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Clinical Investigation

Factors Associated With Radiation Pneumonitis in Patients Receiving Electron Boost Radiation for Breast-Conserving Therapy: A Retrospective Review

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Abstract

Purpose: This study aimed to investigate risk factors for radiation pneumonitis (RP) caused by electron beam (EB) boost irradiation during breast-conserving therapy.

Methods and Materials: This single-institution retrospective study included patients with breast cancer treated with breast-conserving therapy from 2013 to 2019. Radiation therapy comprised whole-breast irradiation with a dose of 50 Gy and 10 Gy EB boost dose to the tumor bed. EB energies were 4, 6, 9, 12, and 15 MeV. The lung volume receiving ≥1.25 Gy (V1.25) was calculated and considered because the EB energies have a short range. All patients underwent computed tomography and positron emission tomography/computed tomography within 1 year of irradiation. Imaging evaluation was based on the Common Terminology Criteria for Adverse Events, version 5.0.

Results: Overall, 105 patients (median age, 62 years; range, 33-85) were included for analysis with a median follow-up period of 5 months. Average area of EB boost irradiation was 72 cm^2 (range, 36-196). Grade 1 RP developed in the EB irradiation field in 22 (20.6%) patients; grade 2 RP developed in 1 (0.93%) patient. Even in patients with central lung distance (CLD) ≥1.8 cm, a positive correlation was found between RP and both energy (r = 0.36; *P* = .005) and V1.25 (r = 0.26; *P* = .04). No correlation was found between RP and irradiation field size (*P* = .47). The EB energy and V1.25 cutoff values were 12 MeV and 24 cm^3, respectively.

Conclusions: CLD of ≥1.8 cm, EB energy of ≥12 MeV, and V1.25 of ≥24 cm^3 were risk factors associated with RP. Although the frequency of severe RP was not high, patients receiving high-energy electron treatment and those with a large CLD should be closely monitored.

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Introduction

Breast-conserving therapy (BCT) combines breast-conserving surgery (BCS) and postoperative irradiation for the treatment of early stage breast cancers. Recently, hormone therapy and chemotherapy have been commonly used concurrently or sequentially with BCT. Although the most frequent adverse effect of BCT is acute dermatitis, radiation pneumonitis (RP) is a well-known adverse effect that is rare but significant. RP that requires medical treatment reportedly occurs in approximately 2% of patients with breast cancer who receive BCT.[1-9] Reported risk factors include none,[2,3] age,[4,5] large irradiated lung volume,[6] concurrent hormone therapy,[4,6,7] and boost irradiation.[6,7] However, the significance of these risk factors remains unclear and controversial because of the rarity of RP. For many Asians, boost therapy of 10 Gy/2Gy/5 fractions is added to the tumor bed using an electron beam (EB) of appropriate energy. Although boost irradiation reportedly does not affect the incidence of RP,[6] no formal analysis of RP in patients receiving boost irradiation has been conducted. Therefore, this study aimed to examine risk factors for RP caused by EB boost irradiation after BCS.

Methods and Materials

Patients

We retrospectively reviewed the records of 229 newly diagnosed patients with breast cancer who received radiation therapy after BCS between February 2013 and September 2019. Those lost to follow-up within 12 months were excluded (median, 5 months; range, 1-12). By definition,[10] RP occurs within 12 months after BCT. Finally, 105 patients (107 treated breasts) were included for analysis. All patients underwent computed tomography (CT) and positron emission tomography/CT. Imaging evaluation was based on the Japanese translation of the Common Terminology Criteria for Adverse Events, version 5.[11] Institutional review board approval was obtained. All patients provided written informed consent.

Treatment

All patients were treated with radiation after BCS. Radiation therapy comprises whole-breast irradiation with a dose of 50 Gy and 10 Gy EB boost to the tumor bed. The XiO version 5.10 (Elekta, Inc, Crawley, UK) was used as the radiation treatment planning device, and the dose was calculated using the superposition algorithm for whole breast irradiation and the pencil beam algorithm for EB boost irradiation.

The treatment range for whole breast irradiation was as follows: upper edge was the sternal notch, lower edge was 1 cm on the foot side of the inferior mammary groove, medial edge was the midline, and lateral edge was the midaxillary or posterior axillary gland. A margin of 1 to 2 cm was added to the front edge from the nipple considering the movement of the chest wall due to breathing (Fig 1A). The treatment plan for whole breast irradiation was as follows: percentage of the prescription dose covering 95% (D95) of the planning target volume (whole-breast), ≥47.5 Gy; D_{max}, ≤55 Gy (110%); and lung volume receiving ≥20 Gy of the ipsilateral lung (V20), ≤25%.

The EB boost energies were 4, 6, 9, 12, and 15 MeV, and these EB energies were chosen so that 80% dose reached the pectoral muscle surface (Fig 1B). A surgical clip was placed on the tumor bed at the time of surgery to determine the boost position. The size of the irradiation field depended on the stump condition, which is generally about 6 to 10 cm.

Evaluation of risk factors

Factors evaluated in the analysis were as follows: age (<50 or ≥50 years), side affected (right or left, unilateral or bilateral), central lung distance (CLD) (<1.8 or ≥1.8 cm), V20 (<10 or ≥10%), concurrent hormone therapy (with or without), and chemotherapy (with or without). CLD was measured as the greatest distance between the posterior border of the irradiation field and the chest wall on the axial image of the treatment planning CT (Fig 1A). In cases with CLD ≥1.8 cm, EB energy, irradiation field size, and dose-volume histogram were also evaluated. The lung volume receiving ≥1.25 Gy (V1.25) was calculated and considered because the EB energies have a short range.

Statistical analysis

Statistical analyses were performed using the Fisher exact probability test and Spearman's rank correlation with Statcel4 software (OMS Ltd, Saitama, Japan). Moreover, the cutoff value was obtained from the receiver operating characteristic (ROC) analysis, and multivariate analysis was performed, including EB energy, V1.25, V20, CLD, irradiation field size, and age, using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan).[12] P values of $< .05$ were considered significant. Spearman's rank correlation coefficient (r) of <0.80 indicated very strong correlation; $0.60 < r < 0.79$ indicated strong correlation; $0.40 < r < 0.59$ indicated moderate correlation; $0.20 < r < 0.39$ indicated weak correlation; and $0 < r < 0.19$ indicated very weak correlation.

Results

Patient characteristics are shown in Table 1. Median age was 62 years (range, 33-85). Median follow-up was 5 months (range, 1-12). The sides affected were left, right, and bilateral in 48, 55, and 2 patients, respectively. Hormone therapy was administered to 83 patients (79.0%). Thirty-one patients (29.5%) received chemotherapy; 29 of these received chemotherapy before BCT.

RP developed in 23 (21.5%) of the 107 irradiated breasts (105 patients). The median CLD was 1.9 cm (range, 0.7-3.35). Table 2 shows the univariate analysis of items that can be considered as risk factors for RP. CLD ≥1.8 cm and bilateral irradiation were significantly associated with the development of RP (P = .001 and .031, respectively); other factors were not. Particularly, V20 of the ipsilateral lung and ventilation dysfunction or underlying pulmonary disease were not significant factors for the occurrence of RP. Considering only cases with CLD of ≥1.8 cm, a positive correlation was observed between RP and both EB energy (r = 0.36, P = .005) and V1.25 (r = 0.26, P = .04). No correlation was observed between RP and irradiation field size (P = .47; Table 3). Table 4 shows the patient characteristics of 23 patients who developed RP. RP occurred within the EB irradiation range in all patients (Fig 2). Grade 1 RP was noted in 22 (20.6%) patients, and grade 2 was noted in 1 (0.93%). Average area of EB boost irradiation was 72 cm^2 (range, 36-196). In the single grade 2 RP patient, the energy was 9 MeV, with a bolus of 5 mm and an irradiation field of 100 cm^2. From the ROC analysis, the EB energy and V1.25 cutoff values were 12 MeV and 24 cm^3, respectively. Logistic regression analysis was performed for the RP group and the non-RP group with EB energy, V1.25, V20, CLD, irradiation field size, and age as objective functions. As a result, the EB energy (odds ratio, 1.48; 95% confidence interval, 1.13-1.94) was selected as a significant variable (Table 3).

Discussion

Approximately 2% of patients with breast cancer who receive BCT develop RP that requires medical treatment. Naturally, chest radiography and CT detection rates differ. Kahan et al[13] reported a 37% frequency of grade 1 or higher RP on CT 3 months after radiation therapy. In another previous study, the incidence of radiologic RP (grade 1) ranged from 27% to 40%, with clinical RP (grade 2 or higher) ranging between zero and 10%.[14] This study found that grade 1 RP occurred in the EB irradiation field in 20.6% of patients, with grade 2 occurring in only 0.93%. Even after adding boost irradiation, the RP incidence rates in this study are similar to previous reports.[9]

RP risk factors remain unclear and controversial; several factors have been reported such as age, hormone therapy, chemotherapy, irradiated lung volume, and boost irradiated lung volume.[2-5,7] Katayama et al[4] reported that age ≥50 years was a risk factor in patients with breast cancer treated with BCT. However, several other reports including this study did not find age to be a risk factor.[2,3,6,7] Similarly, concurrent hormone therapy has been reported as a RP risk factor in some studies[4] but not others.[5,7,8] This study found no significant correlation between hormone therapy and the incidence of RP. In addition, we also found that chemotherapy is not significantly correlated with the incidence of RP, in agreement with earlier reports.[6,7] Kubo et al[6] reported that CLD <1.8 cm significantly correlated with the development of RP. Our findings were the same. Paradoxically, Katayama et al[4] reported that CLD ≥3 cm was not a risk factor for RP after BCT. Although the extent of irradiation of the lung field in BCT remains controversial, V20 is used as

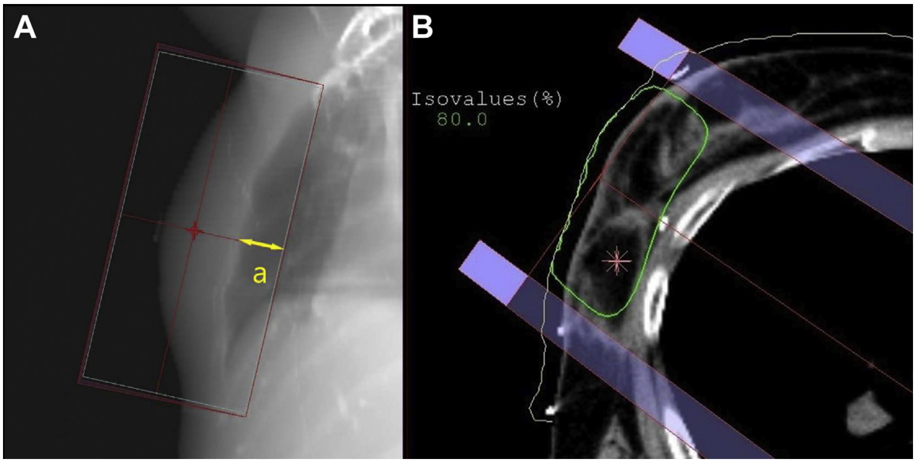

Figure 1 The treatment range for whole breast and electron boost irradiation. (A) Whole breast irradiation. "a" is indicated central lung distance. (B) Electron beam boost irradiation. Green line means a 80% of the prescribed dose isoline, which is a guide for appropriate energy selection.

Table 1 Patient characteristics*

Sex	
Male	0
Female	105
Side affected	
Left	48
Right	55
Bilateral	2
Central lung distance	Median 1.9 cm (range, 0.7-3.4)
<1.8 cm	45
≥1.8 cm	62
V20	Median 10.2% (range, 2.2-18.9)
<10%	51
≥10%	56
Ventilation dysfunction or underlying pulmonary disease	
Yes	8
No	97
Hormone therapy	
Yes	83
Antiestrogen	23
Aromatase inhibitor	53
LH-RH analog + antiestrogen	7
No	22
Chemotherapy	
Yes	31
Before BCT	29
After BCT	2
TC	10
FEC	1
FEC + DTX	6
EC	2
EC + DTX	4
EC + w-PTX	4
nab-PTX	1
nab-PTX + FEC	1
UFT	2
No	74

Abbreviations: BCT = breast-conserving therapy; DTX = docetaxel; EC = epirubicin + cyclophosphamide; FEC = 5-fluorouracil + epirubicin + cyclophosphamide; LH = luteinizing hormone; nab-PTX = nanoparticle albumin-bound-paclitaxel; RH = releasing hormone; TC = docetaxel + cyclophosphamide; UFT = tegafur + uracil; V20 = the lung volume receiving ≥20 Gy; w-PTX = weekly paclitaxel.

* For "Sex" and "Side affected," numbers of patients are provided. For other categories, numbers of treated breasts are provided.

an important index of RP in radiation therapy for lung cancer.[15,16] For V20 of lung cancer, ≤30% to 35% is recommended; however, V20 of BCT rarely exceeds this value. Therefore, in the present study, we used a strict criterion of ≤10%, which is an index of V20 after pneumonia in the mesothelioma.[17] This study found no significant differences between RP and both V20 of the ipsilateral lung and ventilation dysfunction or underlying pulmonary disease.

Table 2 Univariate analysis of variables

	Variables	n	RP	%	*P* value
Age	<50	28	6	21.4	.642
	≥50	77	16	20.8	
Side	Left	48	6	12.5	.078*
	Right	55	14	25.5	
	Bilateral	2(4 fields)	3	75.0	.031*
CLD	<1.8 cm	45	3	6.7	.001
	≥1.8 cm	62	20	32.3	
V20	<10 %	51	7	13.7	.051
	≥10 %	56	16	28.6	
Hormone therapy	with	83	17	20.5	.337
	without	22	6	27.3	
Chemotherapy	with	31	5	16.1	.256
	without	74	18	24.3	

Abbreviations: CLD = central lung distance; RP = radiation pneumonitis; V20 = the lung volume receiving ≥20 Gy.

* The comparisons are left versus right and unilateral and bilateral.

Table 3 Univariable analysis and multivariable analysis of variables

Variable	Univariable analysis *P** or *P* value†	Multivariable analysis	
		Odds ratio (95% CI)	*P* value‡
Electron beam energy	.005*	1.48 (1.13-1.94)	.004
V1.25	.04*	1.03 (0.97-1.10)	.34
Irradiation field size	.47*	0.99 (0.96-1.01)	.27
CLD (<1.8 cm vs ≥1.8 cm)	.001†	0.69 (0.13-3.81)	.67
V20 (<10 % vs ≥10 %)	.051†	1.31 (0.99-1.74)	.06
Age (<50 vs ≥50)	.642†	1.01 (0.97-1.06)	.67

Abbreviations: CI = confidence interval; CLD = central lung distance; V1.25 = the lung volume receiving ≥1.25 Gy; V20 = the lung volume receiving ≥20 Gy.

* Spearman's rank correlation

† Fisher exact probability test

‡ Logistic regression analysis

To eliminate the effect of x-ray irradiation as much as possible, we performed a subgroup analysis of cases with CLD of ≥1.8 cm and found a positive correlation between RP and both EB energy and V1.25. The EB energy was also selected as a significant variable in multivariate analysis. From the ROC analysis, the EB energy and V1.25 cutoff values were 12 MeV and 24 cm^3, respectively. The advantage of EB is the rapid dose reduction when reaching a certain depth. However, as the EB energy increases, the percentage depth dose curve shows less dose reduction in the deeper areas than the depth of

Table 4 Patient characteristics of radiologic RP (grade 1) and clinical RP (≥grade 2)*

Age	Median 62 (range, 38-85)
<50	6
≥50	16
Side affected	
Left	7
Right	14
Bilateral	1
RP	
Grade 1	22
Grade 2	1
CLD	Median 2.2 cm (range, 0.8-3.2)
<1.8 cm	2
≥1.8 cm	21
Electron energy	Cutoff value 12 MeV
<12 MeV	8
≥12 MeV	15
V1.25	Cutoff value 24 cm^3 (range, 3-38)
<24 cm^3	14
≥24 cm^3	9

Abbreviations: CLD = central lung distance; RP = radiation pneumonitis; V1.25 = the lung volume receiving ≥1.25 Gy.

* For "Sex" and "Side affected," numbers of patients are provided. For other categories, numbers of treated breasts are provided.

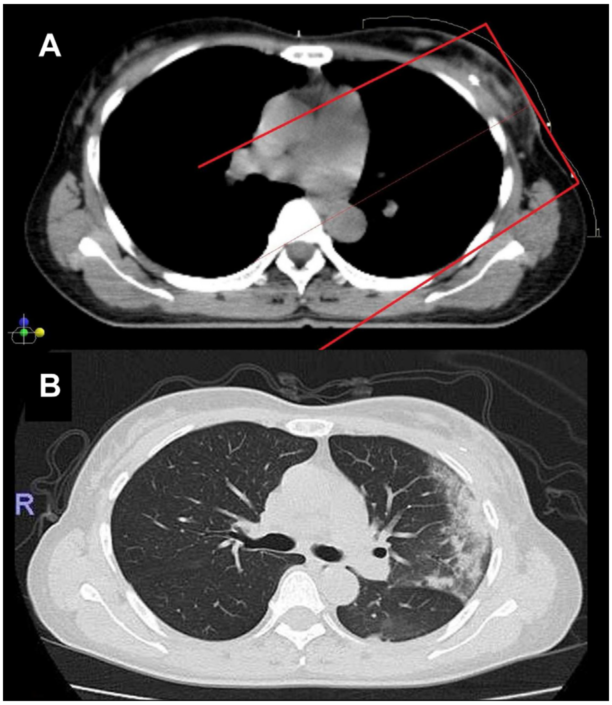

Figure 2 (A) In the single grade 2 RP patient, the energy was 9 MeV, with a bolus of 5 mm and an irradiation field of 100 cm^2. (B) CT images were obtained 3 months after RT. RP occurred within the electron beam irradiation range in all patients. *Abbreviations:* CT = computed tomography; RP = radiation pneumonitis; RT = radiation therapy.

dose maximum. Even if the appropriate energy is selected for the treatment area, the chest-wall side of the lung dose increases. Wennberg et al[18] reported that lung density changes after radiation therapy are associated with the irradiated lung dose. In our study, all cases of RP were consistent with the site of EB irradiation. Therefore, it is necessary to pay attention to energy (≥12 MeV) and small dose volume (V1.25 ≥24 cm^3) rather than the irradiation field.

There are some limitations to this study. First, although this study was performed using the pencil beam algorithm, the dose calculation, including the inhomogeneities, shows an error of <10% compared with the Monte Carlo algorithm.[19] In particular, the pencil beam algorithm overestimates behind a material with a high electron density and underestimates behind a material with a low electron density. Therefore, in the EB boost irradiation plan, including the ribs, it is plausible that V1.25 and V20 may be different when evaluated by the Monte Carlo algorithm. Moreover, this study is limited by an insufficient number of patients with bilateral breast cancer. Future studies are needed to compare the risk of RP between patients with unilateral and bilateral disease.

Conclusions

CLD ≥1.8 cm, electron energy (≥12 MeV), and low-dose area (V1.25 ≥24 cm^3) are risk factors associated with RP in patients with breast cancer treated with BCT. Although the frequency of severe RP was not high, patients receiving high-energy electron treatment and those with a large CLD should be closely monitored.

References

1. Nozaki M, Kagami Y, Mitsumori M, et al. A multicenter investigation of late adverse events in Japanese women treated with breast-conserving surgery plus conventional fractionated whole-breast radiation therapy. *Jpn J Clin Oncol*. 2012;42:522-527.
2. Ogo E, Komaki R, Fujimoto K, et al. A survey of radiation-induced bronchiolitis obliterans organizing pneumonia syndrome after breast-conserving therapy in Japan. *Int J Radiat Oncol Biol Phys*. 2008;71:123-131.
3. Ogo E, Komaki R, Abe T, et al. The clinical characteristics and non-steroidal treatment for radiation-induced bronchiolitis obliterans organizing pneumonia syndrome after breast-conserving therapy. *Radiother Oncol*. 2010;97:95-100.
4. Katayama N, Sato S, Katsui K, et al. Analysis of factors associated with radiation-induced bronchiolitis obliterans organizing pneumonia syndrome after breast-conserving therapy. *Int J Radiat Oncol Biol Phys*. 2009;73:1049-1054.
5. Murofushi KN, Oguchi M, Gosho M, et al. Radiation-induced bronchiolitis obliterans organizing pneumonia (BOOP) syndrome in

breast cancer patients is associated with age. *Radiat Oncol*. 2015;10: 103.
6. Kubo A, Osaki K, Kawanaka T, et al. Risk factors for radiation pneumonitis caused by whole breast irradiation following breast-conserving surgery. *J Med Invest*. 2009;56:99-110.
7. Sato H, Ebi J, Tamaki T, et al. Incidence of organizing pneumonia after whole-breast radiotherapy for breast cancer, and risk factor analysis. *JRR*. 2018;59:298-302.
8. Takigawa N, Segawa Y, Saeki T, et al. Bronchiolitis obliterans organizing pneumonia syndrome in breast-conserving therapy for early breast cancer: radiation-induced lung toxicity. *Int J Radiat Oncol Biol Phys*. 2000;48:751-755.
9. Jeba J, Isiah R, Subhashini J, et al. Radiation pneumonitis after conventional radiotherapy for breast cancer: A prospective study. *J Clin Diagn Res*. 2015;7:XC01-XC05.
10. Otani K, Seo Y, Ogawa K. radiation-induced organizing pneumonia: A characteristic disease that requires symptom-oriented management. *Int J Mol Sci*. 2017;18:E281.
11. The Japanese translation of the Common Terminology Criteria for Adverse Events, version 5. Available at: http://www.jcog.jp/doctor/tool/CTCAEv5J_20181106_v21_1.pdf. Accessed May 25, 2020.
12. Kanda Y. Investigation of the freely available easy-to-use software 'EZR' for medical statistics. *Bone Marrow Transplant*. 2013;48: 452-458.
13. Kahan Z, Csenki M, Varga Z, et al. The risk of early and late lung sequelae after conformal radiotherapy in breast cancer patients. *Int J Radiat Oncol Biol Phys*. 2007;68:637-681.
14. McDonald S, Rubin P, Phillips TL, et al. Injury to the lung from cancer therapy: Clinical syndromes, measurable endpoints, and potential scoring systems. *Int J Radiat Oncol Biol Phys*. 1995;31:1187-1203.
15. Graham MV, Purdy JA, Emami B, et al. Clinical dose-volume histogram analysis for pneumonitis after 3D treatment for non-small cell lung cancer (NSCLC). *Int J Radiat Oncol Biol Phys*. 1999;45:323-329.
16. Tsujino K, Hirota S, Endo M, et al. Predictive value of dose-volume histogram parameters for predicting radiation pneumonitis after concurrent chemoradiation for lung cancer. *Int J Radiat Oncol Biol Phys*. 2003;55:110-115.
17. Marks L, Bentzen S, Deasy J, et al. Radiation dose-volume effects in the lung. *Int J Radiat Oncol Biol Phys*. 2010;76:S70-S76.
18. Wennberg B, Gagliardi G, Sundbom L, et al. Early response of lung in breast cancer irradiation: Radiologic density changes measured by CT and symptomatic radiation pneumonitis. *Int J Radiat Oncol Biol Phys*. 2002;52:1196-1206.
19. Ding G, Cygler J, Yu C, et al. A comparison of electron beam dose calculation accuracy between treatment planning systems using either a pencil beam or a Monte Carlo algorithm. *Int J Radiat Oncol Biol Phys*. 2005;63:622-633.