The Role of Systemic Immune-Inflammation Indices, Dosimetric and Surgical Parameters in the Prediction of Breast Fibrosis after Whole Breast Radiotherapy

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ABSTRACT

Breast fibrosis (BF) is one of the most reported late toxicities following whole breast radiotherapy (WBRT). This study aims to find out biomarkers that can be used in individual risk assessment of BF. The correlation of surgical and dosimetric parameters with BF was also analyzed. Two hundred twenty-three invasive breast carcinoma patients who underwent breast conserving surgery and adjuvant WBRT +/- regional nodal irradiation were included in the study. Age, lumpectomy size, microscopic tumor size, systemic treatment status, the time from surgery to WBRT were the clinicopathological features evaluated. The volume of the whole breast and boost volume and their ratio, the maximum and mean dose of the breast, the dose of 95% of breast volume, the percent of the breast volume that had 50Gy and more (V50), V55, and V60 were the parameters evaluated. Neutrophil/lymphocyte, platelet/lymphocyte, lymphocyte/monocyte, systemic immune-inflammation index, hemoglobin, and C-reactive protein (CRP) levels before WBRT, the ratio of hemoglobin and CRP levels before and after WBRT were the biomarkers that investigated for prediction of BF. The median follow-up time was 22.5 (6-85.29) months. Grade 1 fibrosis was observed in 107 (47%), and grade 2 fibrosis in 7 (3.1%) patients. In the grade 1-2 fibrosis group lymphatics irradiation rate was higher (51.8% vs 35.8%, p= 0.016) and the treated breast in this group were mostly left-sided (left side percentages: 38.5% vs 56.1%; p= 0.008). CRP-Ratio was the only parameter that had statistically significant ROC curve (Area under the curve: 0.412, p= 0.024). The CRP-Ratio value of 0.544 was found to have the best sensitivity (35.65%) and specificity (84.25%).

Keywords: Whole breast radiotherapy, Breast fibrosis, Immune-inflammation index, CRP

INTRODUCTION

Whole breast radiotherapy (WBRT) is the standard approach after breast-conserving surgery (BCS) to improve local control in invasive breast carcinoma cases.[1,2] The primary goals of WBRT planning are to minimize the hot spots and homogenize the dose distribution. In line with this purpose; 3- dimensional conformal radiotherapy (3DCRT) and intensity-modulated radiotherapy (IMRT) were developed after the conventional tangential technique era.[3,4] Such developments reduced the normal tissue toxicity rates as expected.[5-7]

Ipsilateral lung fibrosis, ischemic cardiac diseases (in left-sided cases), lymphedema of the ipsilateral arm, and breast fibrosis (BF) are the most reported late toxicities following WBRT. Severe BF rates are 1%-13%, whereas moderate fibrosis rates are higher (20-58%)[6,8,9] that occurs 4-12 months after WBRT. Skin induration and thickening, breast shrinkage, pain, atrophy, and even muscle shortening are some of the clinical symptoms of BF.[6] Reduced quality of life may come into question due to discomfort of breast and impaired body perception. The pathophysiological mechanism of BF is based on increased fibroblast proliferation and activation of extracellular matrix by radiotherapy (RT).

In contrast, radiosensitivity is an essential factor underlying individual differences in the development and severity of fibrosis between patients and even in different tissues of the same patient.[10] Clinicopathological features and dosimetry of WBRT are the major factors that are considered to be related to BF, although there are conflicting results in the literature. Some could not demonstrate the apparent effect of dosimetry on BF, but they found chemotherapy, re-resection, and large tumor size associated with BF grade ≥ 2 [9] however, others claimed dosimetry as the only predictive variable.[11] Besides, the molecular genomics were evaluated and considered to be predictive for BF like XRCC1 polymorphism[12] and radiation-induced gene expression in subcutaneous fibroblast.[13] Because of the high cost and prolonged results, genomic tests are not utilized in routine clinical practice. Therefore, researchers investigated cheaper and more convenient biomarkers to predict BF. Radiation-induced lymphocyte apoptosis (RILA), which is defined as the percentage of peripheral blood death induced by a particular radiation dose minus the spontaneous cell death, was one of these biomarkers reported to be effective in predicting BF.[14] In this study, we aimed to find out much cheaper, rapid, and reproducible biomarkers that can be used in individual risk assessment of grade 1-2 BF that occurred after WBRT. Neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), lymphocyte to monocyte ratio (LMR) and systemic immune-inflammatory index (SII), the hemoglobin (Hb) and C-reactive protein (CRP) levels which all obtained from the routine blood testings before radiotherapy (RT), were evaluated about the predictive value for BF. The ratio of Hb and CRP levels before and after RT (Hb-R and CRP-R) were also investigated. Since there is no doubt that BF is associated with many factors, surgical and dosimetric parameters were also included in the analysis.

PATIENTS and METHODS

Patients and Clinicopathological Features

Histopathologically confirmed invasive breast carcinoma patients who underwent BCS and adjuvant WBRT with tumor bed boost were the target population of this study. The patients who have lymphatic irradiation or not were both included. Three hundred and two breast cancer patients' data who were treated for WBRT in our radiation oncology department since the departments' initiation in 2012 were reviewed retrospectively, and the ones that met the inclusion criteria were enrolled. Inclusion criteria were as follows: had a WBRT at a dose of at least 50Gy with or without a tumor bed boost; complete blood count and serum CRP levels checked before and after WBRT were accessible in the hospital database; attended surveillance program for at least six months or more.

Age, lumpectomy size (calculated as cc by multiplying three dimensions noted in the macroscopy of the pathological assessment); microscopic tumor size, chemotherapy, hormonotherapy or trastuzumab treatment status, the time between BCS and WBRT were the clinicopathological features evaluated.

The patients had a physical examination for the acute and late side effects on the 10th day after RT completion and then every three months for the first two years. The breast fibrosis grade was evaluated according to Common Terminology Criteria for Adverse Events (CTCAE), version 5.0.[15] The CTCAE criteria for fibrosis are grade 0 (no fibrosis), grade 1 (mild induration, ability to move skin parallel to plane (sliding), and perpendicular to skin), grade 2 (moderate induration, able to slide skin, unable to pinch skin) and grade 3 (severe induration; unable to slide or pinch skin). The grade of fibrosis at the last follow-up (at least the sixth month after RT) was recorded.

The protocol of this study is reviewed and approved by the Suleyman Demirel University Clinical Research Ethics Board of Medical Faculty by the number 26.01.2021/34.

Radiotherapy Planning and the Dose Parameters

RT simulation computed tomography (CT) scans were performed in a supine position with a breast board or a vacuum cushion and wing board. CT images were obtained with a 2.5-mm slice thickness of the thorax region from the upper abdomen to the bottom of the chin. Treatment plans were

created using the Eclipse treatment planning system (TPS) on Varian DHX linear accelerator. A total of 50Gy was planned in 25 fractions with a daily dose of 2Gy/fraction as the prescribed dose. Tumor bed boost was prescribed as 10Gy in 5 fractions or 16Gy in 8 fractions if there is a positive surgical margin. For WBRT, the field-in-field (FIF) planning technique which is also known as forward planned intensity-modulated radiotherapy (forIMRT), was performed with two open tangential fields using 6-18 MV x-rays and in-fields up to 5. All the patients' RT plans were forIMRT. The points under consideration for RT plan evaluation were that 95% of the target volumes had ≥ %95 of the prescribed dose, and the hot spots were under 107%.

The absolute volume of the whole breast and boost volume was calculated by the TPS after target delineation. The ratio of the boost volume and the whole breast (Vboost/Vbreast) was also calculated for each patient. The dose-volume parameters were obtained from the dose-volume histograms (DVH). The maximum dose of the breast (Dmax), the mean of the breast (Dmean), the dose of 95% of breast volume (D95), the percent of the breast volume that had 50Gy and more (V50), 55Gy, and more (V55) and 60Gy and more (V60) were the dose parameters recalculated and collected.

Immune-Inflammation Indices

The immune-inflammation indices were calculated by the absolute values obtained from the complete blood count test at the initiation of RT and by the following formulas: NLR= Neutrophil/lymphocyte, PLR= platelet/lymphocyte, LMR=lymphocyte/monocyte, and SII= Neutrophil x platelet / lymphocyte. The Hb and CRP values before RT treatment; the ratio of Hb and CRP levels before and after RT (Hb-R and CRP-R) were also saved and calculated.

Statistical Analysis

The characteristics of the patients were presented by descriptive statistics. The Chi-square or Fisher's exact test was used to compare the categorical features of grade 0 and grade 1-2 BF groups. The distributions of variables were evaluated by normality tests, and according to the non-parametric features, the age, the lumpectomy volume, the tumor size, and the time between surgery to WBRT were compared by Mann-Whitney U tests between BF groups. Spearman's correlation test was conducted to evaluate the correlations of dosimetric, clinicopathologic features, and immune-inflammatory indices with BF grade. The cut-off values of continuous variables for grade 1-2 BF were investigated by Receiver operating characteristic (ROC) curves. All the statistical analyses were conducted by using software IBM SPSS statistics version 21.0. The p-values < 0.05 were considered to be statistically significant.

RESULTS

Totally 223 patients who had WBRT met the inclusion criteria and enrolled in the study. 102 (43.4%) patients also had lymphatic irradiation: axillary, infra- supraclavicular, and internal mammary nodes region as if indicated. 217 (92.4%) patients had 10Gy, and 8 (3.4%) patients had 16Gy tumor bed boost following WBRT. The median follow-up time was 22.5 (6-85.29) months. Grade 0 fibrosis was observed in 109 (48.9%) patients, grade 1 fibrosis was observed in 107 (47%), and grade 2 fibrosis was observed in 7 (3.1%) patients.

The clinicopathologic features of grade 0 and grade 1-2 patients were compared detailed in Table 1. There was no statistically significant difference between the two groups except RT target volumes and side of treated breast. In the grade 1-2 fibrosis group, the percentage of cases with lymphatic irradiation was higher (51.8% vs. 35.8%, p= 0.016). The grade 0 fibrosis group cases were mostly right breast-sided, although the grade 1-2 fibrosis group were mostly left-sided (right side percentages were 61.5% vs. 43.9%; p= 0.008). Additionally, it is notable that the median lumpectomy size was slightly greater in the grade 1-2 group, but the difference was not statistically significant (p= 0.182).

The median values of all cases' volumetric, dosimetric parameters, and immune-inflammation indices are presented in Table 2. Firstly the correlations between all clinicopathological features, dosimetric parameters, immune-inflammation in-

Table 1. Comparison of clinicopathologic characteristics of grade 0 and grade 1-2 patient groups

Characteristic	Grade 0 fibrosis (n= 109)	Grade 1-2 fibrosis (n= 114)	p-value	Total
Age *	53 (28-77)	55 (26-85)	0.300	54 (26-85)
Treated breast				
Left	42 (38.5%)	64 (56.1 %)	0.008	106 (47.5%)
Right	67 (61.5%)	50 (43.9%)		117 (52.5%)
Lumpectomy volume (cc)*	365 (95-1566)	397.37 (58.7-2584)	0.182	385 (58.7-2584)
Tumor size (mm)*	21 (1-50)	22.5 (3.5-105)	0.215	22 (1-105)
Surgery-RT time (months) *	5.02 (0.62-10.32)	6.4 (0.43-10.5)	0.219	5.91 (0.43-10.5)
RT target volume				
WB + TB boost	70 (64.2%)	55 (48.2%)	0.016	125 (56.1%)
WB+TB boost +lymphatics	39 (35.8%)	59(51.8%)		98 (43.9%)
Chemotherapy				
Adjuvant	78 (71.6%)	85 (74.6%)	0.696	163 (73.1%)
Neoadjuvant	6 (5.5%)	4 (3.5%)		10 (4.5%)
No	25 (22.9%)	25 (21.9%)		50 (22.4%)
Hormonotherapy				
Yes	94 (86.2%)	95 (83.3%)	0.581	189 (84.8%)
No	15 (13.8%)	19 (16.7%)		34 (15.2%)
Trastuzumab				
Yes	22 (20.2%)	21 (18.4%)	0.794	43 (19.3%)
No	87 (79.8%)	93 (82.4%)		180 (80.7%)

*RT: radiotherapy, WB: whole breast, TB: tumor bed. * The values are presented as median(range)*

dices, and fibrosis status were evaluated by Spearmans' test. Treated breast side, RT target volume and CPR-R had weakly correlations with fibrosis status whereas the p values were statistically significant (Correlation coefficients (CC) and p-values are respectively: CC: 0.176 (p= 0.008), CC: 0.161 (p= 0.016), CC: 0.158 (p= 0.018)).

Secondly, ROC curve analyzes were conducted for the volumetric, dosimetric parameters, and immune-inflammation indices to determine their effect on fibrosis status. As a result, CRP-R was the only parameter with statistical significance in ROC curve analysis (Area under the curve: 0.412, p= 0.024) (Figure 1). The CRP-R value with the best sensitivity and specificity was 0.544 (Sensitivity: 35.65% and specificity 84.25%).

To evaluate why the RT target volume was correlated with fibrosis status, the dosimetric parameters were compared between WB and WB+lymphatic irradiated groups. There was no statistically significant difference between breast and boost volumes or Vboost/Vbreast. Breast D95 and Breast V50 were significantly higher in cases with lymphatics irradiated (p= 0.001 and 0.004 respectively) (Table 3).

DISCUSSION

Fibrosis is a common RT side effect that refers to an irregular buildup of the extracellular matrix. It may often result in the failure of the organ in question. Mostly nonspecific histologic changes are seen in the vascular connective tissues, such as extracellular matrix deposition, fibroblast proliferation, and inflammatory infiltration.[16] Pre-fibrotic phase, developed fibrosis, late fibrosis, and atrophy/necrosis are the four stages of fibrosis in response to stress.[17]

In our study, the grade 1-2 BF rate was 50.1%, and it was similar to the previous reports. When the grade 0 fibrosis cases and the grade 1-2 fibrosis cases were compared, it was noteworthy that the grade

Table 2. Median values of volumetric, dosimetric parameters, and immune-inflammation indices of all cases

	Median	Range
Breast volume (cc)	812.67	162.56-2197.89
Boost volume (cc)	31.36	3.32-421.47
Vboost/Vbreast	0.043	0.003-0.298
Breast Dmax (Gy)	63.80	61.34-71.34
Breast Dmean (Gy)	54.38	42.58-62.34
Breast D95 (Gy)	49.40	41.39-51.49
Breast V50 (%)	92.51	71.45-98.84
Breast V55 (%)	33.28	5.49-90.02
Breast V60 (%)	19.09	2.64-70.45
NLR	2.35	0.33-9.67
LMR	2.84	0.25-22.5
PLR	174.8	22.11-970
SII	632.22	46.67-5142.67
CRP-pre	4.36	0.29-78.6
Hb-pre	12.1	8.6-15.1
CRP-R	1	0.01-9.02
Hb-r	0.95	0.65-1.06

Vboost/Vbreast: boost volume/ breast volume, Dmax: maximum dose, Dmean: mean dose, D95: the dose of 95% of breast volume, V50, V55, V60: the percentage volume that has 50Gy, 55Gy, and V60Gy more.

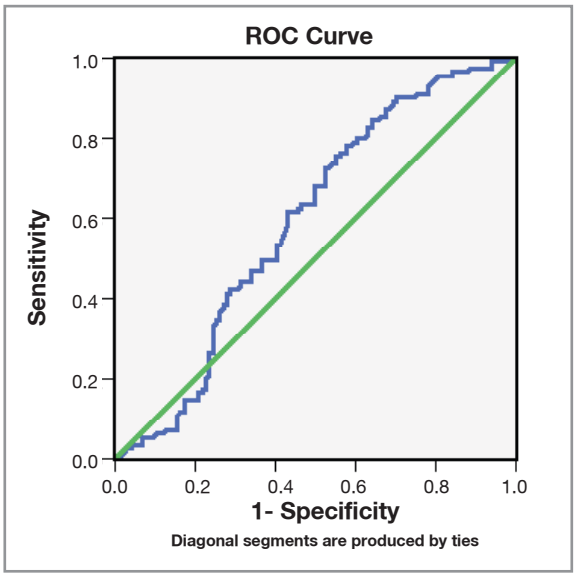

Figure 1. Receiver operating characteristics (ROC) curve analysis on breast fibrosis status for pre and post-radiotherapy C reactive protein-ratio. Area under the curve (AUC)= 0.591, p= 0.018, 95% CI: 0.516-0.667.

1-2 fibrosis cases were mostly left-sided (left side percentages: 38.5% in grade 0 fibrosis and 56.1% in grade 1-2 fibrosis). There is no such finding in any of the previous studies. To our knowledge, the lateralization of tumors is not investigated in any published literature focused on factors affecting radiation-induced breast fibrosis.

Another statistically significant result was that the rate of lymphatic irradiation was higher in patients with grade 1-2 fibrosis (lymphatic irradiation percentages: 35.8% in grade 0 fibrosis and 51.8% in grade 1-2 fibrosis cases). When it is considered that in the patients who underwent lymphatic irradiation with clinical-stage IIb or III, the chest wall, including the pectoralis muscles and ribs, is also included in the RT target volume[18], this is an expected result. The increased exposure of muscle tissue to RT may be related to the increase in the grade of BF in the patient, as assessed by physical examination. Breast size is also reported as an effective factor in breast fibrosis by Barnett et al.[19]

The authors have shown that a larger breast volume increases the risk of late toxicity. This is attributed to dose inhomogeneity and self-bolusing of the breast over the inframammary fold or possible greater radiation damage on fat cells than normal breast tissue, which may cause consequential late effects in some additional confirmatory studies.[20,21] Pignol et al. also found breast volume as a predictive factor for acute toxicity. Conclusively, breast volume has been accepted as a baseline characteristic predictive for radiation-induced late toxicity.[22] However, there was no difference between the median Vbreast and Vboost values of the patients with grade 0 and grade 1-2 late toxicity in our study.

Large size tissue resection in order to achieve adequate margins may also influence late toxicity.[19] Alexander et al. generated dose-volume data via estimating parameters for a seriality model and Lyman model.[23] The authors conclusively suggested a parallel architecture for breast tissue strongly affecting breast fibrosis. We found that median lumpectomy size was slightly greater in the grade 1-2 group, which did not reach statistical significance (p= 0.182).

Table 3. Comparison of dosimetric and volumetric parameters in between the RT target volume groups

	WB+TB boost	WB+TB boost+ LMP	p value
Breast volume(cc)	789.49 (193.53-1689.54)	856.68 (162.56-2197.89)	0.376
Boost volume(cc)	29.51 (3.32-218.85)	35.33 (4.42-421.47)	0.319
Vboost/Vbreast	0.045 (0.005-0.233)	0.044 (0.003-0.298)	0.653
Breast Dmax (Gy)	63.76 (62.29-70.50)	63.86 (61.34-71.37)	0.707
Breast Dmean (Gy)	54.25 (51.85-60.01)	54.53 (42.58-62.34)	0.352
Breast D95 (Gy)	49.20 (41.39-51.49)	49.62 (42.80-51.20)	0.001
Breast V50 (%)	91.86 (74.32-98.84)	93.43 (71.45-98.61)	0.004
Breast V55 (%)	33.48 (5.49-90.02)	32.68 (8.94-62.74)	0.616
Breast V60 (%)	20.40 (2.64-70.45)	18.22 (2.92-51.65)	0.310

WB: whole breast, TB: tumor bed, LMP: lymphatics, Vboost/Vbreast: boost volume/ breast volume, Dmax: maximum dose, Dmean: mean dose, D95: the dose of 95% of breast volume, V50: the percentage volume that has 50Gy and more

To look beyond the surface of dose-volume effects for breast tissue in breast RT became mandatory in the era of non-uniform irradiation such as accelerated partial breast irradiation, simultaneous integrated boost, and risk-adapted RT.[24,25] Barnett et al. suggested to minimize volume receiving more than 107% of the prescribed dose and prefer boost administration for the patients who are at high risk of local recurrence.[19] BF nomogram suggested by the EORTC 22881-10882 trial found a strong association between RT dose, large boost volumes, and fibrosis.[26] We evaluated breast D95 and breast V50 values as dosimetric parameters, and both were significantly higher in cases with lymphatics irradiated (p= 0.001 and 0.004 respectively) (Table 3). However, no significant correlation between these dosimetric parameters and BF was found.

CRP-R was the only biomarker that we found to be predictive for BF. However, it should be considered that the cut-off value's sensitivity and specificity are not quite sufficient (Sensitivity: 35.65% and specificity 84.25%). CRP binds to its receptor, CD32/CD64, to activate the NF-B signaling pathway, which causes inflammation. CRP also plays a role in tissue fibrosis in various cardiovascular and kidney diseases by triggering TGF/ Smad signaling through TGF-1/ Smad-dependent and independent mechanisms. CRP binds to FcRII and stimulates TGF/Smad3 and non-TGF/Smad3 signaling pathways, causing inflammation and fibrosis both directly and indirectly.[27] All these pathways may explain the higher BF rate in patients with increased CRP levels after WBRT.

Hormonal therapy is another factor investigated in terms of the effect on the incidence of radiation pneumonitis, breast fibrosis, cosmesis. There are conflicting results on the effects of sequential or concurrent tamoxifen administration in the literature.28-30 A retrospective study suggested an increase in breast fibrosis with concurrent tamoxifen compared to sequential utilization[28], where two others could not find any difference.[29,30] In our study, adjuvant hormonal therapy was used sequentially with RT in hormone receptor-positive cases.

In studies using identical RT dose-fractionation schedules as in our data, genetic and epigenetic factors are also suggested as the cause for 70% of individual variation in late normal tissue toxicity.[31]

There are several limitations of this study. First, the evaluation of BF is regardless of site, such as boost area or out of boost area, which may influence the results of dose effects. The subjective recording of fibrosis grading is another critical limitation destroying the credibility of our data set. Second is the lack of data on smoking, diabetes, detailed information about surgery, post-operative complications, chemotherapy details, and genetic factors, all of which can affect breast fibrosis.[26] There is no case of breast cancer treated with 3DCRT or inverse planned IMRT in our radiation oncology department. For this reason, it could not be investigated whether the immune-inflammatory indices differ between these two treatment techniques. It is known that IMRT provides more homogeneous dose distributions compared to 3DCRT. Evaluation

of dosimetric parameters in our study ultimately investigates the effect of radiotherapy dose distributions on breast fibrosis. In addition, since the present study is in a retrospective intent, patients with CRP results in control blood tests before and after RT were included in the study. Considering that CRP may be elevated in many inflammatory processes, it is necessary to evaluate the value of CRP-R in predicting BF in a controlled randomized prospective study. This retrospective study may lead to prospective studies.

Conclusion

We found that grade 1-2 BF due to WBRT is more common in left-sided breasts and lymphatics irradiated cases. We could not demonstrate any predictive value of pre-RT NLR, PLR, LMR, SII, Hb, CRP, or Hb-R on BF. CRP-R was the only biomarker that could be predictive for BF if below 0.544. BF is a complex process considered multifactorial, and still, accurate prediction of it remains complicated before conventional fractionated WBRT.

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