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Helical tomotherapy experience in breast cancer adjuvant radiotherapy and acute toxicity results

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ABSTRACT

Background: This study aimed to evaluate acute toxicity and oncological outcomes of breast cancer patients who underwent adjuvant radiotherapy (RT) with tomotherapy.

Materials and methods: The results of 114 patients who underwent adjuvant RT with Tomotherapy device between 17.08.10–12.06.2021 in Ankara Atatürk Training and Research Hospital and Ankara City Hospital were evaluated retrospectively. The primary endpoint of the study was acute adverse events, and the secondary endpoints were overall survival (OS) and disease-free survival (DFS).

Results: The results of 103 patients who met the inclusion criteria were analyzed. The median follow-up was 21 (range 1–125.8) months. Grade +3 esophagitis was not observed in any patient; no esophagitis was observed in 60 (58.3%) patients. Grade 3 dermatitis was observed in 3 (2.9%) patients. In addition, dermatitis was not observed in 47 (45.6%) patients. The relationship between chest wall volume and esophagitis development was statistically significant ($p = 0.006$; Z score: –2769). The median OS was 24.1 (range 1–128.5) and median disease-free survival was 21.1 (range 1–125.8) months. Five patients (4.9%) died and 9 patients (8.7%) relapsed. Local recurrence was observed in only 1 (1%) patient. There was a statistically significant correlation between OS and contralateral lung V20 dose [$p < 0.001$; Spearman Correlation Coefficient (SCC) –406) and heart mean dose ($p < 0.001$; SCC –370)]. There was a statically significant correlation between DFS and cN ($p < 0.001$); pN ($p < 0.001$); heart mean dose ($p < 0.001$; SCC –351); contralateral lung V5 dose ($p = 0.041$; SCC –213); contralateral lung V20 dose ($p < 0.001$; SCC –434).

Conclusion: Acute toxicity results show improvement in breast cancer adjuvant radiotherapy with helical tomotherapy.

Key words: tomotherapy; acute side effect; breast cancer

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Introduction

Adjuvant radiotherapy in breast cancer (BC) treatment is essential in reducing breast cancer-related deaths [1, 2]. The main purpose of radiotherapy is to give high doses to the target tissue while sparing the adjacent normal tissue as much as possible. Newly developed technologies and techniques are trying to achieve this goal in breast radiotherapy. Especially in treating cancers such as breast and prostate, which have long survival rates, the toxicity rates due to radiotherapy are tried to be reduced. For this purpose, breast radiotherapy is increasingly applied

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with many different techniques today [3]. Here, it primarily aims to decrease the dose values of parameters such as the dose received by the anterior descending artery and the mean dose of the heart, and better dose conformity is also provided with the newly developed techniques. Many studies compare tangential irradiation, a technique from the past, and new techniques [4–7]. However, most of these studies are dosimetric. The number of studies evaluating the clinical results of new techniques on patients is limited.

Helical tomotherapy (HT) is a new technique in the treatment of breast cancer and is not part of the routine practice. However, it is sometimes preferred because it provides dosimetric advantages. The clinical meaning of the dosimetric advantage is that there will be fewer acute and chronic side effects. This study aimed to retrospectively analyze the acute toxicity and oncological outcomes of patients who underwent adjuvant radiotherapy using HT for breast cancer.

Materials and methods

Patients who received adjuvant RT with tomotherapy device with the diagnosis of breast cancer in Ankara Atatürk Training and Research Hospital and Ankara City Hospital were evaluated retrospectively. Patient file information, patient interview notes, electronic system records and dose volume histograms were used to obtain data. The American Joint Committee on Cancer (AJCC) guidelines were used for staging. Demographic characteristics of the patients, planning parameters (modulation factor, pitch factor, treatment duration, monitor unit values, homogeneity index, conformity index), treatment details, acute side effects, recurrence status, and last status information were noted.

In our clinic, breast radiotherapy is applied with tangential, 3D and Intensity modulated RT (IMRT). Our main indications for the use of HT in breast cancer are as follows: patients with pectus excavatum anatomy, pendulum breast, failure to meet RT dose limits with other devices, and bilateral breast irradiation indications. The reason why the patients in this study were treated with tomotherapy was the pendulum breast and the inability to meet RT dose limits with other devices.

Patient selection

Breast cancer patients who received curative RT on a tomotherapy device for adjuvant purposes, had pathological evidence and had complete file information were included in the study. Patients who received treatment with devices other than tomotherapy, who received palliative RT, and whose file and electronic system information were missing were excluded from the study.

Primary and secondary endpoints

The primary endpoint of the study was acute adverse events. The Common Toxicity Criteria for Adverse Events (CTCAE) ver. 5.0 was used for side effect assessment8. The study's secondary endpoint was overall survival (OS) and disease-free survival (DFS). The start date for OS was the date of diagnosis; the end date was the last control date for living patients, the exitus date for ex-patients. The start date for DFS is the RT start date; the end date is the last control date for non-relapsed patients, the relapse date for relapsed patients.

Patient immobilization

The CT simulation was performed in a supine position with the midsternal line parallel to the breast bed and with an angle of 7–15 degrees to the breast bed. Only one patient (who would not fit into the device field of view (FOV) aperture due to her anatomy) was simulated with a T-board device. Surgical scars and drain points were marked with a lead marker.

Target volume delineation

PTV margin definitions differed among clinicians. In cases where BCS was applied, a median 5 mm (range 3–7 mm) PTV border was applied to the breast, and in chest wall irradiations, the skin was included in the CTV, and a median 5mm (range 0–5 mm) margin was given to create a PTV. In general, the patients were contoured based on the RTOG breast contouring guide[9].

Statistical analysis

Analyses were performed with IBM SPSS Package Program version 26.0 (IBM Corporation, Armonk, NY, United States). Descriptive statistics, mean, standard deviation, minimum-maximum and median values for continuous (quantitative) variables were presented. Categorical variables were

expressed as number (n) and ratio (%). Categorical demographic characteristics of the patients were calculated with Fisher's exact test and Chi-square. Kaplan Meier was used in univariate survey analyses and compared with the log-rank test. Cox regression test was used in multivariate analysis. The conformity of the variables to the normal distribution was evaluated with Kolmogorov–Smirnov and Shapiro–Wilk tests, and nonparametric tests were used because they did not fit the normal distribution. Spearman's rank correlation test was used for Univariate correlation analysis. Statistical significance level was accepted as $p \leq 0.05$.

Results

The 114 patients who underwent curative HT with a breast cancer diagnosis in Ankara Atatürk Training and Research Hospital and Ankara City Hospital between 17.08.10–12.06.2021 were evaluated retrospectively. Eleven of the 114 patients examined were excluded from the study due to lack of data, and 103 patients were analyzed. Patient and treatment details are summarized in Table 1. The median follow-up period of the patients from the beginning of RT was 21 (range 1–125.8) months. During the follow-up period, five patients died (four patients due to distant metastasis and the remaining one due to non-cancer-related disease) (4.9%), and 9 (8.7%) patients relapsed, and among relapses, only 1 (1%) patient had local recurrence. The median OS was 24.1 (range 1–128.5) months from diagnosis. The median disease-free survival was 21.1 (range 1–125.8) months (Fig. 1).

Acute side effects evaluation

Patient file data were reviewed retrospectively. Files and electronic system data contain only reports of acute side effects related to esophagitis and dermatitis. In this study, chronic side effects were not evaluated. No patient developed grade +3 esophagitis, and more than half of the patients (n = 60, 58.3%) had no complaints of esophagitis during treatment. Grade 3 dermatitis developed in only 3 (2.9%) patients. In addition, no complaints of dermatitis were reported in 47 (45.6%) patients (Tab. 2).

There was no significant relationship between observed dermatitis and lateralization (right *vs* left) ($p = 0.250$); presence *vs* absence of neoadjuvant therapy ($p = 0.309$); age ($p = 0.194$); BMI ($p = 0.416$); breast *vs* chest wall RT ($p = 0.186$); CW volume ($p = 0.645$); breast volume ($p = 0.343$); boost is simultaneous integrated (SIB) or sequential ($p = 0.543$).

There was no significant relationship between observed esophagitis and lateralization (right *vs.* left) ($p = 0.111$); presence *vs* absence of neoadjuvant therapy ($p = 0.287$); age ($p = 0.793$); BMI ($p = 0.283$); breast *vs* chest wall RT ($p = 0.558$); breast volume ($p = 0.334$); boost is SIB or Sequential ($p = 0.352$). The relationship between chest wall volume and esophagitis development was statistically significant ($p = 0.006$; Z score: –2769) (Fig. 2). In patients without esophagitis, the median CW volume was 656 (range 288–1159); In patients with esophagitis, the median CW volume was 826 (range 519–1783) cc.

Detailed OS and DFS analysis

Factors affecting OS were analyzed, lateralization ($p = 0.390$); cT ($p = 0.973$); cN ($p = 0.240$); cM ($p = 0.563$); pathology ($p = 0.580$); pT ($p = 0.967$); pN ($p = 0.168$) had no statistically significant effect. There was no statistically significant correlation between OS and CW (cc) (= 0.596); contralateral lung V5 ($p = 0.109$); ipsilateral lung V20 ($p = 0.319$); ipsilateral lung V5 ($p = 0.161$). However, there was a negative, moderate and statically significant correlation between OS and contralateral lung V20 dose ($p < 0.001$, Spearman correlation coefficient –406) and heart mean dose ($p < 0.001$ Spearman correlation coefficient –370).

Parameters with an effect on DFS were analyzed; lateralization ($p = 0.293$); age at diagnosis ($p = 0.985$); cT($p = 0.673$); cM ($p = 0.572$); pathology ($p = 0.922$); pT ($p = 0.929$); CW(cc) ($p = 0.649$); ipsilateral lung V5 ($p = 0.158$); ipsilateral lung V20 ($p = 0.392$) had no statistically significant effect. However, there was a negative and statically significant correlation between DFS and cN ($p < 0.001$) (Fig. 3); pN ($p < 0.001$) (Fig. 4); heart mean dose ($p < 0.001$, Spearman correlation coefficient -351);contralateral lung V5 dose ($p = 0.041$, Spearman Correlation Coefficient –213); contralateral lung V20 dose ($p < 0.001$, Spearman Correlation Coefficient –434).

Discussion

The primary purpose of the current study was to evaluate the suitability and treatment results of

Table 1. The patient and treatment details

Age	
Median (range)	50 (30–83)
Mean (SE)	51.6 ± 1.04
BMI	
Median (range)	28.7 (17–64)
Mean (SE)	30.1 ± 1.17
Lateralization	
Right	63 (61.2%)
Left	40 (38.8)
Clinic T	
T1a	3(2.9%)
T1b	3(2.9%)
T1c	15 (14.6%)
T2	59 (57.3%)
T3	18 (17.5%)
T4a	1 (1%)
T4b	4 (3.9%)
Clinic N	
N0	21 (20.4%)
N1	49 (47.6%)
N2	15 (14.6%)
N3	18 (17.5%)
Clinic M	
M0	101 (98.1%)
M1	2 (1.9%)
Surgery	
BCS + SLNB	17 (16.5%)
BCS + ALND	19 (18.4%)
Simple mastectomy	1 (1%)
MRM + SLNB	5 (4.9%)
MRM + ALND	59 (57.3%)
None	1 (1%)
Pathology	
IDC	82 (79.6%)
ILC	5 (4.9%)
Mix carcinoma	11 (10.7%)
Medullary	3 (2.9%)
Tubular	1 (1%)
Musineous	1 (1%)
Cerb B2	
Negative	54 (52.5%)
+	13(12%6)
++	20 (19.4%)
+++	16 (15.5%)
Treatment time	
Median (range)	473 (161–921)
Mean (SE)	506 ± 16.64
Field with	
Median (range)	5 (2.5–5.2)
Mean (SE)	4.80 ± 0.51
Pitch factor	
Median (range)	0.21 (0.12–0.43)
Mean (SE)	0.23 ± 0.005
CI	
Median (range)	1.51 (0.84–15.7)
Mean (SE)	3.5 ± 1.65
nCI	
Median (range)	1.93 (1.27–37.5)
Mean (SE)	6.15 ± 1.33
HI	
Median (range)	1.13 (1–124)
Mean (SE)	6.91 ± 4.03
CW [cc]	
Median (range)	712 (288–1783)
Mean (SE)	783 ± 325
Breast [cc]	
Median (range)	1158 (250–2168)
Mean (SE)	1180 ± 83.3
Heart mean doses [cGy]	
Median (range)	352 (1.42–1772)
Mean (SE)	361.9 ± 33.3
Ipsilateral lung V5 doses	
Median (range)	42 (12–53)
Mean (SE)	40.2 ± 1.72
Ipsilateral lung V20 doses	
Median (range)	26 (8–37)
Mean (SE)	24.6 ± 0.66
Contralateral lung V5 doses	
Median (range)	7 (3–43)
Mean (SE)	9.1 ± 0.61
Contralateral lung V20 doses	
Median (range)	4.5 (2–13)
Mean (SE)	4.9 ± 0.20

BMI — body mass index; T — tumor; N — nodal; M — metastasis; BCS — breast conserving surgery; SLNB — sentinel lymph node biopsy; ALND — axillary lymph node dissection; MRM — modified radical mastectomy; IDC — invasive ductal carcinoma; ILC — invasive lobular carcinoma; CI — conformity index; nCI — new conformity index; HI — homogeneity index; CW — chest wall;V5 — volume receiving 5 Gy; V10 — volume receiving 10 Gy

adjuvant breast radiotherapy applied with HT. According to the results of our study, no patient developed grade 3 esophagitis, and grade 3 dermatitis developed in only 3 (2.9%) patients. No grade 4 side effects were observed in any patient. Another remarkable result was that esophagitis (n = 60,

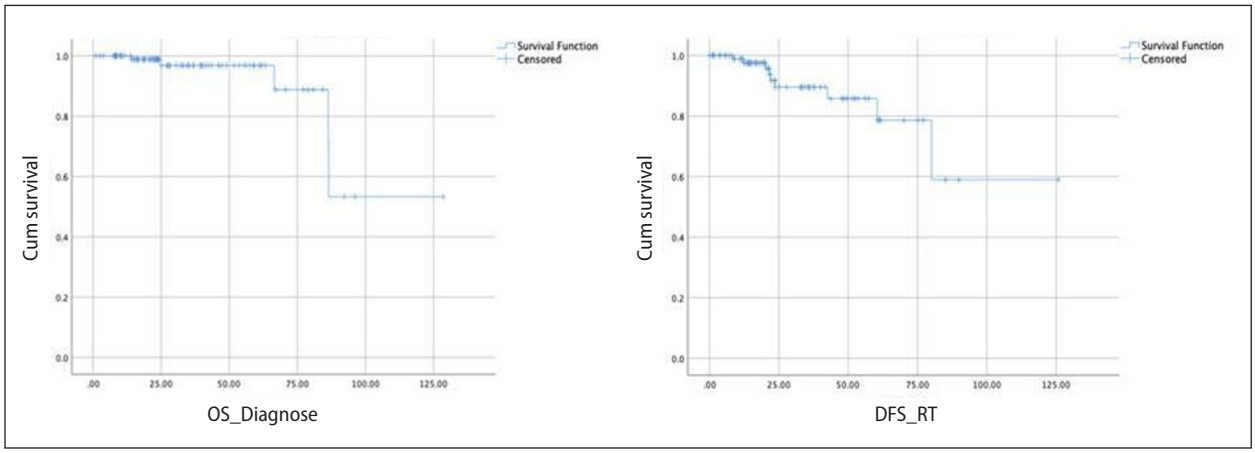

Figure 1. Kaplan-Meier overall survival (OS) and disease-free survival (DFS) visual analysis results

Table 2. Acute side effect detailed evaluation

Dermatitis	
None	47 (45.6%)
Grade 1	44 (42.7%)
Grade 2	8 (7.8%)
Grade 3	3(2.9%)
Missing	1(1%)
Esophagitis	
0	60(58.3%)
Grade 1	27(26.1%)
Grade 2	14(13.9%)
Missing	2(1.9%)

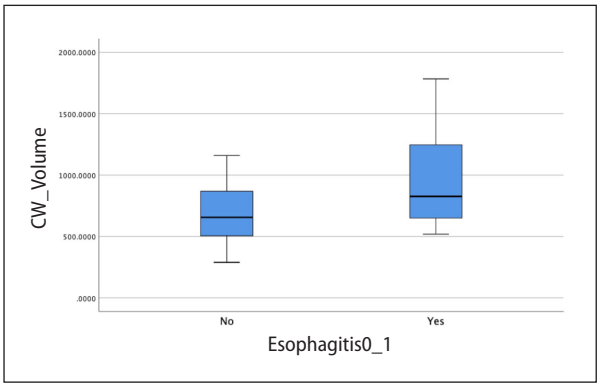

Figure 2. As the chest wall volume increases, the risk of esophagitis increases

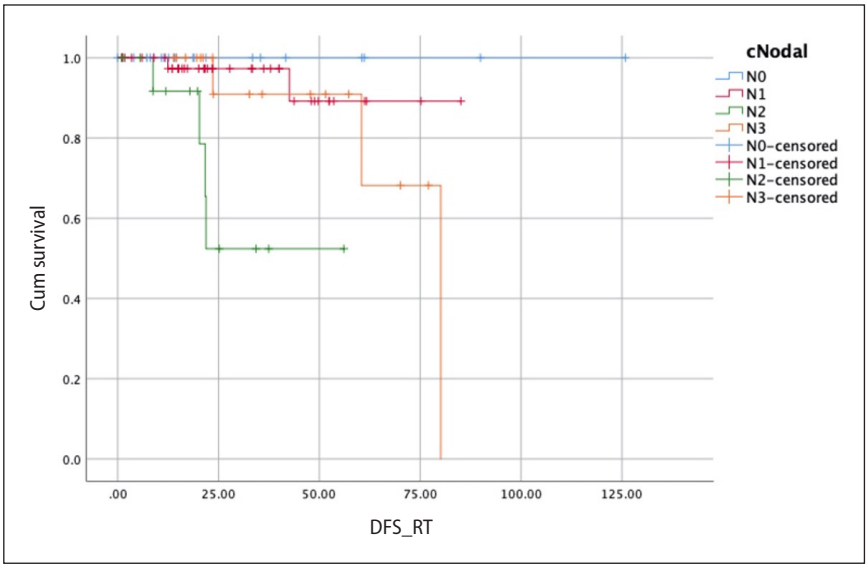

Figure 3. Relationship between disease-free survival (DFS) and clinical nodal status

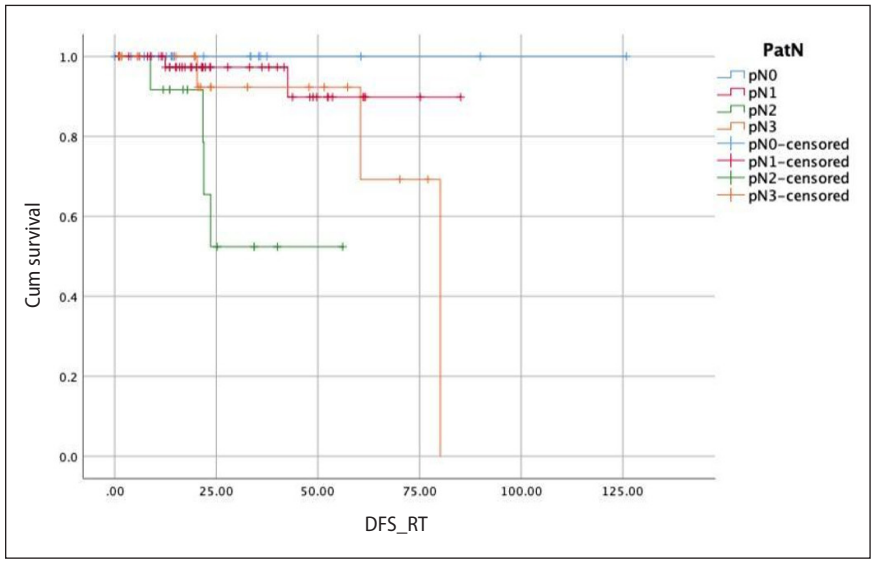

Figure 4. Relationship between disease-free survival (DFS) and pathological nodal status

58.3%) and dermatitis (n = 47, 45.6%) complaints were not observed in almost half of the patients. The relationship between chest wall volume and esophagitis development was statistically significant (p = 0.006; Z score: –2769). There was a statistically significant correlation between OS and contralateral lung V20 dose, and heart mean dose. There is a statistically significant correlation between DFS and cN, pN, heart mean dose, contralateral lung V5 dose, contralateral lung V20 dose. The results of our study revealed low acute side effects with tomotherapy.

The advantage of helical IMRT was tested with dosimetric studies before it was included in breast cancer treatment [10]. Along with the dosimetric advantages it provides, some uncertainties have come to the fore with the helical IMRT application. The first of these is the difference in dose distribution that may occur on the skin surface and lung depending on the breathing movement and dose leakages that may occur in the target volume. This effect can be avoided thanks to the fall-off given due to the nature of tangential irradiation. However, the lack of a breath monitoring system in reported helical IMRT applications has brought this question again. In a critical study on this subject, breath movement was simulated. The surface doses of the plans made with different margins were measured dosimetrically [11]. Study findings revealed that an effective surface dose was achieved with helical IMRT independent of respiratory movement. Numerous dosimetric studies in the literature evaluated the dose distribution of helical-IMRT in the treatment of breast cancer, and the appropriateness of the dose distribution was reported [5, 6, 12–15]. These studies are summarized in Table 3.

Clinical experience has primarily evaluated the patients with RT indication due to bilateral breast cancer or for whom physical planning is difficult due to their anatomical features (pandule breast, pectus excavatum) [16–18]. After the demonstration of dosimetric advantages, routine practice experiences of different clinics began to take place in the literature. In this transition, especially in skin toxicities, the benefit obtained with static IMRT was demonstrated by phase 3 studies and different IMRT techniques aimed at similar or lower acute toxicity profiles [19, 20]. One of the first studies reporting clinical results in the treatment of breast cancer with HT is the series of 179 patients reported by Arsene Henry et al. In the study, where the median follow-up period was reported as 38 months, locoregional recurrence was reported in 3 patients, and distant metastasis was reported in 6 patients. It has been reported that RNI was applied in 85% of patients. Gr 3 acute skin toxicity was reported in only 3%, Gr3 and higher esophagitis was not reported [3]. In the retrospective analysis performed by Lauche et al., dosimetric and acute toxicity results of helical IMRT and VMAT applications applied in patients with dosimetric disadvantages due to anatomy were reported [21]. Although

Table 3. Dosimetric studies comparing helical intensity-modulated radiotherapy (IMRT) and different radiotherapy techniques in left breast cancer radiotherapy

Study	Breast cancer characteristic	Number of patients	Compared radiotherapy techniques	Compared parameters	Results
Mast et al., 2015 [11]	Left-sided Early stage, after BCT WBI No RNI	20	Tang IMRT with BH Tang IMRT without BH Hel IMRT with BH	Heart V5 Gy, V10 Gy, V20 Gy, V30 Gy Mean contlateral lung dose Mean bilateral lung dose	V20Gy for the heart was significantly lower in Hel IMRT plans compared to tangential IMRT with BH Techniques are comparable for lung dose parameters
Yeh et al. 2019 [12]	Left-sided, locally advanced breast cancer, RNI with IMN	10	5F-IMRT CB HT OBDB HT CDCB with different restricted angles (beam angles of 0, 10, 15, and 20 degrees)	Conformity index (CI) Uniformity index (UI) PTV D5%, D95%, V95%, V109% Ipsilateral mean lung dose, V5, V10, and V20 Mean LAD	OBDB plan had better conformity (0.73) than the other plans OBDB plan had the lowest D5% The CDCB15 and CDCB20 plans had the lowest ipsilateral mean lung dose, V5, V10, and V20
Schubert et al., 2011 [5]	Left-sided WBI	10	3DCRT For-IMRT Inv-IMRT HT Topotherapy	Target Dmin, D max, D mean, coverage Heart Dmin-max, V5, V10, V20, V50 Ipsilateral lung Contlateral breast	HT resulted in the lowest heart and ipsilateral lung max doses but had higher mean doses HT results in increased low doses to the large volume of normal tissue
Erdiş et al., 2020 [13]	Negative lymph nodes Breast-conserving surgery WBI	30	3D-CRT Tomo-helical IMRT Direct IMRT	Heart mean, V10 Ipsi- and contlateral lung V5, V10, V20 Contlateral breast mean, max	Dose homogeneity was best achieved using the Tomohelical IMRT 3D-CRT was superior for the V5 volume of the body
Shiau et al. 2014 [14]	Left-sided Early stage WBI	30	Hybrid IMRT Limited tomotherapy	PTV HI, CI Heart mean, V10, V25, V35, V45 Lung V5, V10, V20	Similar target coverage Dose reductions in both high and low dose regions for ipsilateral lung and heart
Hacıislamoğlu et al. 2015 [6]	Left-sided BI	15	3DCRT For-IMRT Inv-IMRT HT VMAT	Target coverage, HI Heart Dmax, Dmean, V5, V10, V20, and V30 LAD Dmax and Dmean Ipsilateral lung Dmax, Dmean, V5, V10, and V20 Contlateral breast Dmax, Dmean, V3, V5, and V10	Similar target coverage Lowest max doses delivered to the heart, LAD, and ipsilateral lung with HT HT resulted in increased low doses to a large volume of healthy tissue

Tang IMRT — tangential IMRT; BH — breath-hold; BCT — breast conserving therapy; RNI — regional nodal irradiation; IMN — intramammary nodal station; WBI — whole breast irradiation; 5F-IMRT — five fields IMRT; CB-HT — complete block helical tomotherapy; OBDB — organ-based directional block; CDCB — complete-directional-complete block; LAD — low anterior ascending artery

the target coverage results reported in this study were optimal, grade skin toxicity was reported at a maximum rate of 5% in both groups. These studies and our study reported similar results in terms of the side effect profile. Grade 3+ esophagitis was not observed in any patient who underwent HT in our clinic. Grade 3 radiodermatitis was seen in only 3 (2.9%) patients.

In a newly published single phase 3 study to evaluate the benefit of HT on skin toxicity, researchers compared FINF IMRT and HT-IMRT in patients with early-stage breast cancer [22]. Results of 177 patients included in the study were reported with a median follow-up period of 73.1 months. According to the study findings, erythema and wet desquamation rates were statistically significantly lower with HT-IMRT. Although target coverage is not targeted primarily, it has been reported that HT-IMRT is better in terms of target Dmax, Dmin, and conformity. Although the study was

not planned for chronic skin toxicity, a difference was found between the two RT techniques only in terms of hyperpigmentation. The skin toxicity of HT reported by Lee et al. was evaluated differently. This study evaluated 216 patients (41 HT-SIB *vs.* 175 IMRT-SIB) who received radiotherapy with the SIB technique retrospectively [23]. Only one patient reported grade 3 toxicity. It was emphasized that this patient was in the patient group who received IMRT-SIB. On the other hand, it was reported that grade 2 toxicity was less common in the HT arm. All patients in our study were treated with tomotherapy and Hel-IMRT was not compared with any other technique. According to our results, SIB or sequential administration of boost was not effective on acute radiodermatitis or esophagitis.

A relatively recent study has been published. Modern rotational radiotherapy techniques, VMAT and HT were compared in terms of organ at risk doses [21]. In the study, 108 patients evaluated retrospectively (70 patients VMAT/38 patients HT) were compared in terms of cardiac dose parameters, lung dose parameters in terms of the contralateral breast, esophagus, and thyroid mean dose, and the dose distribution obtained with VMAT was found to be superior for all parameters except thyroid mean dose. Researchers emphasized that VMAT provides better protection for organs at risk, especially in cases where IMN is included in the RNI field. In the current study, dose of organ at risk limitations were provided in all patients. There was a statistically significant correlation between OS and contralateral lung V20 dose, and mean heart dose. And also, there was a statistically significant correlation between DFS heart mean dose, contralateral lung V5 dose, and contralateral lung V20 dose. Whether this relationship is still significant in the longer follow up is yet to be found.

Our study will contribute to the literature on adjuvant breast radiotherapy with HT with the high number of cases and acute toxicity data. However, the factors such as the short follow-up period, the plans made by two different medical physicists in different clinics, and the differences between clinicians in the contours limit the study data analysis.

The superiority in acute toxicity results of HT in breast cancer radiotherapy was revealed in our study, similar to the literature. However, studies with long-term follow-up and a high number of cases are needed in terms of long-term toxicities due to increasing low dose volumes and problems in local control due to technical differences and experience.

Conclusion

Acute toxicity results show improvement in breast cancer adjuvant radiotherapy with HT. Long-term follow-up data are needed to evaluate survival and long-term toxicity outcomes.

Compliance with ethical standards

The study was conducted in accordance with the Declaration of Helsinki and this was approved by the Ankara City Hospital Ethics Committee with the number E21/2022.

Conflicts of interest

The authors have no conflicts of interest to declare.

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