This is a provisional PDF only. Copyedited and fully formatted version will be made available soon.

REPORTS OF PRACTICAL
ONCOLOGY AND
RADIOTHERAPY

Comparison of helical and TomoDirect techniques with simultaneous integrated boost in early breast cancer patients

Authors: Cem Onal, Recep Bozca, Ezgi Oymak, Ozan Cem Guler

Comparison of helical and TomoDirect techniques with simultaneous integrated boost in early breast cancer patients

Short title: Tomotherapy in breast cancer radiotherapy

Cem Onal(0000-0002-2742-9021)[1–3] Recep Bozca[2], Ezgi Oymak[1], Ozan Cem Guler[2]

[1]Division of Radiation Oncology, Iskenderun Gelisim Hospital, Hatay, Türkiye

[2]Department of Radiation Oncology, Baskent University Faculty of Medicine Adana Dr Turgut Noyan Research and Treatment Center, Adana, Türkiye

[3]Department of Radiation Oncology, Baskent University Faculty of Medicine, Ankara, Türkiye

Correspondence to: Cem Onal, MD, Department of Radiation Oncology, Faculty of Medicine, Baskent University, Adana Dr. Turgut Noyan Research and Treatment Center, 01120 Adana, *Türkiye,* tel: +90-322-3444444/1304, fax: +90-322-3444445; e-mail: hcemonal@hotmail.com

ABSTRACT

Background: The aim of the study was to perform dosimetric comparisons of helical (H) and TomoDirect (TD) plans for whole-breast irradiation (WBI) with simultaneous integrated boost (SIB) in early-stage breast cancer patients undergoing breast conserving surgery.

Materials and methods: Fifty patients, 25 with left-side and 25 with right-side tumors, were determined for a treatment planning system for a total dose of 50.4Gy in 1.8Gy per fraction to WBI, with a SIB of 2.3Gy per fraction delivered to the tumor bed. The planning target volume (PTV) doses and the conformity (CI) and homogeneity indices (HI) for PTV_{breast} and PTV_{boost}, as well as organ-at-risk (OAR) doses and treatment times, were compared between the H and TD plans.

Results: All plans met the PTV coverage criteria for the H plan, except for mean V107 of PTV_{breast} for TD plan. The H plan yielded better homogeneity and conformity of dose distribution compared to the TD plan. The ipsilateral mean lung doses were not significantly

different between the two plans. The TD plans is advantageous for mean doses to the heart, contralateral breast and lung, spinal cord, and esophagus than the H plans. In both the H and TD plans, the right-sided breast patients had lower heart dose parameters than the left-sided breast patients. The TD plan is superior to the H plan in sparing the contralateral breast and lung by decreasing low-dose volumes.

Conclusions: While the OAR dose advantages of TD are appealing, shorter treatment times or improved dose homogeneity and conformity for target volume may be advantageous for H plan.

Key words: breast cancer; radiotherapy; helical tomotherapy; tomodirect; dosimetry

Introduction

Breast cancer (BC) is the most frequently diagnosed cancer and the leading cause of cancer death among the female population [1]. Adjuvant radiotherapy (RT) after breast conserving surgery (BCS) is accepted as standard-of-care [2]. Furthermore, boost dose to tumor bed increase the local control rates [3]. However, due to the convexity of the breast and the higher doses delivered to the tumor bed, homogeneous dose distribution is technically difficult to achieve. Because dose homogeneity influences acute and chronic toxicities, the goal of developing new irradiation techniques is to achieve homogeneous dose distribution, increase local control, and improve cosmetic outcomes for whole-breast irradiation (WBI) after BCS [4].

Modern RT techniques, including field-in-field irradiation, intensity modulated RT (IMRT), volumetric arc therapy (VMAT), and helical tomotherapy (HT), improve target volume dose distribution and reduce dose exposure to organs at risk (OARs) [5–10]. Additionally, modern irradiation techniques enable the boost to be delivered concurrently with WBI, a technique known as a simultaneous-integrated boost (SIB). The benefit of the SIB technique is its ability to increase the dose in the area of highest risk without extending the treatment duration. Previous studies have demonstrated the dosimetric feasibility of the SIB technique in BC patients [11, 12]. Furthermore, we recently demonstrated that the SIB technique improved target volume dose distribution in both helical tomotherapy and VMAT plans, as well as OAR doses in HT [5].

Two modes of breast irradiation with HT have increased in popularity: helical mode (H) and TomoDirect (TD). Although previous studies have demonstrated the clinical outcomes of WBI with SIB using helical tomotherapy in the H [13] and TD modes [14–16], the dosimetric comparison of these two techniques is not readily available. Therefore, we performed dosimetric comparisons of HT using the H and TD modes with the SIB technique for WBI in early-stage BC patients who had undergone BCS.

Materials and methods

Fifty patients, 25 with left-side tumors and 25 with right-side tumors, who were previously treated with RT following BCS for early BC were enrolled in this study.

Target volumes

All patients had undergone a 2.5-mm slice thickness, free-breathing computed tomography (CT) scan in the supine position on a 10°–15° angle breast-tilting board with both arms elevated for treatment planning purposes, as previously described [17]. All target volumes and OARs were delineated according to the Radiation Oncology Group (RTOG) recommendations and the European Society for Radiotherapy and Oncology (ESTRO) guidelines [18, 19]. The clinical target volume (CTV) included whole breast tissue. The tumor bed was delineated according to preoperative images, operative notes, and scar tissue, and encompassed metal clips placed during BCS or the post-operative residual seroma. The planning target volume for the entire breast (PTV_{breast}) was created by a 5-mm expansion of CTV in all directions around the tumor bed, excluding a 2-mm strip of skin. The lung and heart were also excluded from the PTV. The PTV_{boost} was created by a 5-mm expansion in all directions of the delineated tumor bed.

The delineated OARs included the ipsilateral lung, the contralateral breast and lung, heart, spinal cord, and liver. The heart was delineated from the pulmonary trunk to its most distant extent near the diaphragm, excluding pericardial fat tissue.

Treatment planning

For each patient, two different SIB plans were generated using the same CT images and volumes delineated using a Hi-Art Tomotherapy system (TomoTherapy Inc., Madison,

USA), a helical fan-beam IMRT system equipped with inverse planning software and a 6-MV photon beam. A total dose of 50.4 Gy in 1.8 Gy per fraction was prescribed to the WBI, with an integrated boost of 2.3 Gy per fraction (for a total dose of 64.4 Gy in 28 fractions) delivered to the tumor bed.

In H mode, the target volume is irradiated using thousands of narrow beamlets that are individually optimized for the target via continuous gantry rotations around the patient. The TD, on the other hand, is a non-rotational treatment based on coplanar static beams, with the couch moving at a constant speed through a fixed binary multileaf collimator (MLC) that modulates the beam. After the patient has been treated at one gantry angle, the gantry is rotated to a different angle, and the patient is again passed through the bore for the delivery of subsequent fields [20].

The H plans were made for the TomoEdge Dynamic Jaws system of the TomoHDA series. A collimator aperture of 2.5 cm, pitch of 0.25, and modulation factor of 5.0 were used. Dose calculations were performed using the fine-dose calculation grid (3 mm in the craniocaudal direction over a 256×256 matrix in the axial plane from the original CT scan). The contralateral breast, hemibody, and posterior portion of the ipsilateral side of the body were blocked during planning in order to restrict beamlets passing through the virtual contour on CT image in dose optimization, reducing the dose to OARs. For the TD plan, the jaw width was 5 cm, the pitch was 0.25, and the modulation factor was 5.0. Breast and tumor bed irradiation was performed using six IMRT beams. Another beam in the anterior oblique direction was used to improve the homogeneity of the PTV_{boost} dose.

Dose constraints

The plan was optimized to ensure that 95% of PTV_{breast} and PTV_{boost} received at least 95% of the prescribed dose. The volume receiving more than 107% of the prescribed dose should be less than 1%. The dose constraints prescribed for OARs were: (a) < 10% and < 30% of the heart volume may receive > 25 Gy and > 5 Gy, respectively; (b) < 5% and < 20% of the ipsilateral lung may receive > 50 Gy and > 15 Gy, respectively, and the mean dose should be less than 12 Gy; and (c) the mean doses and < 5% of the contralateral breast and lung should be limited to < 3 Gy and < 5 Gy, respectively. The maximum spinal cord dose must be less than 30 Gy. Same dose constraints were used for left and right sided targets.

The volume of target volumes receiving 95% (V95) and 107% (V107) of the prescribed dose was calculated. Target homogeneity (HI) and conformity indices (CI) were

compared. The HI was calculated as HI = [(D2–D98)/D50], where the D2 and D98 (minimal doses to 2% and 98% of the target volumes, respectively) were used as surrogates for maximum and minimum doses. A greater HI value indicates poorer uniformity of the dose distribution. The CI was calculated as: $(VT_{ref}/VT) \times (VT_{ref}/V_{ref})$, where VT_{ref} represents the target volume covered by isodose, VT represents the target volume, and V_{ref} represents the total volume covered by 95% of isodose. The value of CI ranged from 0–1, with a value closer to 1 indicating better conformity of the dose to the PTV.

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics 22 (IBM Corp., Armonk, NY, USA). Descriptive analysis was performed by calculating the means and standard deviations, ranges, and medians. Dn and Vn were calculated for the PTV and OARs. Vn represents the percentage of organ volume receiving $\geq n$Gy and Dn represents the percentage of organ receiving n% of the prescribed dose. The target volume doses, CI, and HI for PTV_{breast} and PTV_{boost} were compared between the H and TD plans. Additionally, the OAR doses and treatment times were compared between the two plans. A further comparison was made between patients with large and small breasts, as well as those with large and small tumors. The breast and tumor volume groups were defined based on the median PTV_{breast} and PTV_{boost}. The results are presented as mean ± standard deviation, unless otherwise specified. A one-way analysis of variance (ANOVA) test and Wilcoxon's matched-pairs test were executed to determine the significance of differences between doses in the H and TD plans. All p values reported are two-sided, and $p < 0.05$ was considered statistically significant.

Results

Target volume doses

The mean breast and tumor bed volumes were 1064.8 ± 443.1 cm³ and 24.7 ± 21.4 cm³, respectively. The mean PTV_{breast} and PTV_{boost} were 1356.1 ± 497.0 cm³ and 65.5 ± 34.4 cm³, respectively. Figure 1 shows axial sections depicting the PTV_{breast} and PTV_{boost} dose distributions for the H and TD plans of representative patients, respectively. The dosimetric parameters for PTV_{breast} and PTV_{boost} are summarized in Table 1. All plans met the criteria for PTV_{breast} coverage for the H plan, but the mean V107 of PTV_{breast} for the TD plan was higher than 1%. Only two TD plans met the acceptable PTV_{breast} V107% of less than 1%. In the H

plans, the HI was significantly lower and the CI was significantly higher, which indicates better homogeneity and conformity of dose distribution for PTV$_{breast}$ compared to TD plans.

All plans met the criteria for PTV$_{boost}$ coverage in both plans. The D2, D98, and mean doses of PTV$_{boost}$ were significantly lower in the H plan than in the TD plan. Similarly, when compared to the TD plan, the H plan achieved better dose conformity and homogeneity for PTV$_{boost}$.

Organs at risk doses

The average dosimetric data on OAR for the H and TD techniques are presented in Table 2. All plans complied with OAR dose constraints. There was no significant difference in the mean lung doses for the ipsilateral lung between the two plans. Additionally, the heart (Fig. 2A), spinal cord and esophagus doses were significantly reduced in the TD plans compared to H plans.

The mean heart doses for patients with right-side tumors were significantly lower compared to left-side tumors in both the H (4.58 ± 0.73 Gy vs. 1.67 ± 0.93 Gy; $p < 0.001$) and TD plans (5.83 ± 0.83 Gy vs. 4.53 ± 1.33 Gy; $p < 0.001$). Similarly, all parameters of heart doses were significantly better in right-side breasts compared to left-side breasts in both the H and TD plans, except for V30Gy in the H plan, which was higher in the left-side breast than in the right-side breast (Fig. 2B–C).

The contralateral breast and lung mean doses and V5Gy values were significantly higher in the H plan than in the TD plan. As demonstrated in Figure 3, the low-dose volumes in the contralateral and breast were lower in the TD plan compared to the H plan.

The median treatment time in the H and TD plans was 6.5 min (range: 4.9–8.8 min) and 8.8 min (range: 6.8–11.0 min) ($p < 0.001$), respectively. Furthermore, the median planning time for H plan was 83 min (range: 67–101 min), and it was 43 min (range: 30–60 min) for TD plan, with statistically significant difference ($p < 0.001$).

Comparison according to breast and tumor volumes

Target volume doses did not differ significantly between patients with large breasts (> 1350 cc) and small breasts (≤ 1350 cc). However, CI of PTV$_{breast}$ was significantly higher in large breast patients in both the H plan (0.81 ± 0.04 vs. 0.78 ± 0.05; p = 0.04) and the TD plan (0.74 ± 0.05 vs. 0.70 ± 0.05; p = 0.004) than in small breast patients. OAR dosimetric parameters did not differ significantly based on breast volume. Patients with large breasts had significantly longer treatment times in the H plan (7.1 ± 0.7 min vs. 6.0 ± 0.8 min; p < 0.001) and TD plan (9.2 ± 1.0 min vs. 8.3 ± 0.8 min; p = 0.002) than patients with small breasts.

The D2 of PTV$_{breast}$ calculated in the TD plan was significantly higher in patients with large tumors (> 65 cc) than in patients with small tumors (≤ 65 cc) (52.5 ± 0.5 Gy vs. 51.9 ± 0.6 Gy; p = 0.007). PTV$_{breast}$ and PTV$_{boost}$ mean doses were also significantly higher in the TD plan for patients with large tumors compared to those with small tumors. Furthermore, in both the H and TD plans, the CIs for patients with larger tumors were significantly higher than those for patients with smaller tumors (0.59 ± 0.05 vs. 0.52 ± 0.10; p = 0.006). However, treatment times based on tumor volume did not differ significantly between the H and TD plans.

Regardless of breast volume or tumor size, target volume doses were significantly higher in the H plan compared to the TD plan. In all breast and tumor volume groups, lung V5 was significantly higher in the H plan than in the TD plan, whereas lung V30 was significantly lower in the TD plan than in the H plan, except for patients with smaller tumors, where no significant difference in lung V30 value was observed. Similarly, regardless of breast and tumor volumes, heart low dose volume (V5) and mean heart doses were significantly higher in the H plan than the TD plan, and heart high dose volume (V30) was significantly lower in the H plan than the TD plan. In all breast and tumor volume groups, the TD plan is superior to the H plan in terms of sparing contralateral breast and lung.

Discussion

Our findings indicate that the H plan outperformed the TD plan in terms of target volume coverage, regardless of breast size and tumor volume. Except for the V30Gy value, which was lower in the H plan than in the TD plan, the ipsilateral lung dose volume parameters were significantly better in the TD plan. Despite the fact that both plans met all OAR dose constraints, the doses for the heart, spinal cord, and esophagus in the TD plan were

significantly lower than in the H plan. Furthermore, the TD plan performed well in heart doses for both the right and left breasts. In terms of low-dose volumes of the contralateral breast and lung, the TD plan outperformed the H plan, which favors the prevention of secondary malignancy risk. Be that as it may, the total treatment time was significantly longer for the TD technique than for the H technique. Nonetheless, TD plan required less time for planning than H plan did.

The tumor-bed boost can be delivered either sequentially after WBI or with the SIB technique. Granting that previous studies have demonstrated the dosimetric advantages of SIB over the application of the sequential boost technique after BCS, there is no standard technique for SIB in WBI after BCS. The different RT techniques, treatment planning systems, and dose constraints for OARs used in these studies caused conflicting results [5, 11, 21–24]. Maier et al. [23] demonstrated that best target coverage and homogeneity was observed with VMAT, and lowest doses to the contralateral lung and breast were observed with tangential arc VMAT. Hijal et al. [24] found that both HT and 3DCRT provided adequate target volume doses with lower heart doses, and HT decreased ipsilateral lung doses. Michalski et al. [11] found that HT offered superior target-volume doses and lower doses to ipsilateral lung and heart, compared to 3D-CRT and IMRT. Recently, in a dosimetric study comparing HT and VMAT for WBI with SIB following BCS, we found that HT plan had superior target-volume coverage and delivered lower doses to the contralateral breast and lung than VMAT plan [5]. Furthermore, HT has shown superiority with absence of higher doses in standard boost plan, and significantly lower HI compared to VMAT in SB and SIB plans, which potentially reduces the risk of breast fibrosis.

Few clinical studies have yet to evaluate the feasibility of the SIB technique in patients treated with HT [13, 15, 25, 26], and with other modern RT techniques [27–29]. In a randomized trial comparing conventional RT and hypofractionated RT using HT with the SIB technique, van Parijs et al. displayed the feasibility and safety of the HT with SIB technique compared to conventional RT [26]. Despite the fact that dosimetric and clinical studies indicated that HT with the SIB technique is feasible, there is no direct comparison of two HT treatment techniques — the H and TD plans. We demonstrated that the H technique outperformed TD in terms of target volume dose distribution and dose homogeneity, resulting in less toxicity and improved cosmesis. Furthermore, no significant difference in target volume doses was found between patients with small and large breast volumes, as well as

patients with small and large tumors. However, regardless of breast or tumor volume, the H plan outperformed the TD plan in terms of target volume doses.

Dose limitations and low dose volumes, as established by clinical 'Quantitative Analyses of Normal Tissue Effects' (QUANTEC), must be considered when evaluating radiation exposure to OARs [30]. According to the literature, the TD technique was found to be superior in terms of preserving surrounding organs and, in particular, regulating the low dose spread to contralateral breast and lung, which may potentially reduce the risk of secondary malignancy [6, 7, 31]. Low-dose spread, represented by lung V5Gy, has been acknowledged as an important factor in predicting lung toxicity since the development of IMRT, alongside traditional dosimetric factors, such as V20Gy and mean lung doses [32, 33]. In BC patients receiving postoperative RT, including chest wall and lymphatics, Takano et al. found that ipsilateral lung V5Gy was significantly lower in the TD plan compared to the H plan ($22.49 \pm 2.69\%$ vs. $94.59 \pm 4.26\%$; $p = 0.001$) [7]. Similarly, Dicuonzo et al. demonstrated that in BC patients receiving hypofractionated post-mastectomy RT, V4Gy was significantly lower in the TD plan compared to the H plan (37.4% vs. 96.9%; $p < 0.001$) [31]. Nevertheless, in the current study, we found that the ipsilateral lung V5Gy value calculated for the H plan ($41.66 \pm 4.82\%$) was lower than those reported in previous studies [7, 31], which might be attributable to the absence of nodal irradiation in this study. In the current study, TD significantly decreased V5Gy relative to the H plan, exhibited a marginally significant increase in V20Gy, with no significant difference in mean lung doses, and showed a significant increase in lung V30Gy in entire group, as well as in patients with small and large breast volumes and small and big tumors, for which QUANTEC made no recommendations.

Limiting the cardiac radiation dose is another crucial factor, and improvements in treatment planning and RT administration have significantly decreased the incidence of cardiac toxicity [34, 35]. Darby et al. reported a mean cardiac dose of 4.9 Gy overall, and a 1 Gy increase was associated with a 7.4% relative increase in cardiac events, with no apparent threshold below which there is no risk [2, 34]. Another study investigated the association between the relative volumes of irradiated heart or pericardium and late cardiac toxicity, and V25 Gy < 10% was associated with 1% mortality over 15 years following RT [36]. In the current study, TD significantly reduced the mean heart dose and V30Gy when compared to the H plan. The heart dose levels for both plans stayed within the QUANTEC guidelines in our study, and for both plans, the V30 Gy of the heart was less than the recommended limit of

5%. Although recent publications have addressed the evaluation of doses to the coronary artery and the left ventricle, which is an important topic, the dose constraints for the coronary artery and the left ventricle were not assigned during this planning and optimization process, and more research is needed to determine whether H or TD is better for the heart [37, 38]. Further studies evaluating the long-term cardiac and pulmonary effects of VMAT and HT technologies deployed with the SIB technique are warranted.

Another important aspect of modern irradiation techniques, particularly in helical treatment, is the high contralateral breast and lung doses, which raise concerns about secondary malignancies, especially in patients with early-stage BC. According to Santos et al., the lungs and contralateral breast have a high life-related risk of developing a second primary cancer [39]. Breast tissue had a much higher estimated relative risk of secondary primary cancer than other organs [40, 41], and Stovall et al. found that receiving a maximum dose of more than 1 Gy to breast tissue increased the risk of secondary breast cancer in the contralateral breast in women younger than 40 years old [42]. These findings suggest that low-dose spread should be avoided as much as possible. Although both techniques had very low V5 Gy values and mean doses of breast and lung in this study, TD outperformed H in terms of sparing the contralateral lung and breast. Therefore, referrals to TD should be made for younger patients, those with a family history, and those with clear or suspicious BRCA 1/2 mutations.

This study has some limitations. First, our study evaluates the dosimetric parameters of the SIB technique with H and TD plans; we did not analyze the radiation-associated late toxicities and long-term cosmetic outcomes of these techniques. Second, we did not assess the inaccuracies in the setup of these complicated technologies. To improve accuracy in these complex techniques, strict immobilization and image guidance with daily cone beam CT or breath-hold techniques are required. We only evaluated the dose distribution of H and TD plans for patients with early-stage cancer undergoing BCS. Dosimetric evaluation of more complex plans, such as those involving irradiation of the lymphatic field or chest wall, may be the subject of additional research.

Conclusions

In light of our dosimetric findings, as well as the reviewed literature, it is evident that there is no perfect plan for early BC patients receiving postoperative RT after BCS. Individually, the H plan appeals because of its target coverage, treatment duration, and smaller high dose

volumes (30 Gy) to the ipsilateral lung and heart, which is critical for preventing long-term cardiac and pulmonary effects of radiation. Nonetheless, the TD plan outperformed the H plan in terms of sparing the contralateral lung and breast and delivering a lower dose to the heart and ipsilateral lung, which favors secondary malignancy prevention, especially in younger patients with a family history.

Conflict of interest

The authors declare no conflicts of interest.

Funding

None declared

Data sharing statement

The authors confirm that the data supporting the findings of this study are available within the article and its supplementary materials.

References

1. Ferlay J, Colombet M, Soerjomataram I, et al. Cancer statistics for the year 2020: An overview. Int J Cancer. 2021 [Epub ahead of print], doi: 10.1002/ijc.33588, indexed in Pubmed: 33818764.

2. Darby S, McGale P, Correa C, et al. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). 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 randomised trials. Lancet. 2011; 378(9804): 1707–1716, doi: 10.1016/S0140-6736(11)61629-2, indexed in Pubmed: 22019144.

3. Poortmans PM, Collette S, Kirkove C, et al. EORTC Radiation Oncology and Breast Cancer Groups, European Organisation for Research and Treatment of Cancer Radiation Oncology and Breast Cancer Groups. Whole-breast irradiation with or without a boost for patients treated with breast-conserving surgery for early breast cancer: 20-year follow-up of a randomised phase 3 trial. Lancet Oncol. 2015; 16(1): 47–56, doi: 10.1016/S1470-2045(14)71156-8, indexed in Pubmed: 25500422.

4. Mak KS, Chen YH, Catalano PJ, et al. Dosimetric Inhomogeneity Predicts for Long-Term Breast Pain After Breast-Conserving Therapy. Int J Radiat Oncol Biol Phys. 2015; 93(5): 1087–1095, doi: 10.1016/j.ijrobp.2014.05.021, indexed in Pubmed: 25084611.

5. Onal C, Efe E, Guler OC, et al. Dosimetric Comparison of Sequential Simultaneous-integrated Boost in Early-stage Breast Cancer Patients Treated With Breast-conserving Surgery. In Vivo. 2019; 33(6): 2181–2189, doi: 10.21873/invivo.11720, indexed in Pubmed: 31662554.

6. Nobnop W, Phakoetsuk P, Chitapanarux I, et al. Dosimetric comparison of TomoDirect, helical tomotherapy, and volumetric modulated arc therapy for postmastectomy treatment. J Appl Clin Med Phys. 2020; 21(9): 155–162, doi: 10.1002/acm2.12989, indexed in Pubmed: 32715634.

7. Takano S, Omura M, Suzuki R, et al. Intensity-modulated radiation therapy using TomoDirect for postoperative radiation of left-sided breast cancer including lymph node area: comparison with TomoHelical and three-dimensional conformal radiation therapy. J Radiat Res. 2019; 60(5): 694–704, doi: 10.1093/jrr/rrz052, indexed in Pubmed: 31365118.

8. İnan GA, Aral IP, Arslan A, et al. Helical tomotherapy experience in breast cancer adjuvant radiotherapy and acute toxicity results. Rep Pract Oncol Radiother. 2022; 27(6): 973–981, doi: 10.5603/RPOR.a2022.0121, indexed in Pubmed: 36632291.

9. Matsumoto Y, Kunieda E, Futakami N, et al. Examination of the dose distribution of volumetric modulated arc radiotherapy using a high-definition multi-leaf collimator for breast cancer patients with irradiated regional lymph nodes. Rep Pract Oncol Radiother. 2022; 27(4): 634–643, doi: 10.5603/RPOR.a2022.0081, indexed in Pubmed: 36196412.

10. Goyal S, Tiwari R, Narayanan GS, et al. A comparative study evaluating the dose volume parameters in 3D conformal radiation of left sided whole breast irradiation including regional lymphnodes - a need of resource constrained countries. Rep Pract Oncol Radiother. 2021; 26(6): 1003–1009, doi: 10.5603/RPOR.a2021.0125, indexed in Pubmed: 34992874.

11. Michalski A, Atyeo J, Cox J, et al. A dosimetric comparison of 3D-CRT, IMRT, and static tomotherapy with an SIB for large and small breast volumes. Med Dosim. 2014; 39(2): 163–168, doi: 10.1016/j.meddos.2013.12.003, indexed in Pubmed: 24393498.

12. Wu S, Lai Y, He Z, et al. Dosimetric comparison of the simultaneous integrated boost in whole-breast irradiation after breast-conserving surgery: IMRT, IMRT plus an electron boost and VMAT. PLoS One. 2015; 10(3): e0120811, doi: 10.1371/journal.pone.0120811, indexed in Pubmed: 25781183.

13. Wojcieszynski AP, Olson AK, Rong Yi, et al. Acute Toxicity From Breast Cancer Radiation Using Helical Tomotherapy With a Simultaneous Integrated Boost. Technol Cancer Res Treat. 2016; 15(2): 257–265, doi: 10.1177/1533034615574387, indexed in Pubmed: 25780060.

14. Franco P, Zeverino M, Migliaccio F, et al. Intensity-modulated and hypofractionated simultaneous integrated boost adjuvant breast radiation employing statics ports of tomotherapy (TomoDirect): a prospective phase II trial. J Cancer Res Clin Oncol. 2014; 140(1): 167–177, doi: 10.1007/s00432-013-1560-8, indexed in Pubmed: 24292425.

15. Lee HC, Kim SH, Suh YJ, et al. A prospective cohort study on postoperative radiotherapy with TomoDirect using simultaneous integrated boost technique in early breast cancer. Radiat Oncol. 2014; 9: 244, doi: 10.1186/s13014-014-0244-0, indexed in Pubmed: 25410791.

16. Zwicker F, Hoefel S, Kirchner C, et al. Hypofractionated Radiotherapy With Simultaneous-integrated Boost After Breast-conserving Surgery Compared to Standard Boost-applications Using Helical Tomotherapy With TomoEdge. Anticancer Res. 2021; 41(4): 1909–1920, doi: 10.21873/anticanres.14957, indexed in Pubmed: 33813396.

17. Onal C, Sonmez A, Arslan G, et al. Dosimetric comparison of the field-in-field technique and tangential wedged beams for breast irradiation. Jpn J Radiol. 2012; 30(3): 218–226, doi: 10.1007/s11604-011-0034-7, indexed in Pubmed: 22183829.

18. Gentile MS, Usman AA, Neuschler EI, et al. Contouring Guidelines for the Axillary Lymph Nodes for the Delivery of Radiation Therapy in Breast Cancer: Evaluation of the RTOG

Breast Cancer Atlas. Int J Radiat Oncol Biol Phys. 2015; 93(2): 257–265, doi: 10.1016/j.ijrobp.2015.07.002, indexed in Pubmed: 26383674.
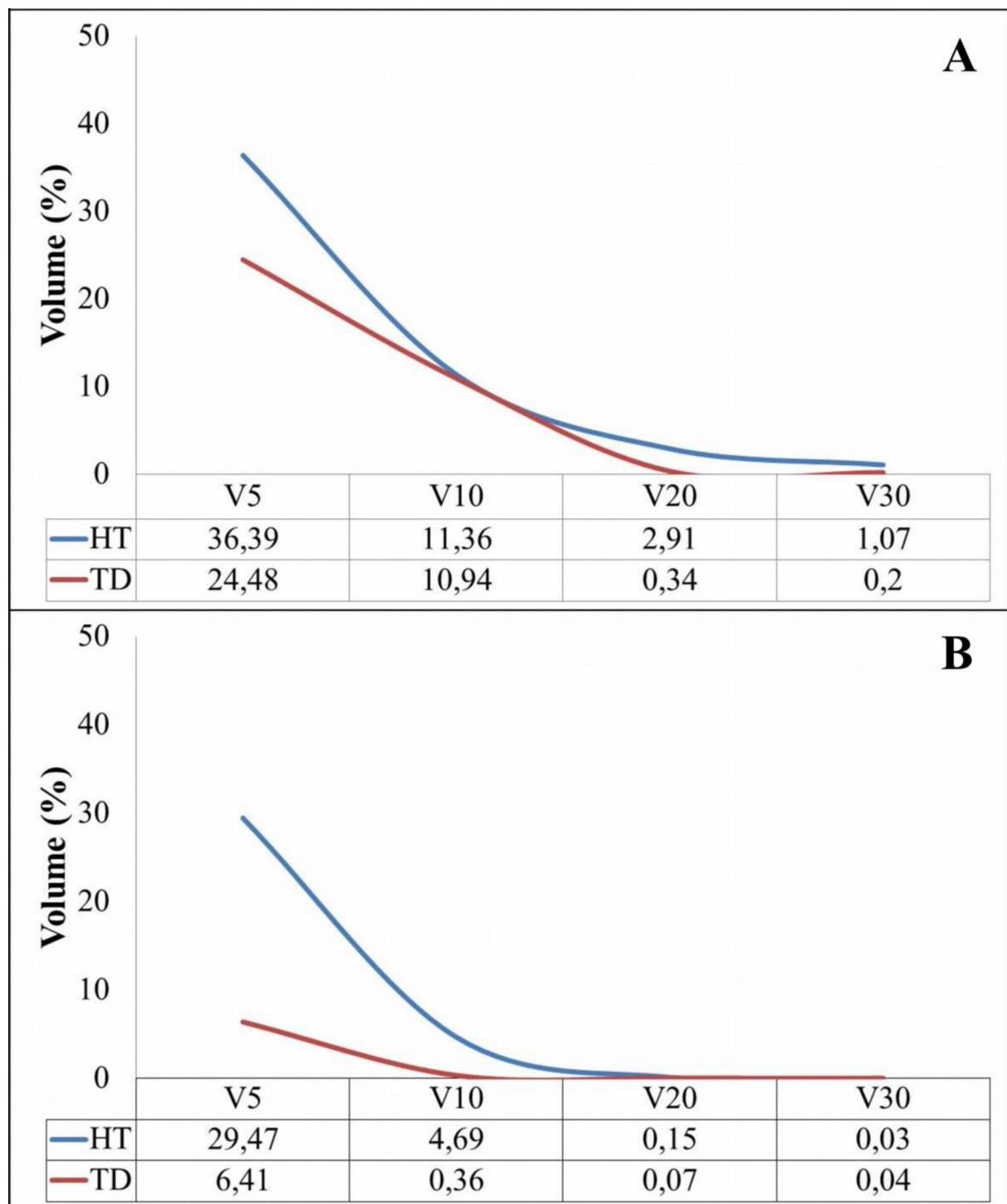
19. Offersen BV, Boersma LJ, Kirkove C, et al. ESTRO consensus guideline on target volume delineation for elective radiation therapy of early stage breast cancer. Radiother Oncol. 2015; 114(1): 3–10, doi: 10.1016/j.radonc.2014.11.030, indexed in Pubmed: 25630428.

20. Catuzzo P, Zenone F, Aimonetto S, et al. Technical note: patient-specific quality assurance methods for TomoDirect(TM) whole breast treatment delivery. Med Phys. 2012; 39(7): 4073–4078, doi: 10.1118/1.4722967, indexed in Pubmed: 22830740.

21. Alford SL, Prassas GN, Vogelesang CR, et al. Adjuvant breast radiotherapy using a simultaneous integrated boost: clinical and dosimetric perspectives. J Med Imaging Radiat Oncol. 2013; 57(2): 222–229, doi: 10.1111/j.1754-9485.2012.02473.x, indexed in Pubmed: 23551785.

22. Van Parijs H, Reynders T, Heuninckx K, et al. Breast conserving treatment for breast cancer: dosimetric comparison of different non-invasive techniques for additional boost delivery. Radiat Oncol. 2014; 9: 36, doi: 10.1186/1748-717X-9-36, indexed in Pubmed: 24467916.

23. Maier J, Knott B, Maerz M, et al. Simultaneous integrated boost (SIB) radiation therapy of right sided breast cancer with and without flattening filter - A treatment planning study. Radiat Oncol. 2016; 11(1): 111, doi: 10.1186/s13014-016-0687-6, indexed in Pubmed: 27577561.

24. Hijal T, Fournier-Bidoz N, Castro-Pena P, et al. Simultaneous integrated boost in breast conserving treatment of breast cancer: a dosimetric comparison of helical tomotherapy and three-dimensional conformal radiotherapy. Radiother Oncol. 2010; 94(3): 300–306, doi: 10.1016/j.radonc.2009.12.043, indexed in Pubmed: 20171752.

25. Dicuonzo S, Leonardi MC, Raimondi S, et al. Acute and intermediate toxicity of 3-week radiotherapy with simultaneous integrated boost using TomoDirect: prospective series of 287 early breast cancer patients. Clin Transl Oncol. 2021; 23(7): 1415–1428, doi: 10.1007/s12094-020-02538-w, indexed in Pubmed: 33537865.

26. Van Parijs H, Miedema G, Vinh-Hung V, et al. Short course radiotherapy with simultaneous integrated boost for stage I-II breast cancer, early toxicities of a randomized clinical trial. Radiat Oncol. 2012; 7: 80, doi: 10.1186/1748-717X-7-80, indexed in Pubmed: 22656865.

27. Dellas K, Vonthein R, Zimmer J, et al. ARO Study Group. Hypofractionation with simultaneous integrated boost for early breast cancer: results of the German multicenter phase II trial (ARO-2010-01). Strahlenther Onkol. 2014; 190(7): 646–653, doi: 10.1007/s00066-014-0658-5, indexed in Pubmed: 24737540.

28. De Rose F, Fogliata A, Franceschini D, et al. Hypofractionated volumetric modulated arc therapy in ductal carcinoma in situ: toxicity and cosmetic outcome from a prospective series. Br J Radiol. 2018; 91(1085): 20170634, doi: 10.1259/bjr.20170634, indexed in Pubmed: 29322827.

29. Scorsetti M, Alongi F, Fogliata A, et al. 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. 2012; 7: 145, doi: 10.1186/1748-717X-7-145, indexed in Pubmed: 22929062.

30. Bentzen SM, Constine LS, Deasy JO, et al. Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC): an introduction to the scientific issues. Int J Radiat Oncol Biol Phys. 2010; 76(3 Suppl): S3–S9, doi: 10.1016/j.ijrobp.2009.09.040, indexed in Pubmed: 20171515.

31. Dicuonzo S, Patti F, Luraschi R, et al. Comparing TomoHelical and TomoDirect in postmastectomy hypofractionated radiotherapy after immediate breast reconstruction. Phys Med. 2021; 90: 66–72, doi: 10.1016/j.ejmp.2021.09.007, indexed in Pubmed: 34563833.

32. Allen AM, Czerminska M, Jänne PA, et al. Fatal pneumonitis associated with intensity-modulated radiation therapy for mesothelioma. Int J Radiat Oncol Biol Phys. 2006; 65(3): 640–645, doi: 10.1016/j.ijrobp.2006.03.012, indexed in Pubmed: 16751058.

33. Song CH, Pyo H, Moon SHo, et al. Treatment-related pneumonitis and acute esophagitis in non-small-cell lung cancer patients treated with chemotherapy and helical tomotherapy. Int J Radiat Oncol Biol Phys. 2010; 78(3): 651–658, doi: 10.1016/j.ijrobp.2009.08.068, indexed in Pubmed: 20207499.

34. Darby SC, McGale P, Taylor CW, et al. Long-term mortality from heart disease and lung cancer after radiotherapy for early breast cancer: prospective cohort study of about 300,000 women in US SEER cancer registries. Lancet Oncol. 2005; 6(8): 557–565, doi: 10.1016/S1470-2045(05)70251-5, indexed in Pubmed: 16054566.

35. Taylor CW, McGale P, Povall JM, et al. Estimating cardiac exposure from breast cancer radiotherapy in clinical practice. Int J Radiat Oncol Biol Phys. 2009; 73(4): 1061–1068, doi: 10.1016/j.ijrobp.2008.05.066, indexed in Pubmed: 18973978.

36. Gagliardi G, Constine LS, Moiseenko V, et al. Radiation dose-volume effects in the heart. Int J Radiat Oncol Biol Phys. 2010; 76(3 Suppl): S77–S85, doi: 10.1016/j.ijrobp.2009.04.093, indexed in Pubmed: 20171522.

37. Duma MN, Herr AC, Borm KJ, et al. Tangential Field Radiotherapy for Breast Cancer-The Dose to the Heart and Heart Subvolumes: What Structures Must Be Contoured in Future Clinical Trials? Front Oncol. 2017; 7: 130, doi: 10.3389/fonc.2017.00130, indexed in Pubmed: 28674678.

38. Piroth MD, Baumann R, Budach W, et al. Heart toxicity from breast cancer radiotherapy : Current findings, assessment, and prevention. Strahlenther Onkol. 2019; 195(1): 1–12, doi: 10.1007/s00066-018-1378-z, indexed in Pubmed: 30310926.

39. Santos AMC, Marcu LG, Wong CM, et al. Risk estimation of second primary cancers after breast radiotherapy. Acta Oncol. 2016; 55(11): 1331–1337, doi: 10.1080/0284186X.2016.1185150, indexed in Pubmed: 27379458.

40. Ng J, Shuryak I. Minimizing second cancer risk following radiotherapy: current perspectives. Cancer Manag Res. 2015; 7: 1–11, doi: 10.2147/CMAR.S47220, indexed in Pubmed: 25565886.

41. Ogino I, Seto H, Shigenaga D, et al. Dose to contralateral breast from whole breast irradiation by automated tangential IMRT planning: comparison of flattening-filter and flattening-filter-free modes. Rep Pract Oncol Radiother. 2022; 27(1): 113–120, doi: 10.5603/RPOR.a2022.0006, indexed in Pubmed: 35402036.

42. Stovall M, Smith SA, Langholz BM, et al. Women's Environmental, Cancer, and Radiation Epidemiology Study Collaborative Group. Dose to the contralateral breast from radiotherapy and risk of second primary breast cancer in the WECARE study. Int J Radiat Oncol Biol Phys. 2008; 72(4): 1021–1030, doi: 10.1016/j.ijrobp.2008.02.040, indexed in Pubmed: 18556141.

Figure 1. Dose distribution demonstrating 50% and 90% of prescribed dose for whole-breast in (**A**) helical and (**B**) TomoDirect plans. The 50% isodose volume (blue area), 90% isodose volume (green area) and tumor-bed boost (orange area)
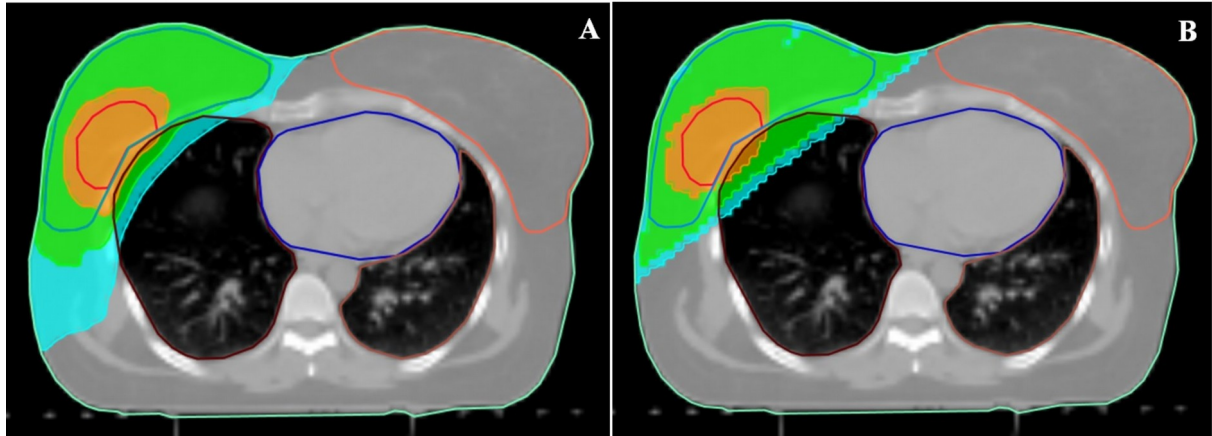
Figure 2. The mean dosimetric indices for heart in (**A**) left-side, and (**B**) right-side breast cancer patients according to the helical plan (blue line) and the TomoDirect plan (red line)

	V5	V10	V20	V30
HT	36,39	11,36	2,91	1,07
TD	24,48	10,94	0,34	0,2

	V5	V10	V20	V30
HT	29,47	4,69	0,15	0,03
TD	6,41	0,36	0,07	0,04

Figure 3. Dose distribution demonstrating the volume receiving 5 Gy (blue area) in the helical plan in (**A**) right-side and (**C**) left-side breast cancer, and 5 Gy dose volume (blue area) in the TomoDirect plan for (**B**) right-side and (**D**) left-side breast cancer
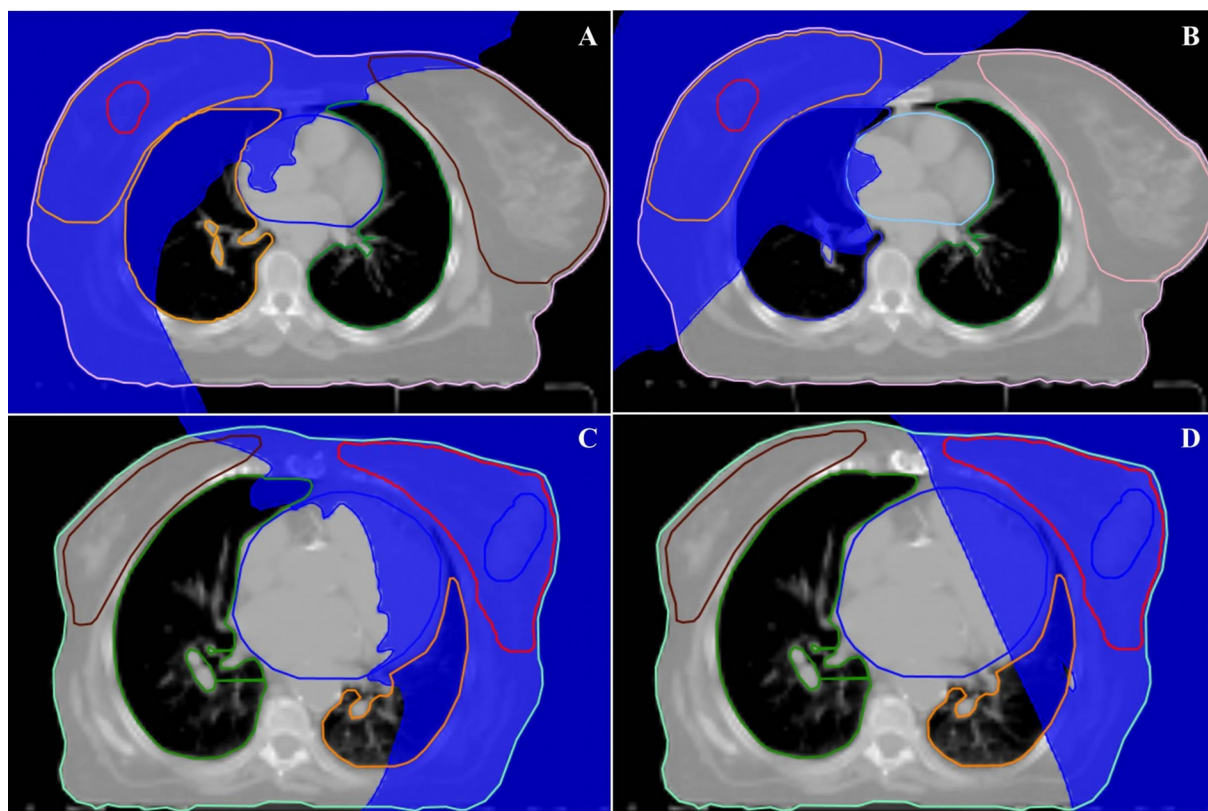
Table 1. Target volume doses according to helical technique (H) and TomoDirect (TD) plans

Parameters	H plan	TD plan	p
PTV$_{breast}$			
D2 [Gy]	52.70 ± 0.66	56.35 ± 1.60	< 0.001
D98 [Gy]	48.76 ± 0.68	48.78 ± 0.89	0.83
Dmean [Gy]	50.89 ± 0.48	52.34 ± 0.61	< 0.001
V95 (%)	99.12 ± .81	98.98 ± 0.74	0.23
V107 (%)	0.58 ± .74	10.39 ± 6.44	< 0.001
HI	0.08 ± 0.02	0.15 ± 0.04	< 0.001
CI	0.55 ± 0.09	0.47 ± 0.16	< 0.001
PTV$_{boost}$			
D2 [Gy]	65.92 ± 0.76	67.19 ± 0.75	< 0.001
D98 [Gy]	63.70 ± 0.42	64.42 ± 0.26	< 0.001
Dmean [Gy]	64.86 ± 0.52	66.01 ± 0.49	< 0.001
V95 (%)	100 ± 0.01	100 ± 0.02	0.57
V107 (%)	0	0.07 ± 0.19	0.009
HI	0.03 ± 0.01	0.04 ± 0.01	0.004
CI	0.56 ± 0.09	0.47 ± 0.16	< 0.001

H — helical; TD — tomodirect; PTV — planning target volume; Gy — Gray; D — dose; V — volume; HI — homogeneity index; CI — conformity index

Table 2. Organs at risk doses according to helical technique (H) and TomoDirect (TD) plans

Parameters	H plan	TD plan	p
Ipsilateral lung			
V$_{5Gy}$ (%)	41.66 ± 4.82	36.33 ± 7.10	< 0.001
V$_{20Gy}$ (%)	13.37 ± 1.56	13.88 ± 2.73	0.06
V$_{30Gy}$ (%)	8.13 ± 0.96	10.13 ± 1.97	< 0.001
D$_{mean}$ [Gy]	9.21 ± 0.77	8.98 ± 1.40	0.13
Heart			
V$_{5Gy}$ (%)	32.93 ± 8.46	15.44 ± 12.91	< 0.001
V$_{10Gy}$ (%)	8.02 ± 5.04	5.65 ± 6.34	< 0.001
V$_{20Gy}$ (%)	1.53 ± 1.79	1.89 ± 2.23	0.01
V$_{30Gy}$ (%)	0.55 ± 0.77	1.16 ± 1.47	< 0.001
D$_{mean}$ [Gy]	5.20 ± 1.00	3.09 ± 1.84	< 0.001
Contralateral lung			
V$_{5Gy}$ (%)	2.69 ± 1.19	0.25 ± 0.56	< 0.001
D$_{mean}$ (Gy)	2.06 ± 0.29	0.59 ± 0.36	< 0.001
Contralateral breast			
V$_{5Gy}$ (%)	4.08 ± 1.04	1.28 ± 1.57	< 0.001
D$_{mean}$ (Gy)	2.18 ± 0.43	0.77 ± 0.35	< 0.001
Spinal cord			
D$_{max}$ [Gy]	3.90 ± 2.78	0.91 ± 0.99	< 0.001
Esophagus			

D_{max} [Gy]	4.74 ± 3.21	1.54 ± 1.51	< 0.001
D_{mean} [Gy]	2.30 ± 1.26	0.86 ± 0.58	< 0.001
Liver			
V_{20Gy} (%)	1.44 ± 1.63	1.67 ± 2.18	0.26
D_{mean} [Gy]	2.82 ± 1.50	1.81 ± 1.58	< 0.001
Time [min]	6.5 ± 0.9	8.7 ± 1.0	< 0.001

H — helical; TD — tomodirect; Gy — Gray; D — dose; V — volume