caused by RT. Even small doses for the heart are thought to increase the risk of cardiac toxicity. Advanced radiation techniques such as intensity-modulated radiation therapy, volumetric-modulated arc RT, deep inspiration breath-hold techniques, and prone positioning for pendular breast can eliminate the heart from the primary beams. In addition to mean heart dose, breast cancer RT planning should also include constraints for cardiac subvolumes. Especially for patients who have pre-existing such as cardiovascular disease, diabetes mellitus, dyslipidemia, arterial hypertension, lifestyle factor (tobacco smoking, alcohol, physical inactivity, and poor nutrition), and physicians have to be careful about cardiotoxicity. Radiation oncologists and cardiology specialists should provide closely cooperating regular and long-term follow-up. This will provide the improvement of patient outcomes.

Keywords: Breast cancer; cardiotoxicity; radiotherapy.

Introduction

In the multimodality treatment of breast cancer, adjuvant radiotherapy (RT) has an important role in achieving local control and increasing survival.[1,2] The local treatment of breast cancer has changed dramatically in the last 100 years, reflecting changes in our understanding of the biology of breast cancer and improvements in diagnostic and therapeutic modalities. It was observed that more extensive surgical procedures did not reduce the risk of distant metastases, and thus we understood that breast cancer is not only a local disease but also a systemic disease. Halstedian principles of radical mastectomy switch to modified radical mastectomy (MRM) appear to differ not the pectoralis major muscle is removed.[3,4] By the end of the 1970s, randomized trials were intended to show the noninferiority of breast conservation surgery (BCS); local excision of the tumor plus breast RT to more radical local treatments mastectomy±postoperative RT.[2,5,6] The Early Breast Cancer Trialists' Collaborative Group in Oxford published a meta-analysis, which was able to assess 15-year outcome data, further demonstrated that the use of radiation could reduce rates of breast cancer death and improve overall survival rates.[5,6] Breast cancer treatment thanks to evolve by these trials. Especially in these days for patients with early-stage breast cancer, the outcomes associated with BCS, sentinel lymph node dissection, RT, and systemic treatments are excellent.[2,6,7] Except for surgery, these anticancer treatments have several potential adverse cardiac effects. Although evolving early breast cancer treatment has BCS and RT, MRM still has performed locally advanced disease or multicentric disease or choice of patient treatment. Post-mastectomy RT

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Turk J Oncol 2022;37(Supp 1):35–43
doi: 10.5505/tjo.2022.S1006

consists of chest wall irradiation plus peripheral lymph node region irradiation and the approach is comprehensive RT.[8] Whether it is BCS or MRM applied, left breast cancer patients should investigate and be careful of cardiac radiation exposure and the long-term radiation-induced coronary artery heart disease or cardiac death. This paper aims to discuss RT-related cardiotoxicity with a focus on patients with left breast cancer.

What is the Meaning of Quantitative Analysis of Normal Tissue Effects In-clinic (Quantec) for Radiation Oncologist?

Except for partial breast RT or hypofractionated RT, often breast cancer RT applies the whole breast 45-50 Gray (Gy)/25 fr/1.8-2 Gy and boost dose 10-16 Gy/5-8 fr/1.8-2 Gy. During planning, physicians notice both homogeneous dose distribution in breast tissue and organ at risk dose restrictions in the lung and heart.[8]

When we applied two-dimensional RT, we used Emami's guide for heart dose restrictions. Hence, the whole of heart tolerance dose (TD) 5/5 40 Gy, 2/3 volume of heart 45 Gy, 1/3 volume of heart 60 Gy.[9] However, radiation-related pericardial, valvular, and myocardial diseases were more common in the past than today. In course of time due to modifications in RT techniques, resulting in lower radiation doses applied to the heart. Breast radiation therapy techniques have evolved in the era of 3-dimensional planning, motivated in part by historical studies linking increased rates of cardiac mortality to radiation treatment for left-sided breast cancer.

When applying two-dimensional radiation therapy, the Emami guideline for cardiac dose restrictions was used. Accordingly, the total cardiac TD 5/5, 40 Gy; 2/3 of heart volume 45 Gy; and 1/3 of the heart volume was limited to 60 Gy. However, with such limitations, radiation-induced pericardial, valve, and myocardial diseases were more common in the past than they are today. Over time, advances in the RT technique have made it easier to lower the radiation doses delivered to the heart.

In 2010, published data for three-dimensional conformal radiation therapy (3D-CRT) to assist clinicians in providing safe, comprehensive care to breast cancer patients, the QUANTEC including dose, volume, outcome data, and expert opinion about limiting the toxicity risk for particular organs, including heart.[10]

According to QUANTEC data, it is recommended that no more than 5% of the whole heart exceeds 20 Gy for the left-sided breast cancers and 0% of the heart exceeds 20 Gy for the right-sided breast cancers. Similarly, no more than 30% of the whole heart exceeds 10 Gy for the left-sided breast cancers and no more than 10% of the heart exceeds 10 Gy for the right-sided breast cancers. Besides, the mean heart dose (MHD) should not exceed 4 Gy. Moreover, the normal tissue complication probability model-based estimates predict that a V25 Gy below 10% (in 2 Gy per fraction) is associated with a <1% probability of cardiac mortality 15 years after RT.[10]

Furthermore, when applied contemporary RT technics, physicians suggest contouring the left anterior descending (LAD) artery, and dose for patients with left-sided breast cancer should be routinely examined (should be kept as low as possible) and reported to clarify its clinical consequences and eventually establish constraints for this artery.[11] Objectives for LAD suggest dose homogeneity for the boost and whole breast; heart; and LAD maximum dose <15 Gy and mean dose <5 Gy.[12]

The German Society of Radiation Oncology (DEGRO) Expert Panel recommended stricter dose constraints to minimize cardiac toxicity. The dose of the left ventricle is also specified in the panel. The DEGRO recommendations are as follows: MHD <2.5 Gy; D_{meanLV} (mean dose left ventricle) <3 Gy; $V5_{LV}$ (volume of LV receiving ≥5 Gy) <17%; $V23_{LV}$ (volüme of LV receiving ≥23 Gy) <5%; $D_{meanLAD}$ (mean dose left descending artery) <10 Gy; $V30_{LAD}$ (volume of LAD receiving ≥30 Gy) <2%; and $V40_{LAD}$ (volume of LAD receiving ≥40 Gy) <1%.[13,14]

In patients with breast cancer, it is recommended that the irradiated heart volume be minimized to the greatest possible degree without compromising the target coverage. For this purpose, the introduction of more has led to a substantial decrease in the radiation dose to the heart. Advanced radiation techniques mean that 3D-CRT, intensity-modulated radiation therapy (IMRT), volumetric-modulated arc radiotherapy (VMAT), deep inspiration breath-hold (DIBH) techniques, and prone positioning for pendular breast can eliminate the heart from the primary beams.[12,15]

Cheng et al. published recently long-term cardiovascular risk in women with breast cancer involving 39 studies. Their study identified that RT was associated with an increased risk for coronary heart disease but not for heart failure, arrhythmia, and valvular heart disease. In subgroup analyses, the increase in risk with RT seemed to be driven by a stronger association among studies, in which breast cancer was diagnosed before 1980. The risk for coronary heart

disease started first decade, whereas the risk for cardiac death started from the second decade after radiation exposure. And contemporary RT techniques may still increase the risk of ischemic heart disease in a proportion of patients, consistent with their findings that risk for coronary heart disease slightly increased for patients irradiated after 1980. Hence, modern RT technics have likely reduced the risk; however, the long-term hazards in the general population still need to be monitored directly.[16-19]

In addition, Boero et al.[19] recently published a study comparing the cardiac outcomes of patients with right or left-sided breast cancer who underwent modern RT. Significant differences between patients with right and left-sided breast cancer included the use of IMRT, which was more common for left-sided tumors. Coronary artery disease and conduction abnormalities/dysrhythmias were the most commonly diagnosed events, with a cumulative incidence of 56% and 64.1%, right and left-sided breast cancer, respectively.

The cumulative incidence of percutaneous coronary intervention (PCI) for patients with left- and right-sided breast cancer was 5.5% and 4.5%, respectively. However, stratifying the incidence of PCI by pre-existing cardiac risk status, the effect of tumor laterality was limited to the high cardiac risk subgroup. In that group, the cumulative incidence of PCI was 10.5% for left-sided breast cancer and 7.7% for right-sided breast cancer (Fig. 1). In addition, who underwent PCI, those with left-sided tumors had a greater risk of death. In a 10-year period for a PCI cohort, the risk of death from breast cancer was 9% in patients with right-sided breast cancer, but 19% in patients with left-sided breast cancer (Fig. 2). Their research found that women with a history of cardiac disease and left-sided breast cancer treated with radiation had greater rates of PCI, a previously unreported association, with higher mortality for left-sided patients who underwent PCI.[19]

A history of smoking and prior diagnosis of ischemic heart disease has been shown to further increase this risk. In a population-based study conducted by Darby et al.,[18] a MHD of 6.6 Gy was reported in left-sided breast irradiation, with 7.4% increased risk of major coronary events with every 1 Gy increase in MHD with no apparent threshold for cardiac complications. This increased risk was shown to begin at 5 years after irradiation and continue for at least 20 years. Cardiac angiography and cardiac stress testing in patients with previous RT treatment for breast cancer demonstrate a higher rate of abnormalities in the LAD coronary artery. In left-sided patients, 85% of stress test abnormalities occurred in the LAD.[20,21]

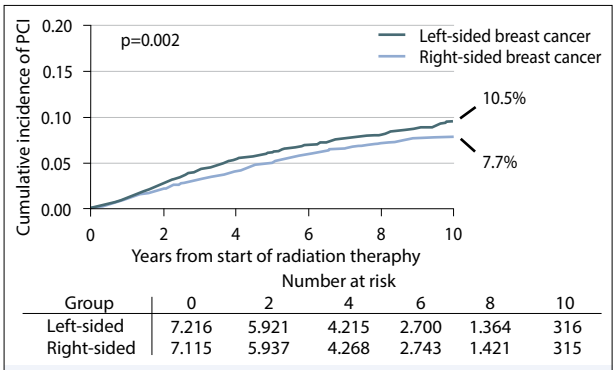

Fig. 1. Boero et al.'s[19] research graphic of cumulative incidence of percutaneous coronary intervention for left- and right-sided breast cancer.
PCI: percutaneous coronary intervention.

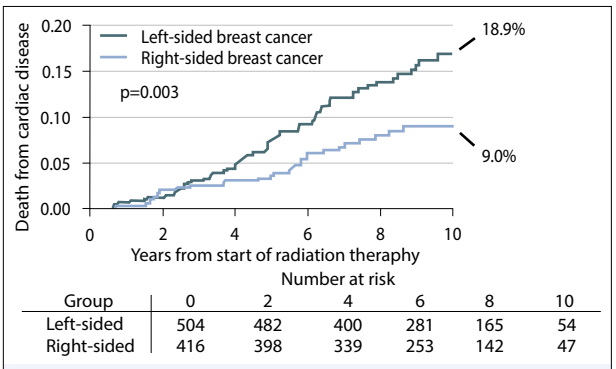

Fig. 2. Boero et al.'s[19] research graphic of cumulative incidence of cardiac-associated mortality for left- and right-sided breast cancer patients who received percutaneous coronary intervention after radiotherapy.

In the present, the current management strategies to assess, monitor, reduce or possibly prevent RT-induced cardiotoxicity, based on recent research evidence. It also outlines the importance of close collaboration between oncologists and cardiologists that is necessary for patient safety, improvement of clinical outcomes, and quality of life.

Interaction with Systemic Treatments

The contribution of systemic therapies in addition to RT remains an important consideration in the development of heart disease in cancer patients and plays an important role as an additional risk factor.

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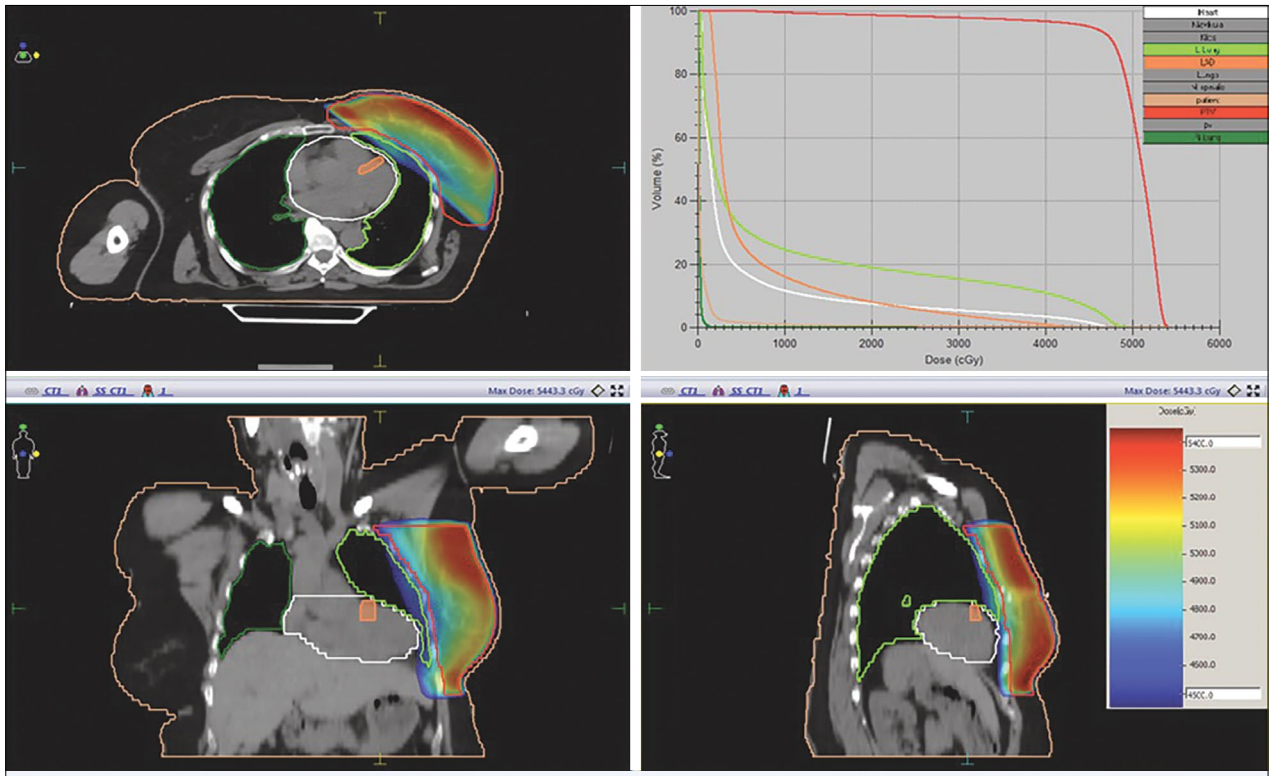

Fig. 3. Example of three-dimensional conformal radiation therapy treatment plan for a patient.

Anthracyclines are used to treat many types of cancer include breast cancer. Doxorubicin and epirubicin are given intravenously and the main toxicity is to the bone marrow, gastrointestinal tract and the heart. Daunorubicin and doxorubicin and, to a much lesser extent, epirubicin, cause cumulative cardiotoxicity and there is a maximum recommended total dose. Acute cardiac toxicity is manifest by arrhythmias and abnormalities of electrical conduction. The chronic effect is a cardiomyopathy (pericarditis and congestive cardiac failure) and, thus, anthracyclines should be avoided if there is the previous history of cardiac failure or ischemic heart disease. Although the toxicity on the heart increases with the sequential applications of RT and anthracycline-based systemic treatment, the biggest negative effect occurs in concomitant applications. [22] Especially in patients with left breast cancers, doxorubicin and RT are not used concomitantly because they increase the risk of cardiac complications.[23]

Monoclonal antibodies represent the paradigm of targeted oncologic treatment and are widely used in the management of many malignancies. In breast cancer, ~15% of all tumors overexpress the cell surface receptor HER2 and traditionally are clinically defined by aggressive behavior and worse prognosis. Accordingly, the presence of the HER2 has served as anoptimal target for biologic therapies. The use of the humanized monoclonal antibody trastuzumab (directed against the HER2 receptor) has revolutionized the treatment of HER2-positive breast cancer, with landmark adjuvant phase III trials demonstrating a 50% reduction in recurrence of disease and a 33% improvement in survival. [24] While Type 1 damage caused by anthracyclines is irreversible due to structural damage in cardiomyocytes, trastuzumab causes reversible heart damage called Type 2. Preclinical data showed that the combined use of trastuzumab with RT may have a synergistic effect on both tumor response and normal tissue toxicity. There is no clear clinical data showing that sequential or concurrent administration increases cardiac toxicity.[22]

Heart-sparing Modern RT Techniques

3D-CRT

The 3D-CRT plan be composed of standard medial and lateral tangent beams with wedges (Fig. 3). MLCs are used to shield the heart and lung tissues. According to the needs, physical wedges and dynamic wedges are used to treat patients. 3D-CRT has been shown to de-

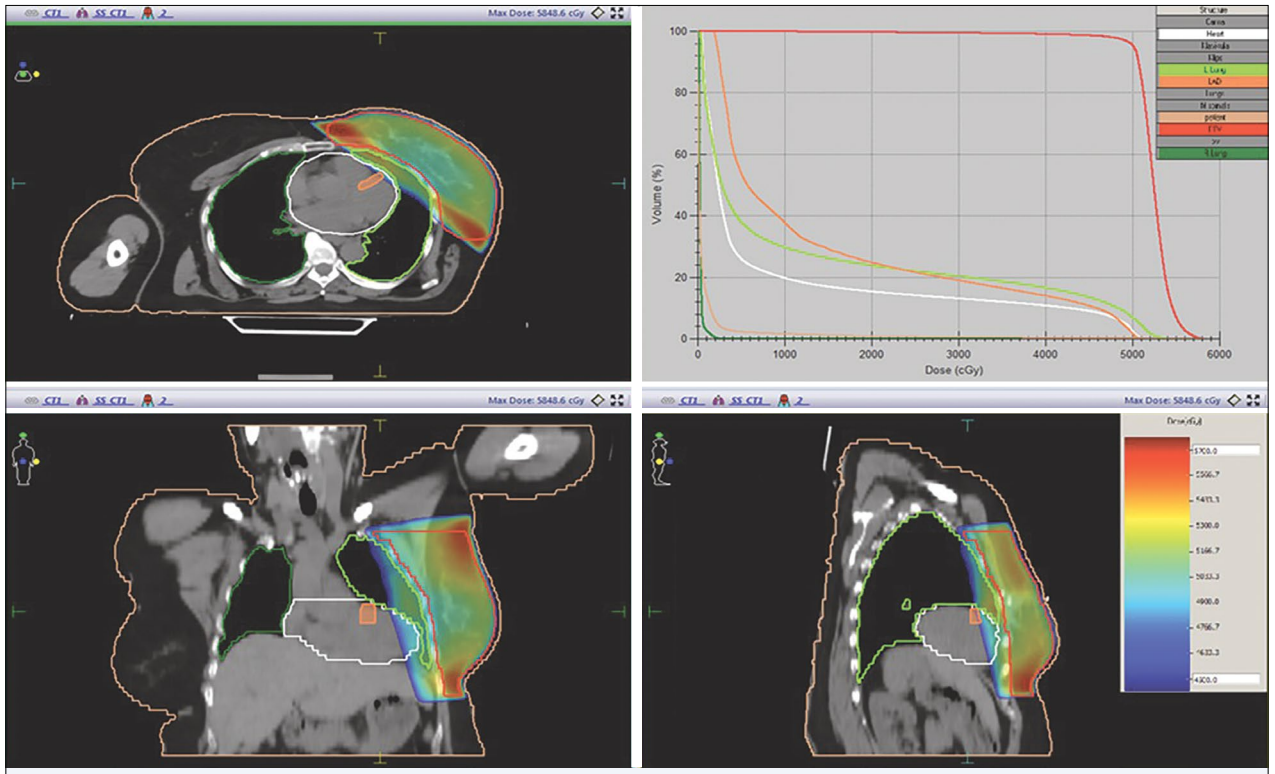

Fig. 4. Example of forward-planned intensity-modulated radiation therapy (field in field) for left-sided breast cancer.

crease the total heart dose and to spare the left circumflex and right coronary artery, but the dose to the LAD artery remained unchanged.[15]

IMRT

As shown in many sites treated with IMRT, in patients with left-sided breast cancer, IMRT limits the heart dose to more acceptable doses. Different techniques, including forward-planned IMRT (Field in Field), inverse-planned IMRT, and modulated arc therapies (Volumetric arc therapy-VMAT), have been studied. IMRT increases improvements in dose distribution to the target volume while reduce the exposure of high doses to heart and lung tissues. Distributing of irradiation to an irregular shape can be optimized with IMRT. Moreover, the technology proposal the capability to generate concavities in the treatment volume so as to improve conformality (Figs. 4, 5).[25]

Supine or Prone Position

Conventionally, breast cancer has been treated in the supine position with arms above the head with two opposed tangential photon fields. Irradiation in the prone position is another useful treatment choice. Many of publications are in support of replacing the supine standard treatment by the prone position for whole-breast irradiation, particularly in patients with large breasts (Fig. 6). Comparing the prone and supine treatment positions in 400 patients, Formenti et al.[26] evaluated the infield volumes of the heart receiving the full dose as a surrogate for normal tissue exposure. They characterized a considerable anatomical variability of the volume range but were also able to display a significantly lower mean dose to the heart in the prone position.

DIBH

Nowadays, the DIBH is progressively used more or less routinely. In deep inspiration, the heart sinks down and the interval to the chest wall increases. DIBH, accomplished by having the patient take and hold a deep inspiration during CT simulation and during treatment every day, has been shown to remarkably decrease heart dose. It has been proposed that the maximum heart distance (e.g., the maximal distance between anterior cardiac contour and posterior tangential field edges) is a reliable predictor of the MHD in the left-tangential breast or chest wall irradiation (Fig. 7). Voluntary breath-hold does not require any additional equipment.[27]

Typically, voluntary breath-hold is not considered an entirely "uncontrolled" technique. To monitor

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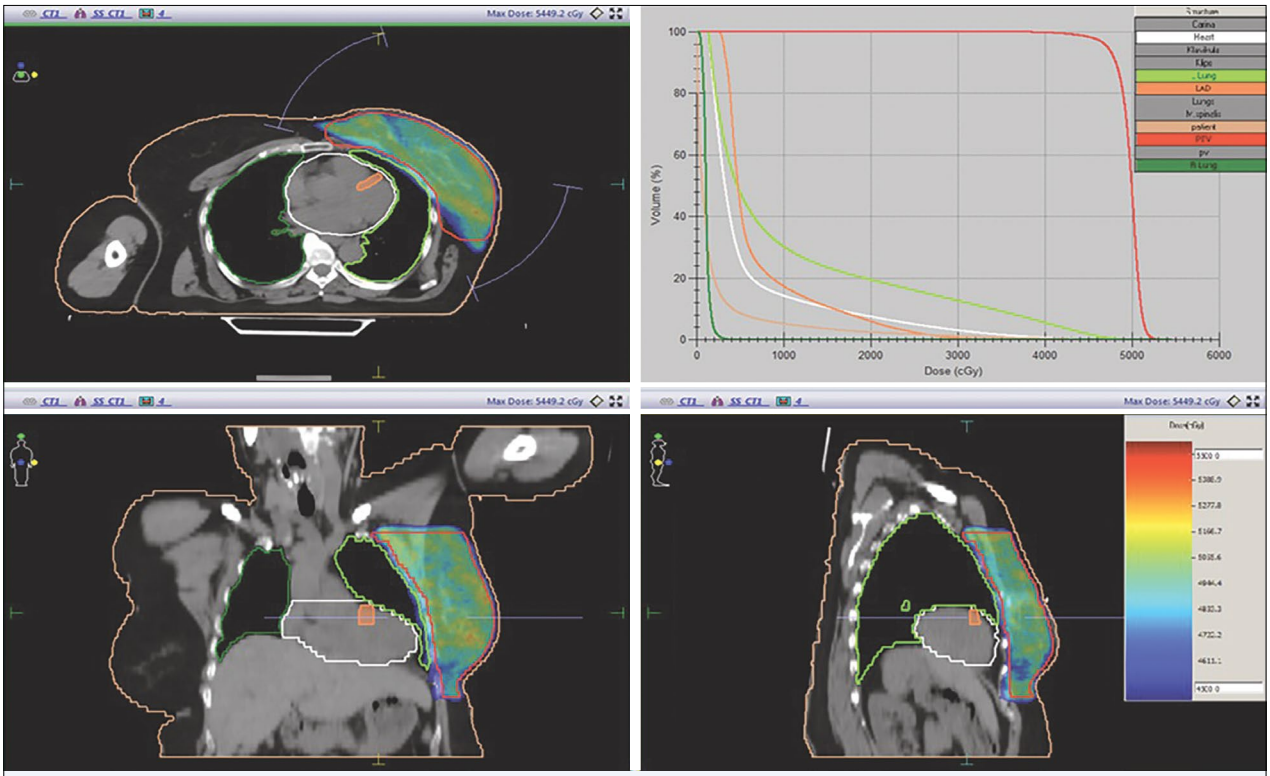

Fig. 5. Example of tangential VMAT technique for left-sided breast cancer.

breath-hold, the distance moved by the anterior and lateral skin marks away from room lasers and additional light field verification can be used.[27] When we use the DIBH technique, we were able to reduce heart doses by 50%. If the patient can get deep inspiration, we prefer this technique in our clinic.

DIBH method can also be performed with computer-controlled breath-hold systems and/or surface guidance techniques. Respiratory volume-based methods measure the inspiratory volume with a spirometer.[27] Patients and staff preferred "voluntary breath-hold" to "computer-controlled breath-hold" because of faster workflow, lower cost, and easier implementation.[28]

Real-time surface monitoring with the systems without markers has been shown to ensure accurate interfraction and intrafraction repositioning. This kind of systems project visible light onto the patient and detect surface of the patient and surface movements caused by breathing. Alderliesten et al. evaluated the accuracy of a 3D surface imaging system compared with CBCT for the guidance of DIBH-RT of left-sided breast cancer and found a good correlation between setup errors detected by both methods.[27,29]

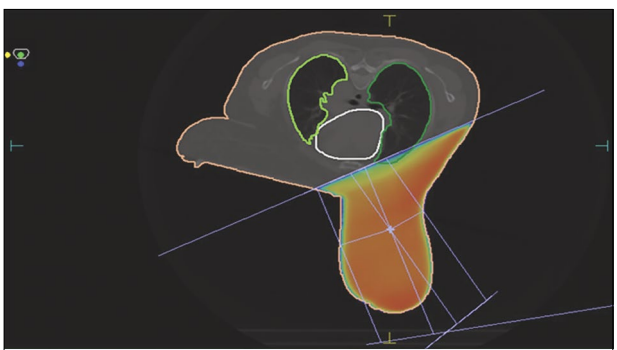

Fig. 6. Examples of prone breast external beam plan.

Fractionation

Both of heart and lung parenchyma have relatively low α/β ratio. That's why, about the accelerated hypofractionated RT, there is an apprehension about the cardiac and pulmonary toxicity. The START trials which included patients treated both by mastectomy and breast-conserving surgery showed no compromise in local control or cosmesis from hypofractionation, some evidence of less late breast toxicity and no increase in cardiotoxicity in the shorter regimen.[30,31] Appelt et al.[32] estimated the fraction size-corrected

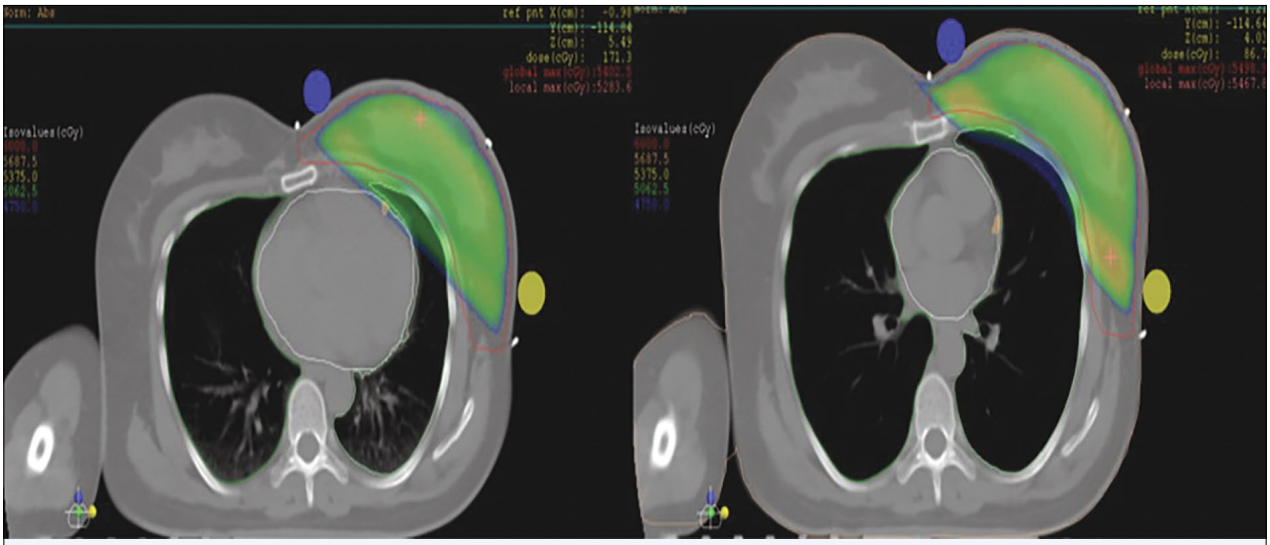

Fig. 7. Transverse dose distribution curves for the deep inspiration breath-hold (DIBH) technique in a representative patient. (a and b) showed the dosage distribution for free-breathing and DIBH, respectively.

dose to the heart for hypofractionation regimens based on the linear-quadratic model. The authors stated that for $\alpha/\beta \geq 1.5$ Gy, the hypofractionation regimens using 40 Gy (2.67 Gy daily), 42.5 Gy (2.65 Gy daily), and 39 Gy (3 Gy daily) result in lower equivalent doses to the heart than the normal fractionation regime (50 Gy/2 Gy). However, there are still concerns about irradiating the breast or chest wall together with lymphatic regions (supra, axilla, and mammaria interna regions) with a hypfractionated scheme and this practice is not routinely applied.

Conclusion

Radiation-induced cardiac toxicity is a late side effect. When a patient with left-sided breast cancer receives radiation therapy, the risk of cardiotoxicity is shown to increase at 5 years after irradiation and continues for at least 20 years. Especially, patients have pre-existing cardiovascular disease, diabetes mellitus, dyslipidemia, arterial hypertension, lifestyle factor (tobacco smoking, alcohol, physical inactivity, and poor nutrition), physicians have to be careful about cardiotoxicity. Hence, RT-induced cardiotoxicity should be minimized using modern RT procedures, as well as considering the estimated comorbid diseases. Radiation oncologists and cardiology specialists should provide closely cooperating regular and long-term follow-up. This will provide the improvement of patient outcomes.

Peer-review: Externally peer-reviewed.

Conflict of Interest: The authors declare that they have no conflict of interest.

Financial Support: The authors declared that this study has received no financial support.

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