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Research Article

Association Between Dosimetric and Toxicity Findings Using Hypo-Fractionated Whole Breast Radiotherapy: A Long-Term Experience

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Abstract

Objectives: This study aimed to assess the toxicity and cosmetic outcomes in breast cancer patients treated with hypofractionated radiotherapy (HFRT) and identify the risk factors for toxicity.

Methods: 56 women with early-stage breast cancer were enrolled in this study. We evaluated physician-rated acute and late RTOG toxicity criteria and cosmetic outcomes during and after RT.

Results: The median age was 64. The median follow-up was 90 months. By the end of RT, 29 of 56 (52 %) patients had no acute toxicity according to the RTOG criteria, while 27 (48%) developed grade 1 and grade 2 acute skin toxicity. Twelve patients developed grade 1 edema and skin hyperemia six months after radiotherapy. In contrast, no worse late skin toxicity was observed in 1 year and five-year follow-ups. Multivariate analyses showed that skin toxicity correlated with surgery type (p=0.043), axillary dissection (p=0.032), and supraclavicular radiotherapy (p=0.043).

Conclusion: These results verified the viability and safety of HFRT in patients with early breast cancer. Surgery type, axillary surgery type, and supraclavicular radiotherapy were significant adverse prognostic factors for late toxicity. Long-term follow-up is required to confirm this finding.

Keywords: Acut toxicity, hypo-fractionated whole breast radiotherapy, late toxicity

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The efficacy of radiotherapy (RT) in adjuvant breast cancer treatment has been proven by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) meta-analysis.[1, 2] After this meta-analysis, with many studies, conventional fractionation (per fractions of 2±0.2 Gy); 46-50 Gy in 23-25 fractions (5 days per week) for the chest wall and breast with or without 10-16 Gy boost to the tumor bed after breast-conserving surgery has become the standard.[3,4] Previous studies have shown that tumor cells are less affected by fraction size than are normal tissues.[5, 6] In addition, the alpha/beta ratio for breast cancer was accepted as = 3, and it was observed to be close to the surrounding normal tissue; therefore, this rate is lower than the predicted late side effect value for normal tissue.[7, 8] Another study emphasized that the biological equivalent dose (BED) is associated with perfect tumor control at doses of 90 Gy (a/b

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= 4) and above.[9] In light of these studies, it was observed that a fraction size of 2-6 Gy was appropriate for the defined alpha/beta ratio and hypofraction applications, where the fraction size was kept below 4 Gy with less fraction number occurring. In four randomized studies, hypofractionated whole-breast radiotherapy (HF-WBRT) was proven safe and cost-effective as conformal RT. It has been proven that the long-term results of these studies are similar to those of conventional schemes in terms of toxicity and cosmetics. [8, 10-16] This study aimed to evaluate the long-term survival, side effects, and dose-volume histogram (DVH) parameters associated with side effects and cosmetic results in patients with breast cancer who received adjuvant HFRT.

Methods

Ethics committee approval was obtained from Kartal Dr. Lutfi Kırdar City Hospital (decision number 2020/514/180/25). 56 patients treated with the hypofractionation scheme in breast cancer adjuvant RT and at least five years of follow-up after RT were included. Male sex and patients with bilateral breast cancer were excluded from the study. All patients were 18 years of age with invasive breast cancer and/or ductal carcinoma in situ (DCIS). After breast-conserving surgery (BCS), 56 patients were treated with HF-WBRT with 42.56 Gy in 16 fractions or 40.5 Gy in 15 fractions and/or boost to the tumor bed.

Radiotherapy

We used the conventional RT technique. A high daily dose (2.66 Gy) was planned with fewer fractions (15/16 fractions and/or boosted) using 6-18 MV photon beams in the tangential areas. Dose prescription was defined so that the prescribed dose was not less than 95% of the minimum and not over 107% of the maximum. RT areas were determined above the suprasternal notch upper limit, medial border mid-sternal line, lateral border mid-axillary line, lower border 2 cm below the infra-mammary space, and 0.5 cm below the anterior skin border, as stated in the Radiation Therapy Oncology Group (RTOG) atlas.[17]

Follow-up

We evaluated patients once a week during RT, for three months for the first two years after RT, six months for 2-5 years, and annual controls after five years. Bilateral mammography and breast and abdominal ultrasonography were performed annually. Radiation dermatitis and other acute and late RT toxicities were assessed using the RTOG side-effect scale in weekly controls during and after RT.[18] Acute toxicity was evaluated during RT and the first six months after RT. Late toxicity was assessed six months after RT.

Statistical Analysis

Statistical analysis was performed using the SPSS v23.0 software package (IBM SPSS, New York, USA). Survival analysis was performed using the Kaplan-Meier method. The log-rank test was used for statistical evaluation for comparison between the groups and the Cox regression test for multivariate analyses.[19, 20]

Results

Fifty-six patients treated with HFRT were included in this study. The median follow-up was 90 (range 45-119) months, and the overall survival was 116 (range 113.8-119.8) months. The median age was 64 years, and 5.4% of the patients were under 50. All patients were treated with a 2.67 Gy/day at 15/16 fraction (40.5 – 42.5 Gy) and/or 4/8 fraction boost (8-16 Gy). The patient characteristics are presented in Table 1.

Dosimetric Evaluation

The mean clinical target volume (CTV) was 789 cc (273-1713.8). The breast separation was 19 cm (15.3-25 cm). The median V95 values of all patients for the planning target volume (PTV) were 95% (69.8%-100%). The maximum dose was 45.6 (39.32-61.7). The median dose was 42.91 Gy, and the median minimum dose (Dmin) was 21.15 (2.87-36.23). Mean volume PTV was calculated as 927 cm3 for the whole breast and 223.1 cm3 for PTV boost. The mean cardiac dose for left and right breast cancer patients was 0.98 Gy (0.36-4.58) and 0.5 Gy (0.24-4.35 Gy), respectively. The left and right heart mean values were 0.98 (0.36-4.58) Gy and 0.50 (0.24-4.35) Gy, respectively. The mean V5 and V10 values for the heart were 0 (0-0,18) Gy and 0 (0-0,05) Gy, respectively. The mean lung dose of the entire study population was 10 Gy (± 3.3 Gy), and the mean V20 was 20% (± 3%). In all patients, the mean lung dose was V20 7.27 (0.50-24.30) Gy. Although the mean dose and V20 values of the ipsilateral lung were appropriate, the mean dose and V5 for the contralateral lung were 4.05 Gy and 12.66%, respectively. Table 2 presents the dosimetric evaluation chart.

Acute-Late Side Effects

Acute and chronic skin toxicities were evaluated using the RTOG Morbidity Scoring Criteria. Acute skin toxicity was observed in 27 patients, and grade 1 toxicity in 23 patients. Grade 2 toxicity was detected in 4 (14%) patients, while grade 3 skin toxicity was not observed. When RT was completed, grades 0, 1, and 2 acute radiation dermatitis were detected in 29, 23, and 4 patients. Grade 1 skin toxicity persisted in 16 patients after three months of radiotherapy. When the patients with early skin side effects were analyzed according to menopause, type of operation,

Table 1. Patient characteristics

	n (%)
Localization	
Right	34 (61)
Left	22 (39)
Histopathology	
IDC	42 (75)
ILC	6 (11)
DCIS	2 (3)
Other	6 (11)
Menopause status	
Pre- menopause	12 (21)
Post- menopause	44 (79)
T stage	
Tis	2 (3)
T1	46 (82)
T2	6 (11)
T3	1 (2)
T4	1 (2)
Lymphovascular invasion	
Yes	3 (5)
Tumor diameter	
Median	1.2 (0.1-7.5) cm
Grade	
1	13 (23)
2	34 (61)
3	9 (16)
Receptor status	
ER positive	51 (91)
PR positive	44 (79)
HER-2 positive	7 (12)
Ki-67 %	
Median	%10 (0-67)
Surgery type	
BCS	54 (96)
MRM	2 (4)
Axillary dissection type	
SLNB	49 (88)
AD	7 (12)
Adjuvant chemotherapy	
Yes	30 (54)
No	26 (46)
Neoadjuvant chemotherapy	
Yes	1 (2)
Adjuvant endocrine therapy	
Yes	49 (88)
No	7 (12)
Radiotherapy target volumes	
Breast	30 (54)
Breast + boost	24 (43)
Chest wall + peripheral lymphatic	2 (3)
Radiotherapy dose	
40.05 (15 * 2.66Gy)	4 (7)
42.56 (16 * 2.67Gy)	28 (50)
50.05 (40.05 + 10Gy)	19 (34)
50.56 (42.56 + 8Gy)	2 (4)
56.05 (40.05 + 16Gy)	3 (5)

Table 2. The dosimetric evaluation chart

	Median (minimum-maximum)
CTV	789 cc (273-1713.8 cc)
Breast	
Breast separation	19 cm (15.3-25 cm)
D max	45.6 (39.32-61.7) Gy
D min	21.15 (2.87-36.23) Gy
D mean	42.91 (35.92-46.94) Gy
V95	Median %95 (%69.8-%100)
Boost Dose	
D max	53.17 (41.13-61.59) Gy
D min	48.36 (24.82-57.58) Gy
D mean	51.93 (40.23-60.03) Gy
Whole heart (Left-sided breast radiotherapy)	
Mean	0.98 (0.36-4.58) Gy
V5	0 (0-0.18) Gy
V10	0 (0-0.05) Gy
Whole heart (Right-sided breast radiotherapy)	
Mean	0.50 (0.24-4.35) Gy
V5	0 (0-0.14) Gy
V10	0 (0-0.05) Gy
LAD (Left-sided breast radiotherapy)	
Mean	1.74 (0-5.38) Gy
V5	0.02 (0-0.50) Gy
V10	0 (0-0.14) Gy
V20	NA
LAD (Right-sided breast radiotherapy)	
Mean	0.10 (0-2.42) Gy
V5	NA
V10	NA
V20	NA
Lung	
V5	15.40 (3.10-35.8) Gy
V10	10.45 (1.4-29.60) Gy
V20	7.27 (0.50-24.30) Gy
Contralateral breast	
D max	1.32 (0.03-22.11) Gy
D mean	0.01 (0.07-0.84) Gy

LAD: left anterior descending artery; CTV: clinical target volume.

presence of boost, RT dose, CT, and whether they received hormone therapy, no significant correlation was observed (P =0.427, P =0.736, P = 0.515, P =0.977, P =0.508, and P =0.541, respectively). Six months after RT, grade 1 toxicity persisted in 12 patients. When the skin reaction at the sixth month and the affecting factors were examined, no factor was significant. In the first-year follow-up, it was observed that the dermatitis findings did not wholly improve in all patients. No visible skin fibrosis, shrinkage, telangiectasia, or breast tissue atrophy was observed in the long-term controls. When factors affecting early and late skin toxic-

ity were evaluated using the Student's t-test and Mann-Whitney U test, it was not found that early skin toxicity was associated with age, RT dose, CTV, or breast separation (p= 0.508, p=0.287, p=0.970, p=0.775, respectively). While no relationship was found with age, CTV, and breast separation for late side effects (p= 0.862, p=0.930, and p=0.583, respectively), a significant correlation was found with surgery type (p=0.043), axillary dissection (p=0.032), and supraclavicular radiotherapy (p=0.043). Anemia was not observed during RT. Grade I dysphagia was found in only one patient at the end of treatment. Radiation pneumonia was not observed six months after RT.

Discussion

Eight published randomized trials have proven that adjuvant HF-WBRT (40 Gy in 15 fractions and 42.56 Gy in 16 fractions) is non-inferior to standard RT (50 Gy in 25 fractions) in local control, acute toxicity, and late toxicity.[21] As in the literature, acute and late skin toxicities were not observed in our study. No fibrosis, shrinkage, or retraction was observed during the 5-year follow-up. In the START A and START B studies, 36% of the patients received chemotherapy, some patients had a boost application, and breast size was not an exclusion criterion.[22] In a Canadian study, adjuvant chemotherapy was administered to 10.9% of the patients, boost was not applied, and those with a large breast size were excluded from the study. This study evaluated late toxicities and cosmetic results using RTOG and the European Organization for Research and Treatment of Cancer (EORTC) late scoring schema for skin and subcutaneous tissues.[23, 24] Adding a boost to the tumor bed in breast cancer reduces local recurrence even if the surgical margin is negative.[25-26, 30-31] It is unclear to whom and when the HFRT adds a boost. Freedman et al. added a concomitant boost to HF-WBRT in 75 early-stage breast cancer patients with intensity-modulated radiation technique (IMRT) at 2.25 Gy* × 20 fractions. A 56 Gy boost was applied to the tumor bed at 2.8 Gy/day, and acute skin toxicity was not found in any case.[27] In another study with a few patients examining the boost and side effects of HF-WBRT, it was reported that acute skin toxicity was 67%, late toxicity grade 1 skin fibrosis was 40%, and grade 2 skin fibrosis was 3%.[28] In addition, there have been studies showing that a boost affects cosmetic results.[29] In our study, a sequential boost was applied to the tumor bed in patients with a high risk of recurrence (high-grade disease, hormone receptor-negative, age < 50 years). A daily boost was administered to 24 patients at doses ranging from 2 Gy/day to 8-16 Gy; acute grade 1 skin toxicity continued in 12 patients, and grade 1 chronic skin toxicity continued in seven patients in the sixth month. In the multivariate analyses, a significant relationship between boost and other factors in terms of the development of toxicity was not observed. However, late skin toxicity was significantly correlated with an increase in the total RT dose (p=0.039).

Studies emphasize that boosting tumors in HF-WBRT and acute toxicity are seen more frequently in patients with a large body mass index (BMI).[30, 31] Although patients' toxicities were not evaluated according to their BMI, the relationship between clinical breast volume and toxicity was examined in our study. According to some studies, large breast size is often associated with dose inhomogeneity and takes over 107% of the prescribed dose, associated with increased acute and late skin toxicity.[32, 9] Many studies have demonstrated a relationship between breast volume and skin toxicity. According to Corbin et al., no increase in acute skin toxicity was observed in women with large breasts.[33] One study reported more acute skin reactions in patients with breasts > 1600 cc than those with breasts < 1600 cc.[34, 35] RTOG grade 3 skin toxicity was not observed in any patient when the breast volume was <975 cc.[35]

Ciamella et al. emphasized a significant relationship between breast volume, acute skin toxicity, and cosmetic results (p=0.01504, p=0.0207).[36] In our study, the CTV was 789 cc (273-1713.8 cc), and as stated in the literature, acute and chronic grade 3 skin toxicity was not observed. When evaluating breast separation, the craniocaudal length was 19 cm (15.3-25 cm), and the relationship between early skin toxicity, CTV volume, and breast separation was insignificant (p=0.970 and 0.775, respectively). In addition, the relationship between late skin toxicity, CTV volume, and separation was negligible (p=0.930 and 0.870, respectively). In the multivariate analyses, skin reactions persisting at the sixth month were associated with surgery type (p=0.043), axillary dissection type (p=0.032), and supraclavicular radiotherapy (p=0.043).

In a phase 3 study of 820 patients, in which the efficacy and side effects of hypofraction were evaluated in the post-mastectomy RT study published in 2019, the 5-year loco-recurrence rate was 8.3% in patients aged 18-75 years, with positive T3-T4 and/or at least four lymph nodes (8.1% in the normofraction). There was no difference in acute and late toxicity between the HFRT and normofractionated groups.[37] In our study, the 3-dimensional conformal RT technique was used in all patients, and side-effect rates were shown in line with the literature. Recent studies related to volumetric arc therapy (VMAT) and simultaneous integrated boost (SIB) in the hypofraction and VMAT and SIB's use in the hypofraction emphasized excellent cosmetic results. These results are similar to those of our study.[38-40]

Our study has some limitations: although side effects and

survival were evaluated in HFRT patients with at least five years of follow-up, and the results were found in line with the literature in our study, the retrospective nature of the study, the small number of patients, and the relationship between patient-related parameters such as BMI and side effects were not evaluated. Visualization of acute and chronic skin reactions, the low number of patients with different boost doses in the dosimetric evaluation, and only two patients with peripheral lymphatic irradiation are also the study's limitations.

Conclusion

Adjuvant hypofractionated radiotherapy is well tolerated as conformal radiotherapy. The literature reports excellent long-term cosmetic results in our patients, often with mild side effects such as grade 1-2 skin reaction, with no treatment interruption.

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