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Simultaneous Bilateral Chest Wall Irradiation, Can Helical Tomotherapy Improve Dose Distribution?

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Background: Radiotherapy to bilateral breast cancer (BBC) is technically challenging because of the proximity to organs as the heart and lungs**.**
Aim: We conducted this study to compare helical tomotherapy (HT) to 3-dimensional conformal radiation therapy (3D-CRT) technique in bilateral chest wall irradiation regarding the coverage of target volume and the doses recorded at adjacent organs at risk.
Methods: Ten patients with synchronous BBC who underwent bilateral mastectomy were included. Two plans were performed for each patient using HT and 3D-CRT.
Results: Target volume included bilateral chest wall, bilateral supraclavicular and level III axillary lymph nodes. Prescription dose was 50 Gy/25 fractions in 5 weeks. The mean chest wall planning target volume (PTV) homogeneity index and conformality index were 0.15 and 1.09 in HT versus 0.37 and 1.43 in 3D-CRT plans (p = 0.012 and 0.031). At least 95% of the prescribed dose was covering 96% and 92% of the chest wall PTV for HT and 3D-CRT plans (p = 0.026). Helical tomotherapy plans achieved significant decrease in all cardiac parameters compared to 3D-CRT plans. Helical tomotherapy also achieved reduction in mean dose and V20 for both lungs in expense of higher low dose to normal healthy tissue and longer treatment time in comparison to 3D-CRT.
Conclusion: For BBC patients treated with bilateral chest wall and supraclavicular lymph nodes irradiation, HT provides more conformal and homogenous plan than conventional 3D-CRT plans. Helical tomotherapy improves chest wall PTV coverage and decreases the dose to the heart and lungs in expense of more volume of normal tissues exposure to low doses of radiation and longer treatment time.

Keywords: Bilateral breast cancer, Chest wall irradiation, Helical tomotherapy, Dose distribution
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INTRODUCTION

Breast cancer is the most frequently diagnosed malignant disease in females with an expected worldwide estimate of more than 2 million new cases and 3,629 new cases in Saudi Arabia in 2018 [1]**.** The incidence of synchronous bilateral breast cancer (BBC) is low accounting for 0.7–3% of all breast cancer cases [2]. Lobular cancer, positive family history of breast cancer, first cancer diagnosed at young age and mutations in BRCA genes are considered as risk factors that are known to increase risk for BBC.

Several controversial issues surround BBC concerning diagnostic criteria and management policies. Frequently, patients with BBC are usually treated with radical surgeries depending on the fact that these tumors are biologically aggressive. However a strong scientific evidence for this principle is still needed. No large studies addressing and analyzing the survival outcomes of BBC. Bilateral modified radical mastectomy (MRM) is the commonest surgical technique applied for cases with BBC. Even though second tumors are diagnosed at an earlier stage than the index tumor, breast conservative surgery (BCS) is not commonly applied mainly due to the stress related to the diagnosis of two cancers. Another determinative factor is the cost and availability of radiotherapy for bilateral breast irradiation following BCS. Heaton et al reported that BCS followed by adjuvant radiation therapy to bilateral breasts is applicable with comparable local recurrence rates to those patients with unilateral disease [3].

Radiotherapy is an essential part of the treatment in some breast cancer patients and has a definite role in reducing local recurrence, hence improving recurrence-free survival [4]. The application of radiotherapy in BBC is technically challenging because of the proximity to organs namely; heart, lungs and esophagus. Bilateral tangential irradiation delivered after surgery can lead to overlapping radiation fields especially in the medial aspects of both target volumes with an increased risk of

skin and soft tissue complications. Computerized tomography (CT) simulation is encouraged in bilateral breast irradiation as the medial margins of radiation portals can be delineated accurately, thereby preventing skin toxicities due to overlapping fields [5]**.** Contemporary radiotherapy techniques; intensity modulated radiotherapy (IMRT), volumetric-modulated arc therapy (VMAT) and helical tomotherapy (HT) can improve the accuracy of radiation delivery while reducing doses to adjacent normal tissues.

The use of HT with a rotating gantry around the patient is usually associated with spillage of low radiation dose to the adjacent critical structures. Therefore, it is not usually adopted in unilateral breast irradiation [6]**.**

We conducted this study aiming to define benefits of using HT in bilateral breast irradiation and to compare it to the conventional 3-dimensional conformal radiation therapy (3D-CRT) tangential fields regarding target volume coverage and doses recorded at adjacent organs at risk.

METHODS

The study included 10 cases of synchronous BBC. All patients underwent bilateral mastectomy with adjuvant or neo-adjuvant chemotherapy. Thereafter, patients were referred for adjuvant radiation therapy in the Radiation Department, Oncology Center, King Faisal Specialist Hospital and Research Center - Riyadh. We retrospectively reviewed these 10 cases and for each case we performed two different plans.

CT simulation

Set up: Using wide bore planning CT, all cases were simulated using a breast board in supine position with both arms above their head. Patients had planning CT of 2 mm slice thickness. Laser and tattoo marks were placed on the skin for daily reproducibility. Planning CT data images were imported to our eclipse as well as tomotherapy planning systems.

Contouring: delineation of both clinical target volumes (CTV) and organ at risk (OAR) were done according to the Radiation Therapy Oncology Group (RTOG) guidelines [7]:

Clinical target volume: Included bilateral chest wall (CW) and bilateral supraclavicular and level III axillary lymph nodes (LNs). Internal mammary chain was not included in any of the cases, as according to our guidelines it is included only in those with clinically involved node or electively in case of tumor located in inner quadrant with ≥ 4 positive axillary LNs.

Planning target volume (PTV)**:** A margin of 5 mm (in medial, lateral, anterior and posterior directions) and 7 mm (in superior and inferior direction) was added to CTV.

Planning target volume for evaluation (PTV eval): as part of the chest wall PTV often extends outside the patient's body, the chest wall PTV is then copied to a PTV eval which is cropped anteriorly excluding the part extending outside the patient's body in addition to the first 5 mm of tissues under the skin for the purpose of dose volume histogram (DVH) analysis with removing most of the buildup region.

Organs at risk: the lungs are usually contoured using the pulmonary windows. Despite contouring each lung separately, but for dosimetry purpose, they should be joined as one structure. Contouring should include all inflated, collapsed, fibrotic and emphysematic lungs; even the small vessels extending beyond the hilar regions should be included. The heart is contoured in conjunction with the pericardial sac. The superior border or the base usually begins at the level of the inferior aspect of the pulmonary artery while passing the midline and extending inferiorly to the apex of the heart.

Planning

For each patient two plans were performed using 3D-CRT and HT:

3D-CRT plan: Two tangential wedged photons fields were used to encompass the entire chest wall aiming for optimal target coverage keeping the radiation therapy dose to OAR within the listed constraints (table 1). Supraclavicular and level III axillary LNs were usually encompassed by a direct anterior field which was usually matched with the 2 tangential fields using the mono-isocenter technique. Collimation and blocks were usually used to improve dose homogeneity. A 0.5 cm bolus was usually applied to the CW for the first 12 fractions in order to increase the skin dose. The used planning system was Eclipse/Varian, Version 13.6.

Table 1: Dose constraints for both PTV coverage and dose to organs at risk

Target volume/OAR	Primary goal	Acceptable deviation
CW PTV eval	V95% > 95%	V90% > 90%
	D max < 115%	D max < 120%
LNs PTV	V95% > 95%	V90% > 90%
	D max < 115%	D max < 120%
Heart	V25 < 12 %	V30 < 12 %
	Mean < 5 Gy	Mean < 6 Gy
Lungs	V20 < 35%	V20 < 40%
	V10 < 60%	V10 < 65%
	V5 < 70%	V5 < 75%
	Mean lung dose < 13 Gy	Mean lung dose < 15 Gy
Esophagus	V50 < 20%	
Spinal cord	Maximum dose = 45 Gy	

PTV: Planning target volume, **CW**: Chest wall, **PTV eval**: Planning target volume for evaluation, **LNs**: Lymph nodes

HT plans: A posterior avoidance structure was created (1.5 cm posterior to the PTV in 3-dimensional way aiming primarily to increase PTV dose conformality and secondarily to reduce dose to nearby OARs such as heart, lungs and spine. All treatments were delivered through a 6 megavolt (MV) photon HT. Depending on the size of the targets; the plans were done using 2.5 or 5 cm y-jaw widths. The used planning system was Tomotherapy planning system/Accuray, Version 5.1.2.

Plan evaluation

Dose volume histograms were generated and used to evaluate the two different plans. For PTV, the a ratio between the volume of body receiving 95% of the prescribed dose and the volume of the PTV. The homogeneity index (HI) was defined as the difference between the dose covering 2% and 98% of the PTV divided by the prescribed dose (PD) (D2%-D98%/PD). For all patients, DVH for OAR (heart, lungs, esophagus and spinal cord) were calculated and compared. For healthy tissue, we recorded the volume of the body minus PTV receiving low doses as (V2, V5, and V10). Table 1 summarizes our dose constraints regarding coverage of PTV and doses recorded at nearby organs at risk.

Statistical methods

Data analysis and management were performed using Statistical Package for Social Sciences (SPSS) vs.23. Numerical data was expressed using means and standard deviations or medians and ranges whatever appropriate. Numerical data was explored for normality using Kolmogrov-Smirnov test and Shapiro-Wilk test. Mann-Whitney test was used to compare between the groups outcome. All p-values were two-sided and *p* values < 0.05 were considered significant.

RESULTS

Ten female patients with BBC were included in this study. Patients' characteristics are summarized in table 2.

Radiation therapy to bilateral CW and bilateral supraclavicular and level III axillary LNs were planned in all cases. Prescription dose aimed at delivering 50 Gy/25 fractions in 5 weeks.

The mean bilateral CW PTV eval volume was 2021 cc, while mean LN PTV volume was 49.8 cc. For HT plans, mean CW PTV eval HI and CI were 0.15 and 1.09 respectively versus 0.37 and 1.43 in 3D-CRT plans (p = 0.012 and 0.031) (table 3).

At least 95% of the PD was covering 96% and 92% of the CW PTV for HT and 3D-CRT plans (p = 0.026). The mean volume of LN PTV covered with at least 95% of the PD was 97% and 93% for HT and 3D-CRT plans(p = 0.261). An average of 99% and 95% of the CW PTV eval were covered with at least 90% of the PD for HT and 3D-CRT plans (p = 0.037). Correspondingly, an average of 100% and 97% of the LN PTV were covered with at least 90% of the PD for HT and 3D-CRT plans (p = 0.312). Figures 1 and 2 show comparative examples for PTV coverage in both techniques using color wash dose distribution and DVH.

HT plans achieved significant decrease in all cardiac parameters compared to 3D-CRT plans, mean heart dose was 6.8±1.0 and 12.2±0.9 Gy for HT and 3D-CRT plans (p = 0.023). V25 was 7.5±1.3% and 17±5.1% for HT and 3D-CRT plans (p = 0.028). Regarding lung doses, HT plans also achieved significant decrease in both V20 and mean dose for both lungs. V20 was found to be 23.8±2.2% and 32.4±2.4% for HT and 3D-CRT plans (p = 0.042), while mean lung dose was 9.8±2.1 Gy and 14±1.6 Gy for HT and 3D-CRT plans (p = 0.041). On the contrary, the 3D-CRT significantly decreased lung V5 that was recorded to be 67±10% and 50±8.3% for HT and 3D-CRT plans (p = 0.037). The detailed values of doses recorded at OAR are listed in table 3.

An example of lung and heart DVH comparison is shown in figure 3.

Table 2: Clinicaopathological characteristics of patients

Characteristic	
	Median (range)
Age (years)	48 (25-60)
	Mean (range)
Number of dissected axillary lymph nodes	9 (7-14)
	***n* (%)**
Clinical stage	
IIB	2 (20)
IIIA	4 (40)
IIIB	4 (40)
Chemotherapy	
Neoadjuvant	6 (60)
Adjuvant	4 (40)
Hormonal treatment	
Yes	7 (70)
No	3 (30)
Her-2 target therapy	
Yes	2 (20)
No	8 (80

DISCUSSION

Bilateral breast cancer is mostly thought to be independent primary tumors rather than secondary to metastatic spread from a primary tumor as in many cases different histopathologies or grades of differentiation were found between the 2 tumors [8, 9]. Post mastectomy conventional radiotherapy techniques have produced impressive loco-regional control and overall survival rates but in expense of late toxicities especially the cardiac toxicity in the form of ischemic heart disease and cardiac mortality, though the absolute risks are small, and less than the risk of omitting radiation for appropriately selected patients [10, 11].

In our study, HT plan achieved better CW PTV coverage (V90%, V95%, D max, CI and HI) than 3D-CRT plans. Any attempt to enhance coverage of PTV in 3D-CRT plans was hindered by unacceptable high doses in the overlapping area. The decision whether to compromise target coverage or to accept high dose in the overlapping areas depends on the clinical characteristics of the patient (medially located tumor and positive resection margin). In such cases we accepted higher doses in the overlapping areas.

In our data, HT plans decreased all cardiac parameters (mean dose, V25 and V30) compared to 3D-CRT. These findings are consistent with Sas-Korczyńska et al published data [12]. In HT plans, the median V25 was Ekici et al study had conservative surgery [13], while all enrolled patients in our study had bilateral mastectomy resulting in larger volume of heart exposed to significant doses of radiation.

We primarily aimed to keep mean heart dose below 5 Gy or 6 Gy as an acceptable deviation. The goal was achieved in 4 patients in the HT arm. The great concern about mean heart dose came from its correlation with cardiac events. With each increase of 1 Gy in mean heart dose the absolute risk of a major coronary event or death from ischemic heart disease increases. If a mean heart dose is 3 Gy, risk of dying of ischemic heart disease in a women aged 50-year that had no other coronary risk factors prior to age 80 years would increase from 1.9 to 2.4 %, while the risk of having at least one major coronary event would increase from 4.5 to 5.4 % while if the mean heart dose was 10 Gy , the risk of dying would increase from 1.9 to 3.4%, and the risk of having at least one acute coronary event would increase from 4.5 to 7.7 % [14]**.**

7.5 Gy (range 4.6-9 Gy) which is comparable to that reported by Ekici et al [13] where the median V25 heart was 6 Gy (range 0-13). Despite that 50% of the cases in

Deep inspiration breath hold (DIBH) is a technique enables radiation administration to the patients while taking a deep breath and then holding it for a period of time ,thus allowing for a decrease in the radiation dose to the heart preferably in left sided breast cancer [15]. Many dosimetric comparisons have stated the benefits of DIBH with a decrease of 25–67% in the mean heart doses and 20–73% in the mean left anterior descending artery (LAD) doses in comparison to the same patients planned with free breathing technique [16-24], however there is no direct comparison between DIBH and HT in BBC patients. Despite the tolerability of DIBH technique in most of the patients, they should be carefully selected to be able to tolerate the technique. Helical tomotherapy is still a valid option for these patients who cannot tolerate DIBH technique.

Radiation induced pneumonitis occurs in 1–10% of irradiated patients with breast cancer [25]. Multiple parameters such as mean lung dose and V20 were used to assess incidence of symptomatic pneumonitis,

Table 3: Comparison between the 2 techniques regarding PTV coverage and doses to OARs

Structure	Parameter	3D-CRT	HT	*P*- value
CW PTV eval	V90% (mean ±SD)	95±1 %	99±0.6%	0.037*
	V95% (mean ±SD)	92±1.1 %	96±0.8 %	0.026*
	D max	130±2%	112±0.9%	0.022*
	HI (mean ±SD)	0.37±0.03	0.15± 0.01	0.012*
	CI (mean ±SD)	1.43±0.28	1.09±0.06	0.031*
	Volume in cm^3 (mean± SD)	2021±70		
LN PTV	V90% (mean ±SD)	97±1.4%	100%	0.312
	V95% (mean ±SD)	93±3.1%	97±1.8%	0.261
	D max	118±2.3%	106±1.1%	0.018*
	Volume in cm^3 (mean± SD)	49.8±4		
Heart	V25 Gy (mean± SD)	17±5.1%	7.5±1.3%	0.028*
	V30 Gy (mean± SD)	10.1±3.7%	5±2.32 %	0.071
	Mean heart dose (mean± SD)	12.2±0.9 Gy	6.8±1.0 Gy	0.023*
Both lungs	V20 Gy (mean ±SD)	32.4±2.4%	23.8±2.2%	0.042*
	V10 Gy (mean ±SD)	40±8.0%	37±10.0%	0.118
	V5 Gy (mean ±SD)	50±8.3%	67±10%	0.037**
	Mean lung dose (mean± SD)	14±1.6 Gy	9.8±2.1 Gy	0.041*
Esophagus	V50 Gy (mean± SD)	1.8±1.7%	8±2.0%	0.011**
	D max (mean± SD)	28±2.5 Gy	45±1.7 Gy	0.013**
Spinal cord	D max (mean± SD)	22±1.8Gy	28±2.2 Gy	0.038**
Unspecified normal tissue	V2 (mean)	8084 cc	13129 cc	0.017**
	V5 (mean)	4120 cc	11715 cc	0.002**
	V10 (mean)	3692 cc	10250 cc	0.024**
Treatment time	Median (range)	5 (4-6.5) min.	10.5(9-13) min.	0.015**

PTV: Planning target volume, **3D-CRT**: 3-dimensional conformal radiation therapy, **HT**: Helical tomotherapy, **OARs**: Organs at risk, **CW**: Chest wall, **PTV eval**: Planning target volume for evaluation, **LN**: Lymph nodes; * Denotes statistically significant difference favoring HT over 3D-CRT plans, ** Denotes statistically significant difference favoring 3D-CRT over HT plans.

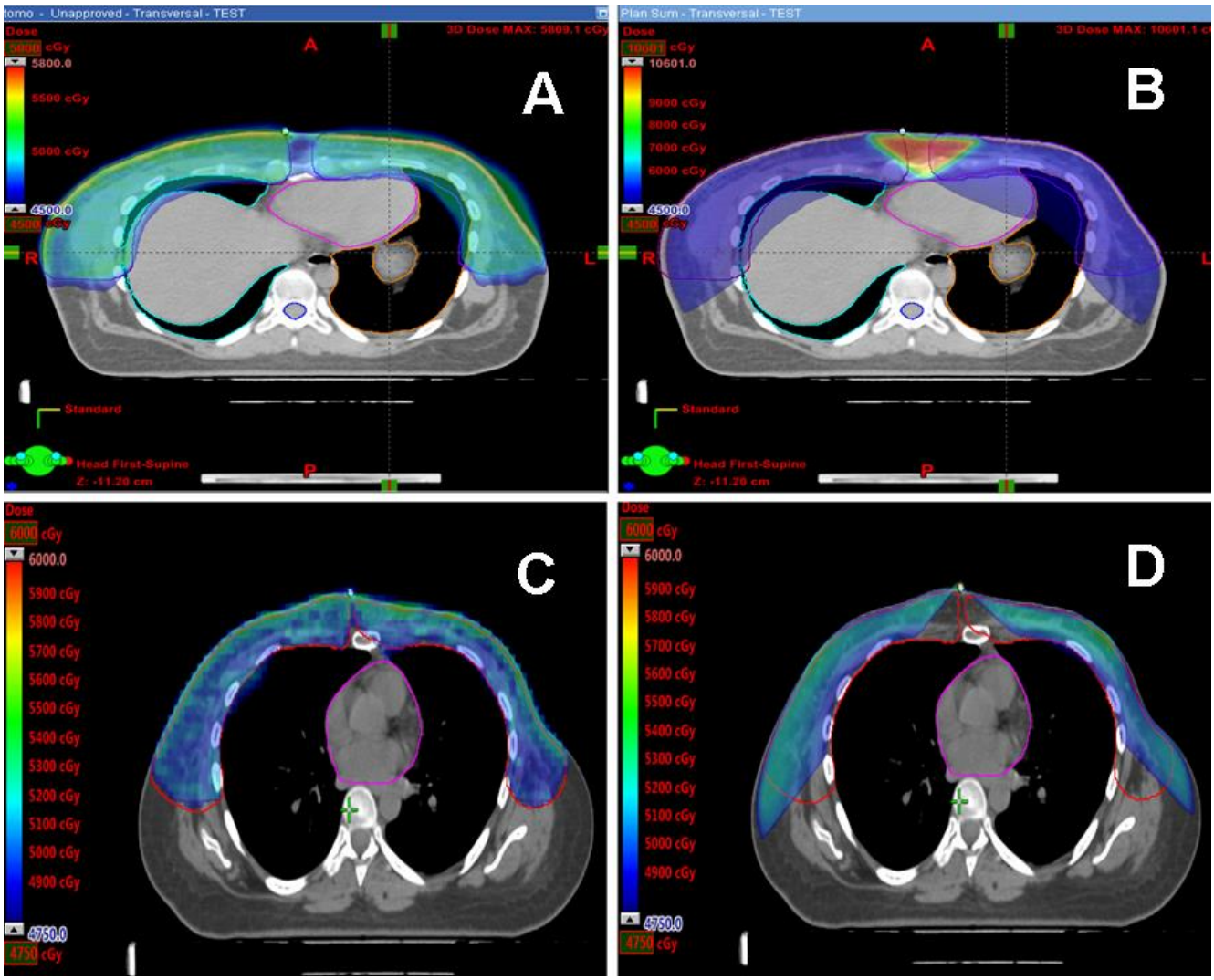

Figure 1: Dose distribution comparison between the 2 plans in 2 cases. In an attempt to have adequate PTV coverage in case number 1, 3D-CRT plan **(1B)** shows unacceptable high doses in the overlapping area compared to HT **(1A)**. In an attempt to avoid unacceptable high doses in case number 2, 3D-CRT plan **(1D)** shows compromised target coverage compared to HT **(1C)**

according to Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC), the incidence of symptomatic pneumonitis is 5%, 10%, 20% and 30% for mean lung dose of 7, 13, 20 and 24Gy respectively , while incidence of <20% with V20 ≤30% [26, 27]. Regarding our data, HT achieved reduction in mean dose and V20 for both lungs in comparison to 3D-CRT, as confirmed before in many studies with dosimetric differences favoring IMRT over 3D-CRT [25].

In HT plans, the median V20 and V10 were 22.5% (20-25%) and 35.5% (33-40 %). Ekici et al reported a median V20 and V10 of 18.51% (6.90–25.50%) and 24.25% (22.04–59.53%). The difference in V20 and V10 parameter between our study and Ekici et al study may be due to the previously mentioned factor, 50% of the cases in Ekici et al had conservative surgery while in our study all the patients enrolled had bilateral mastectomy. In addition, we included irradiation of supraclavicular lymphatics in our cohort that resulted in exposure of more lung tissues to considerable radiation dose.

The use of 3D-CRT decreased radiation dose to the esophagus and the spinal cord in comparison to HT plans. According to QUANTEC, incidence of grade ≥2 esophagitis is < 30% if the V50 < 40% [26, 27]**.** Our dose constraints kept the V50 < 20% and it was achieved in both arm. Though not clinically significant, 3D-CRT resulted in lower doses to the spinal cord and the esophagus compared to HT. Such lower doses might be attributed to the usual use of multi-leaf collimator in the supraclavicular field blocking these structures in addition to the use of 10 degree tilted-gantry angle keeping dose to the spinal cord and the esophagus as low as possible. These modifications cannot be applied in HT plans which depend on inverse planning and rotational treatment with spillage of low doses to a larger volume of OAR. The D max to the spinal cord and the esophagus was comparable between our HT data and Ekici et al study, as the median spinal cord D max was 25 (11-40) Gy in our HT data versus 23.91(11.02-40.47) Gy in Ekici et al study. The median esophageal D max was 42 (20-56) Gy versus 43.14 (8.28–67.54) Gy in Ekici et al study.

Conventional 3D-CRT plans decrease the spillage of lower radiation doses to healthy normal tissues outside the breast compared to HT plans. This finding was consistent in all parameters including V2, V5 and V10.

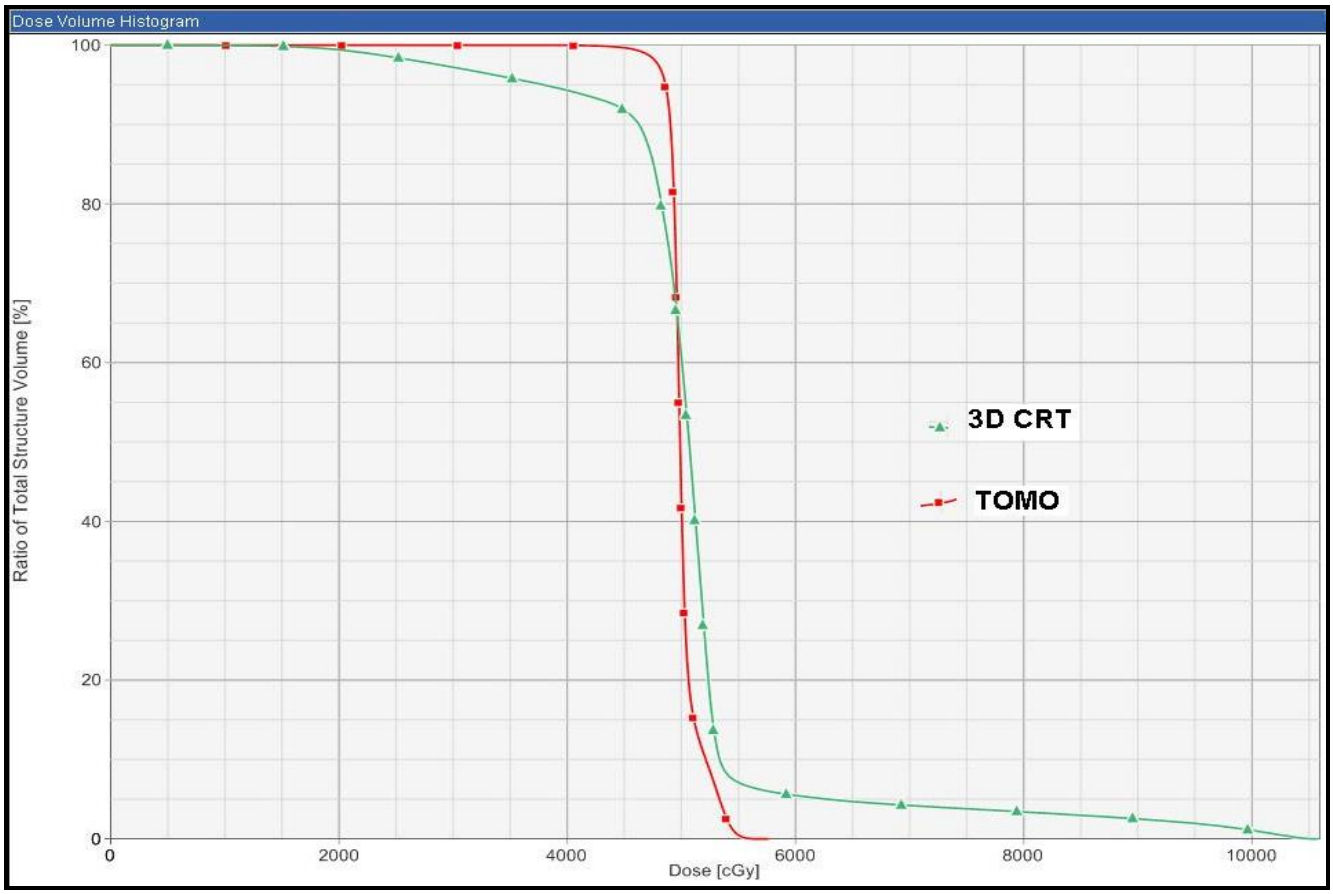

Figure 2: Chest wall planning target volume coverage comparison between the 3D-CRT and HT

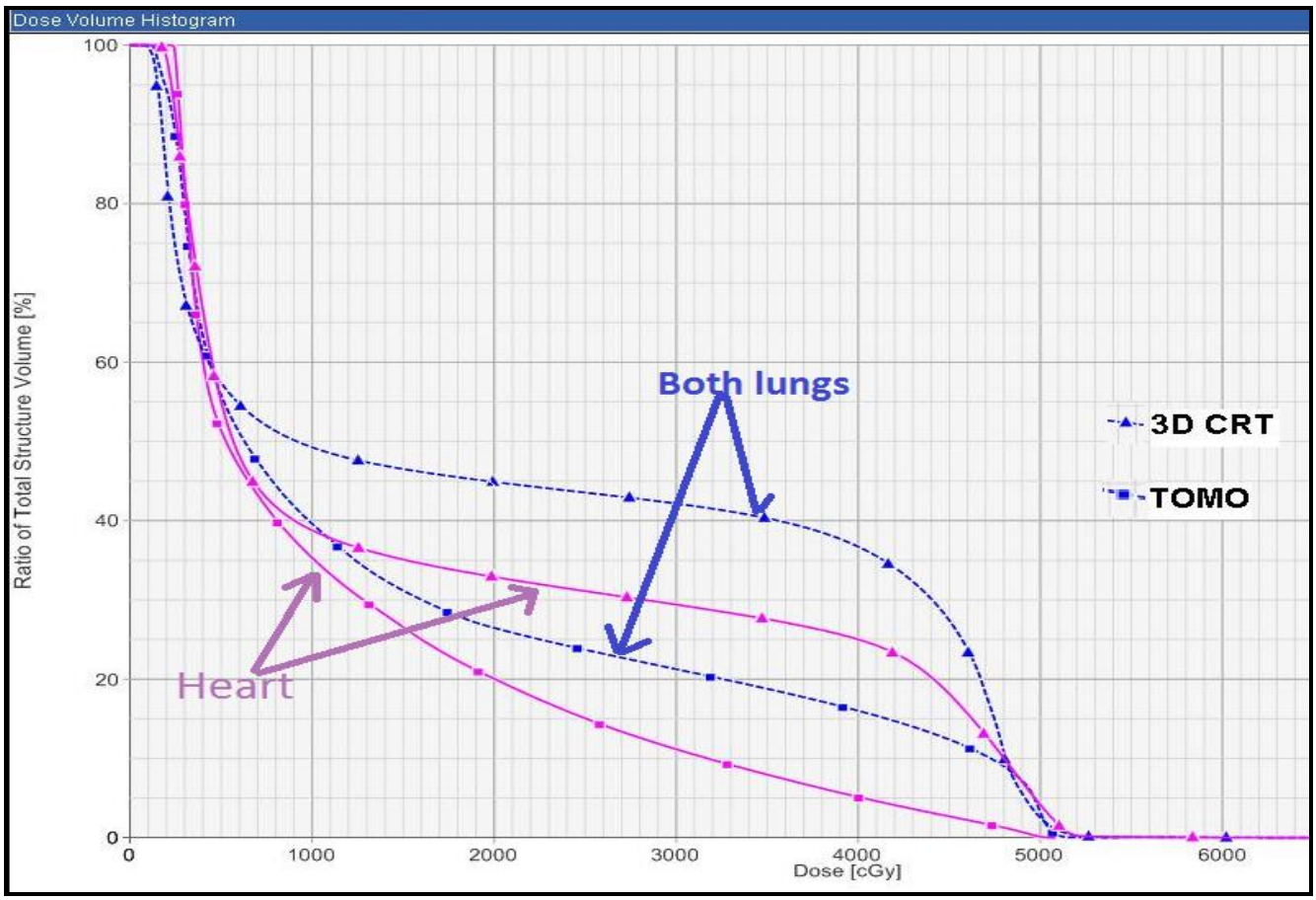

Figure 3: Dose volume histogram comparison between the 2 plans regarding doses to the heart and lungs.

Considering the expected long survival of breast cancer patients, exposure of larger volumes of normal structures to low doses of radiation may be of great importance regarding the long-term effects especially second malignancies [28]. Another potential disadvantage for HT plans is the longer treatment time, as reported in our study, the median treatment time in HT plan was 10.5 minutes versus 5 minutes in 3D-CRT plan.

Conclusion

For BBC patients treated with bilateral chest wall and supraclavicular lymph nodes irradiation, HT provides more conformal and homogenous plan than conventional 3D-CRT. Helical tomotherapy improves chest wall PTV coverage and decreases the dose to the heart and lungs, in expense of more volume of normal tissues is exposed to low doses of radiation and longer treatment time.

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