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Does shortening the duration of radiotherapy treatment in breast cancer increase the risk of radiation pneumonia

A retrospective study

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Abstract

Randomized studies evaluating hypofractionation and conventional fractionation radiotherapy treatments (RT) in patients with breast cancer have shown that hypofractionation achieves similar results to conventional fractionation in terms of survival and local control rates. It has also been shown that their long-term toxicities are similar. This study aimed to evaluate the effects of hypofractionated radiotherapy (H-RT) and conventional radiotherapy (C-RT) on lung toxicity and identify factors affecting this toxicity in patients with breast cancer. The study included 118 patients who underwent adjuvant RT following breast-conserving surgery (BCS). Out of these, 63 patients were assigned to receive C-RT, while the remaining 55 were assigned to receive H-RT. To clarify, we treated 63 patients with C-RT and 55 patients with H-RT. 60 patients were treated using 3-dimensional conformal radiotherapy (3DCRT) and 58 patients were treated using intensity modulated radiotherapy (IMRT). The patients were evaluated weekly for toxicity during radiotherapy (RT) treatment and were called every 3 months for routine controls after the treatment. The first control was performed 1 month after the treatment. Statistical analysis was performed using the SPSS20 program, and a *P* value of <.005 was considered statistically significant. The study found that the median age of the participants was 54.9 years and tomographic findings were observed in 70 patients. Radiological findings were detected at a median of 5 months after RT. The mean lung dose (MLD) on the treated breast side (referred to as ipsilateral lung or OAR) was 10.4 Gy for the entire group. Among patients who received 18 MV energy in RT, those with an area volume (V20) of the lung on the treated breast side >18.5%, those with a mean dose of the treated breast side lung (ipsilateral lung) >10.5 Gy, and those who received concurrent hormone therapy had significantly more tomographic findings. However, patients treated with YART had fewer tomographic findings. No symptomatic patients were observed during the follow-up period. Our findings show that the risk of lung toxicity is similar with H-RT and C-RT, and H-RT can be considered an effective and safe treatment option for breast cancer. The key factors affecting the development of lung toxicity were found to be the type of RT energy used, RT to the side breast, volume receiving 20 Gy in the side lung, side lung mean dose, and simultaneous hormonal therapy.

Abbreviations: 3DCRT = 3-dimensional conformal radiotherapy, BCS = breast-conserving surgery, C-RT = conventional radiotherapy, DVH = dose volume histogram, H-RT = hypofractionated radiotherapy, IMRT = intensity modulated radiotherapy, MLD = mean lung dose, RP = radiation pneumonia, RT = radiotherapy, RTOG = radiation therapy oncology group.

Keywords: BCS, C-RT, GGO, H-RT, IMRT, MLD

1. Introduction

Radiation therapy (RT) is an important component of breast cancer treatment, as it increases local control and thereby improves patient survival. Technological advances in RT have enabled more targeted delivery of radiation doses to the affected area, while minimizing the risk of side effects to normal tissues. Techniques such as 3-dimensional conformal radiation therapy, intensity-modulated radiation therapy, helical radiation therapy, and volumetric arc radiation therapy have reduced the risk of organ toxicity in high-risk areas. The standard treatment approach for breast cancer is conventional RT (C-RT), which involves daily doses of 1.8 to 2 Gy for 5 days a week, for a total of 45 to 50 Gy over 25-28 days. In recent years, hypofractionated RT (H-RT) regimens, which involve the completion of RT

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in a shorter time by administering higher fraction doses, have gained prominence. Evidence of the feasibility and applicability of H-RT is growing, and studies have shown that hypofractionation is comparable to conventional fractionation in terms of survival rates, local control rates, and long-term toxicity. Radiation pneumonia (RP) is a major dose-limiting factor in RT for breast cancer. This study aimed to evaluate the impact of hypofractionated treatment and conventional treatment on lung toxicity and the factors affecting toxicity in patients with breast cancer.[1]

2. Materials and methods

In this study, 118 patients who underwent breast-conserving surgery (BCS) and received adjuvant RT were included, with 63 in the conventional arm and 55 in the hypofractionation arm. 60 patients received treatment using 3-dimensional conformal radiotherapy (3DCRT) and 58 using intensity modulated radiotherapy (IMRT). Our treatment center conducts follow-up appointments for patients who have received oncologic chemotherapy and RT within the first year after treatment. As part of our diagnostic tests, these appointments include blood biochemistry, regional ultrasound, and chest CT examinations. Chest CT images were analyzed for signs of ground-glass opacities, consolidation, reticular pattern, and architectural distortion in the irradiated field. Ground-glass opacities indicates an area of increased lung density with visible bronchial and vascular structures, which represents pulmonary edema. Consolidation is defined as the filling of alveolar air spaces with fluid, cells, or other substances, and the presence of air bronchograms in the radiation field suggests RP. The reticular pattern refers to linear opacification in the lung and smooth reticulations in the peripheral radiation field indicate lung fibrosis. After treatment, patients were followed up every 3 months, with the first checkup 1 month after treatment and routine checkups thereafter. Toxicity was assessed on a weekly basis during treatment, and symptoms of RP such as dyspnea, fever, and dry cough were evaluated using the Radiation Therapy Oncology Group (RTOG) clinical rating scale and EORTC LENT-SOMA toxicity score (Table 1). Statistical analysis was conducted using IBM SPSS Statistics v20.0 software. Descriptive statistics such as mean, standard deviation, median, minimum and maximum values, and frequencies were used to summarize data. Pearson correlation was used to analyze the relationship between 2 quantitative variables if the data followed a normal distribution, and Spearman correlation was used if the data did not fit the normal distribution. The chi-squared test was used for cross-tabulation of qualitative data with ≥ 5 samples, and Fisher exact test was used for cross-tabulation of data with < 5 samples. A *P* value <.05 was considered statistically significant. The study was approved by the Kartal Dr Lutfi Kirdar City Hospital Clinical Research Ethics Committee on December 6, 2019 (reference number 514/167/16) and was conducted in accordance with the Principles of Helsinki and with informed consent from all participating patients.

3. Results

Of the 118 patients evaluated after receiving adjuvant RT following BCS, the median age was 54.95 (range 28–84). 25 patients (21.2%) were active smokers and 92 (78%) had never smoked in their lifetime. Seven patients (5.9%) had heart disease, 12 (10.2%) had asthma, and 1 (0.8%) had chronic obstructive pulmonary disease. 50% of the patients had no additional diseases. BCS was performed on all patients, with axillary dissection performed in 27.1% and sentinel lymph node dissection performed in the rest. Lymphatic field RT was received by 61 patients (51.7%) and the tumor was in the right breast in 62 patients (52.5%). Invasive ductal carcinoma was present in 89.8% of the patients and luminal type B was found in 58.5% through immunohistopathology. 94 patients (79.7%) had received chemotherapy prior to RT. Of the 118 patients evaluated, 92 (78%) received adjuvant hormone therapy, with 32 (27.1%) using additional hormones. These patients were divided into 2 groups, with 63 receiving conventional treatment and 55 receiving hypofractionation. The conventional treatment involved daily doses of 1.8 to 2 Gy administered over 25 to 28 days for a total of 45 to 50 Gy, with an additional 10 Gy in 5 fractions to the tumor site for a total of 60 Gy radiation therapy. The hypofractionated group received 2.66 fractions of 40 to 42 Gy for 15/16 days and an additional 10 Gy in 4 fractions for a total of 50 to 52 Gy radiation therapy at the tumor site (Table 2). 3DCRT was used in 60 patients (50.8%) and IMRT was used in 58 patients (49.2%) during treatment. 77 patients (65.3%) received 6MV energies and 41 patients (34.7%) received 6 to 18 MV energies. 45.8% of patients (54 individuals) had a lung volume of 18.5 and received 20 Gy. 57.6% of patients (68 individuals) had a mean lung dose (MLD) <10.5 Gy. No patients reported any symptoms during the follow-up period. The 70 patients who had mild radiological findings without symptoms were evaluated as grade I according to the RTOG assessment. Grade II toxicity was not observed. According to the EORTC LENT-SOMA toxicity score, the patients were also evaluated as grade I. During follow-up, 59.3% of patients (70 individuals) showed CT findings, with the most common being the reticular pattern at 26.3%. CT findings are summarized in (Table 3). The presence of tomography findings was significantly higher in patients who used 18 MV energy (p:.000026), received RT to the right breast (p:.002), received 20 Gy in the lung with a volume of 18.5 or above (p:.000037), had a MLD of 10.5 Gy or above (p:.000088), and received concomitant hormone therapy (p:.011). In the multifactorial Cox regression analysis, the use of concomitant hormone therapy loses its statistical significance. The results showed no significant difference in the development of tomography findings between conventional and hypofractionated regimens. Patients treated with IMRT had fewer

Table 1

Radiation therapy oncology group (RTOG) clinical rating scale and EORTC LENT-SOMA toxicity score.

Grade system	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
RTOG	Asymptomatic or mild symptoms	Moderate symptoms of pneumonitis (severe cough) and radiographic changes (radiographic patches)	Severe symptoms of pneumonitis, dense radiographic changes	Symptoms of severe respiratory failure requesting assisted ventilation or continuous O_2	Death-related late effects of radiotherapy
LENT-SOMA	Asymptomatic or mild symptoms; Mild radiographic changes	Moderate symptoms; Moderate radiographic changes	Severe symptoms; Severe radiographic changes	Serious symptoms requiring continuous O_2 or assisted ventilation	Death

EORTC = European Organisation for Research and Treatment of Cancer, LENT-SOMA = Late Effects Normal Tissue Task Force-Subjective, Objective, Management, Analytic, RTOG = radiation therapy oncology group.

Table 2

General characteristics of included patients.

Characteristic	Number of patients (n)	Percentage (%)
Breast		
• Right	62	52.5
• Left	56	47.5
Histology		
• Invasive ductal	106	89.8
• Invasive lobular	2	1.7
• Other	10	8.5
Type of operation		
• BCS	2	1.7
• BCS + SLND	84	71.2
• BCS + SLND + ALND	19	16.1
• BCS + ALND	13	11.0
Age		
• 28–60	41	34.7
• 60–84	77	65.3
Receptor status		
• Estrogen (+)	91	77.1
• Estrogen (–)	27	22.9
• Progesterone (+)	76	64.4
• Progesterone (–)	42	35.6
• cERBB2 (+)	32	27.1
• cERBB2 (–)	86	72.9
Concomitant use of hormones		
• Yes	32	27.1
• No	86	72.9
Use of chemotherapy		
• Yes	94	79.7
• No	24	20.3
Luminal classification		
• Triple-negative	22	18.6
• Luminal a	69	58.5
• Luminal b	18	15.3
• HER2 (+)	9	7.6
Chemotherapy regimen		
• 12P	24	20.3
• 12PH	5	4.2
• 1AC	1	0.8
• 3AC + 12P + H	1	0.8
• 3AC + 9P	1	0.8
• 4AC	10	2.5
• 4AC + 4	5	8.5
Pertuzumab + H + T	1	4.2
• 4AC + 10P	35	0.8
• 4AC + 12P	23	29.7
• 4AC + 12P + H	1	19.5
• 4FEC	7	0.8
• 4TC	1	5.9
• 4TC + 17H		0.8
Smoking		
• Never	92	78.0
• Active	25	21.2
• Missing system	1	0.8
Heart disease		
• Yes	7	5.9
• No	111	94.1
MLD		
• 10.5 Gy >	68	57.6
• 10.5 Gy <	50	42.4
Lung volume		
Receiving ≥ 20 Gy	54	54.2
Receiving ≤ 20 Gy	64	45.8

A = adriamycin, ALND = axillary lymph node dissection, BCS = breast-conserving surgery, C = cyclophosphamide, E = epirubicin, F = fluorouracil, Gy = gray, H = herceptin, MLD = mean lung dose, P = paclitaxel, SLND = sentinel lymph node dissection, T = taxane.

tomography findings compared to those treated with C-RT (p:.000). Patients receiving concomitant hormone therapy had higher CT findings (78.1%) compared to those not receiving it (52.3%) and the difference was statistically significant (P:.011). There was no significant difference in the tomography findings between patients undergoing nodal RT (p:.2) and smokers, and between the 2 regimens.

4. Discussion

RT plays a significant role in reducing local recurrences and improving survival rates in breast cancer treatment.[2] Advances in RT technology aim to provide the ideal radiation dose to the targeted area while protecting surrounding normal tissues from potential side effects. These advancements have led to new standards in treatment recommendations based on international guidelines. Despite these improvements, some acute and late side effects may still occur due to the nature of RT. RP is a serious side effect that occurs as a result of RT, causing an inflammatory response and accumulation of fluid in the air spaces of the lungs. This can usually develop within 1 to 3 months after RT, particularly in patients who have received RT to the chest wall or within the thorax. However, with the current RT techniques, the incidence of symptomatic RT pneumonitis has decreased significantly. If proper RT techniques are used and there are no underlying risk factors, severe pneumonitis or fibrosis is very rare. Clinical symptoms of RP include dyspnea, fever, and a dry cough. The RTOG clinical rating scale is commonly used to evaluate RP symptoms and response to interventions.[3] Most patients do not experience symptoms despite any radiological changes observed.[4] In this study, all patients included were evaluated using the RTOG clinical scale and no symptoms were present.

The likelihood of lung injury is closely tied to the dose, fractionation, and volume of the lung exposed to RT.[5] Other factors such as age, performance status, chemotherapy, Tamoxifen use, smoking, vital lung capacity, and coexisting medical conditions also play a role. Despite these factors, the incidence of lung injury remains low (<5%).[6]According to the literature, radiological signs of radiation-induced lung injury include ground glass densities or consolidation in the early stage, traction bronchiectasis, volume loss, and consolidation in the late stage.[7–13] CT scans of the thorax are the standard imaging method used to diagnose RP and provide more information than traditional X-rays.[14] Different imaging findings may be seen depending on the stage of pneumonia formation. During the acute exudative phase, which occurs 15 to 20 weeks after radiation therapy, ground glass attenuation or homogeneous consolidation may be seen. In this study, CT findings were also detected at the median 20th week. Early signs include patchy consolidation areas within the radiation-exposed area.[8] The changes in the lungs are usually well-defined and occur in parallel with the RT field. In the later stages of fibrosis, the damage is irreversible, with symptoms such as distorted lung tissue, traction bronchiectasis, and thickening of the pleura. Initially, the changes may have smooth edges, but over time, they may become curved relative to the mediastinum or chest wall. Irregular consolidations turn into linear areas that are connected to the pleura or hilus and become permanent. In some cases, calcifications may also occur.[14–16] The recent advancements in RT techniques (C-RT, IMRT, and volumetric arc treatments) have led to the occurrence of uncommon radiological symptoms. The most common radiological finding is interstitial infiltrates in the RT-applied area, and a reticular pattern is also frequently observed. Most radiation oncology studies focus on using dose volume histogram (DVH) to evaluate 3D conformal planes. DVH divides tissue volume into equal parts and calculates the dose per part, allowing for graphical representation of proportional dose distribution within the tumor and normal tissue volume.[17] In

Table 3

CT findings of the included patients.

CT finding	Number of patients (n)	Percentage (%)
Ground glass	10	8.5
Consolidation	1	0.8
Pleural retraction	1	0.8
Pneumonia	16	13.6
Reticular pattern	31	26.3
Ground glass and reticular pattern	11	9.3
No finding	48	40.7

CT = computed tomography.

breast cancer RT, the irradiated lung volume is evaluated using DVH to assess the risk of pneumonia. A smaller irradiated lung volume results in a lower risk of pneumonia. It important to consider patient anatomy and underlying health conditions when evaluating DVH data, as the perfusion rate in the lower lobes of the lung is higher and radiation therapy in these areas increases the risk of developing RP.[18] The risk of developing RP is challenging to predict, especially in elderly smokers. Studies have not found a correlation between the risk of RP and factors such as age, gender, smoking history, diabetes, chemotherapy regimens, or performance status. However, the risk of developing RP is known to increase with the presence of underlying disease.[19,20] In this study, no significant statistical relationship was found between RP risk and being over 60 years of age, having a history of smoking, or having additional illnesses. This may be due to the small sample size of patients with chronic obstructive pulmonary disease or other underlying diseases. The development of RP is strongly linked to breast cancer treatment. There is a difference in the incidence of RP between standard 3DCRT and IMRT.[21,22] MLD has been identified as the most reliable predictor of RP risk after breast cancer RT, and the incidence of RP increases significantly when MLD values are above 10 Gy.[23]

Oetzel et al conducted a study to determine the relationship between radiation dose and the risk of lung damage. The study found a correlation between the 2 by using MLD and normal tissue complication probability in treatments where lung volume was calculated through tomography in the treatment position before RT planning.[24] A study found that the extent of lung volume receiving 20 Gy dose was the key factor in determining the occurrence of radiation-induced lung damage.[25]Another study conducted in 2012 showed that a lung volume (V5) of 50% or more receiving 5 Gy was a significant factor for the onset of symptomatic pneumonia.[26] The incidence of symptomatic RP ranges from 8% for a minimum lung dose (MLD) of 4 Gy to 24% for an MLD above 10 Gy. The tomography results in this study were significantly higher for patients with a lung volume exceeding 18.5 cm3 receiving 20 Gy in the side lung (P = .000037) and those with a MLD of 10.5 Gy or higher (P = .000088). Photon beams with 6 to 10 MV energy are utilized for breast cancer treatment and studies on orthovoltage therapy have recorded up to 35% occurrence of pneumonia.[27–29] High energies result in higher toxicity and this study saw more tomography findings in patients treated with 18 MV energy. In this study, patients treated with 18 MV energy showed significantly more tomography findings. In addition to RT, chemotherapy and new anticancer agents are also being investigated for their potential to induce toxicity in organs such as the lung,[30–32] Chemotherapy and targeted agents have been reported to cause drug-induced pneumonia.[33–35] In particular, Taxanes have specifically been linked to inducing lung toxicity independently.[36] However, the current data on lung complications from the combination of radiation therapy and systemic therapies is primarily from case reports and small retrospective studies. The exact impact of RT and systemic therapy on the incidence of RP remains unclear. The extent of contribution of RT and systemic therapy to the incidence of RP has not yet been established. In this study, there was no significant difference between chemotherapy regimens (P = .54). The early and late lung tissue responses following adjuvant hormonal therapy have mainly been documented in patients receiving Tamoxifen.[37] The literature does not show a significant increase in the risk of developing RP with the use of aromatase inhibitor therapy along with RT.[38] However, Tamoxifen is believed to potentially induce acute pneumonia and late-onset pulmonary fibrosis.[39,40] In this study, 78.1% of patients using concomitant hormones and 52.3% of those not using hormones had CT findings, suggesting that the concurrent use of hormone therapy may significantly raise lung toxicity (P = .011). There was no difference found between Tamoxifen and Aromatase inhibitors (P = .24).

IMRT is currently one of the options for RT in these patients and is considered an advanced conformal RT technique.[41,42] In IMRT, radiation beams of varying intensities, best suited for the treatment area, are utilized. The literature has shown IMRT to be superior to 3DCRT in terms of target volume dose conformity, homogeneity, and reduced doses to the surrounding organs.[30,31] IMRT has improved dose homogeneity, especially in patients with large breasts who undergo RT after BCS. In this study, CT findings were significantly higher in patients with right-sided breast cancer compared to those with left-sided breast cancer, due to a higher utilization of conformal RT (73.3%) in right-sided tumors and a higher utilization of IMRT (73.3%) in left-sided breast cancer (P = .0000004). One significant study of long-term follow-up of H-RT found that appropriate doses of H-RT were safe and effective in terms of toxicity in patients with early breast cancer and supported the use of 40 Gy in 15 fractions.[43] This study found no difference between C-RT and H-RT regimens in terms of the incidence of tomographic findings (P = .000). Patients treated with IMRT had significantly fewer tomographic findings (P = .000) compared to those treated with conformal RT.

5. Conclusion

In the treatment of breast cancer, it is important to minimize the incidence of radiation-induced pneumonitis by keeping the MLD and the volume receiving 20 Gy low during H-RT, just as with conventional treatment regimens. To reduce the risk of toxicity, it is advisable to avoid high energy radiation and consider using IMRT if possible. Results indicate that hypofractionated treatment regimens have comparable side effects to conventional treatments and can be considered a safe option for patients.

Author contributions

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