ORIGINAL

Risk factors for radiation pneumonitis caused by whole breast irradiation following breast-conserving surgery

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Abstract : We evaluated risk factors of radiation pneumonitis (RP) after whole breast irradiation following breast-conserving surgery. Four hundred and seventy-two cases underwent whole breast irradiation with tangential field following breast-conserving surgery in our hospital, between January 2005 and April 2007. Of these cases, we performed statistical analyses for 423 breasts of 413 patients, using a pulmonary dose-volume histogram. Patient characteristics, treatment regimens and irradiation methods were included as variables in the analyses on risk factors of RP. As a result, 89 breasts of 84 cases (21%) were diagnosed with RP. The version 3.0 of the NCI Common Terminology Criteria for Adverse Events was used to evaluate the grade of pneumonitis : 77 cases (18.2%) were diagnosed as Grade 1 RP, 10 cases (2.3%) as Grade 2, and 2 cases (0.5%) as Grade 3. Multivariate analysis indicated that the significant risk factors for RP were central lung distance (CLD) (>1.8 cm) and the short axis length of the radiation field. The incidence of radiation-induced bronchiolitis obliterans organizing pneumonia (BOOP) syndrome significantly correlated only with CLD. The lung volume within the radiation field was shown to be a significant risk factor for RP and radiation-induced BOOP syndrome. J. Med. Invest. 56 : 99-110, August, 2009

Keywords **:** *radiation pneumonitis, radiation-induced BOOP syndrome, breast cancer, breast-conserving therapy*

INTRODUCTION

Breast-conserving therapy (BCT) has recently become a standard treatment for early breast cancer. The local recurrence rate is decreased using postoperative radiotherapy, which cures minute lesions remaining within the breast (1). In recent years, an increasing number of patients have received breast-conserving surgery. Even locally advanced cancers have received this treatment, following down-staging with neo-adjuvant chemotherapy. The reported frequency of radiation pneumonitis (RP), caused by radiotherapy following breast-conserving surgery, varies greatly ; cumulative incidence rates of 0.9-85% have been reported (2-9). RP occurs locally, in a limited field of an irradiated lung, at an early time after irradiation (10). Among the pulmonary injuries following radiotherapy of whole breast, the most clinical significant pulmonary disorder is radiation-induced bronchiolitis obliterans organizing pneumonia (BOOP) syndrome. Radiation-induced BOOP syndrome is characterized by infiltrative shadow expansions outside the irradiation field of lung and migrates ; however, the frequency of radiation-induced BOOP is low. Crestani described the following factors for diagnosing radiation-induced BOOP

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syndrome (11) : (1) radiotherapy to the breast within the past 12 months, (2) general and/or respiratory symptoms lasting for longer than 2 weeks, (3) radiographic lung infiltrations outside the radiation port and (4) no evidence of a specific cause.

Previous clinical studies investigating RP have reported on several factors involved in the pathogenesis of RP, including patient age, lung volume within an irradiated field, chemotherapy before radiotherapy, prescription of tamoxifen during radiotherapy and smoking history (12-15). In the present study, we evaluated the risk factor for RP, including radiation-induced BOOP syndrome, induced by whole breast irradiation following breast-conserving surgery, with respect to patient background factors and treatment regimens.

MATERIALS AND METHODS

Between January 2005 and April 2007, 472 patient cases were subjected to tangential irradiation following breast-conserving surgery at the Tokushima University Hospital. We conducted follow-up observations for 454 of 472 patients with respect to the occurrence of pulmonary damage using chest radiographs. We excluded cases in which the chest wall had been irradiated after mastectomy, and in which irradiation on axilla and supraclavicular nodal regions had been simultaneously performed. We included only those cases in which whole breast tangential irradiation had been performed. In these cases, we performed statistical analyses for 423 breasts (413 cases) using a pulmonary dose-volume histogram (DVH). DVH was calculated using a three-dimensional treatment planning device (XiO, ver. 4.33.02, manufactured by CMS). Patient characteristics, treatment regimen and irradiation methods were included as variables on the analyses of the risk factors for RP. In 10 cases, tangential irradiation was performed simultaneously for both breasts following breast-conserving surgery.

Patients

The patient background of 413 cases is shown in Tables 1 and 2. With respect to chemotherapy, neo-adjuvant chemotherapy was performed in 49 cases, pre-irradiation adjuvant chemotherapy in 5 cases and post-irradiation adjuvant chemotherapy in 100 cases. Of the 313 cases in which endocrine therapy was conducted, 130 concurrently received both endocrine therapy and radiotherapy, whereas

Table 1. Patient characteristics (n=413)

Age (y), range (median)	24-84(52)
Side (right/left/bilateral)	212/191/10
Collagen vascular disease (yes/no)	6/407
Allergy disease and /or drug allergy (yes/no)	73/340
Diabetes (yes/no)	12/401
Smoking status (yes/no/unknown)	64/283/76
Usage of other medication unrelated to breast cancer (yes/no)	126/297
Clinical stage (UICC)	
0	54
I	206
II A	101
II B	46
III A	9
III B	3
III C	1
Histologic type	
Noninvasive ductal carcinoma	52
Invasive ductal carcinoma	328
other	43
Operation	
Lumpectomy	316
Quadrantectomy	105
other	2
Chemotherapy (yes/no)	143/283
pre-radiotherapy	54
post-radiotherapy	100
Endocrine therapy (yes/no)	313/98
antiestrogen drug	147
aromatase inhibitor	164
Concurrent endocrine therapy(yes/no)	130/293
antiestrogen drug	47
aromatase inhibitor	87

Abbreviations : UICC=International Union Against Cancer.

Table 2. Radiation therapy details (n=423 breast)

Whole breast irradiation		
50 Gy/25 fraction		423
Boost to tumor bed (yes/no)		
10 Gy/5 fraction		114/309
Photon energy (4 MVX/6 MVX)		405/18
Wedge filter (yes/no)		422/1
Central lung distance (cm)		0.8-3.2 (1.8)
Field length, long axis (cm)		14.6-21.6 (17.9)
Field length, short axis (cm)		3.8-11.1 (6.8)
Ipsilateral lung V_{20Gy} (mean : 9.6%)		
	1.8-9.6 (%)	213
	9.7-18.8(%)	210
Ipsilateral lung V_{10Gy} (mean : 12.2%)		
	2.9-12.2(%)	214
	12.3-22.3 (%)	209
Bilateral lung V_{20Gy} (mean : 4.9%)		
	0.8-4.9 (%)	213
	4.9-14.2 (%)	210
Bilateral V_{10Gy} (mean : 6.2%)		
	1.3-6.2(%)	213
	6.3-17.5(%)	210

oral administration was started after radiotherapy in 183 cases. Anti-estrogen agents were administered in 147 cases and aromatase inhibitors (AIs) in 164 cases. In cases where medication was changed during the follow-up period, the medication that was administered initially was recorded. With regard to patient history, there were 6 cases of collagen disease, 30 cases of double cancer (18 cases of contralateral breast cancer), 3 cases of BCT experience for contralateral breast cancer and 73 cases of allergic disease. The use of treatment planning CT confirmed the absence of active pulmonary disease in any of these cases at the beginning of radiotherapy. All patients provided written informed consent before radiotherapy.

Radiotherapy

We used 4 or 6 million volt X-rays for the radiotherapy of remaining breasts, and conducted tangential irradiation of 50 Gy/25 fraction/5 weeks on all breasts in accordance with the Hinge method (using 4 or 6 million volt X-rays, wedge 15°). A 15° wedge filter was used arbitrarily to equalize the dose distribution. The PRIMUS KD-2 (manufactured by Siemens/Toshiba) was used as a linear accelerator. With regard to 114 cases where the resection margins were positive, boost therapy of 10 Gy/5 fractions was added to the tumor beds using electron beams with appropriate energy.

Follow-up

We started the follow up examination with chest radiographs of every 3 months for 1 year after completion of radiotherapy. Based on previous study, radiation pneumonitis tends to occur shortly after the completion of radiotherapy(10). So, after the 1 year follow-up period using chest radiograph, patient's status were obtained by hospital records or interviews. When the chest radiographs showed an abnormal shadow, we performed the further examination using chest CT in order to evaluate the RP and confirm the grade of RP. The median period of the follow-up observation after completion of radiotherapy was 11.9 months (range : 2.9-41.6 months). The grade of RP was evaluated in accordance with version 3.0 of the NCI Common terminology Criteria for Adverse Events (CTC/AE ver. 3.0).

Statistical analysis

We analyzed risk factors for RP using univariate analysis (univariate Cox regression model) and multivariate analysis (Cox regression model). The variables analyzed were : patient age, history of allergic disease, the simultaneous use of systemic medicine (except medicine being used for the treatment of breast cancer), tumor location (every lesion located at the border between the outside and the inside of a breast was regarded as being inside), operative method, presence and timing of chemotherapy, whether the endocrine therapy was used during radiotherapy or in stages, whether the type of drug administered was an anti-estrogen agent or an AI, X-ray energy, total irradiation dose, long and short axis length of the radiation field, central lung distance (CLD) measured from the axial image on the XiO and the volume receiving more than 20 Gy (V_{20Gy}), as well as V_{10Gy}, of ipsilateral and bilateral lungs. Statistical significance was defined as $P < 0.05$ (Figs. 1, 2).

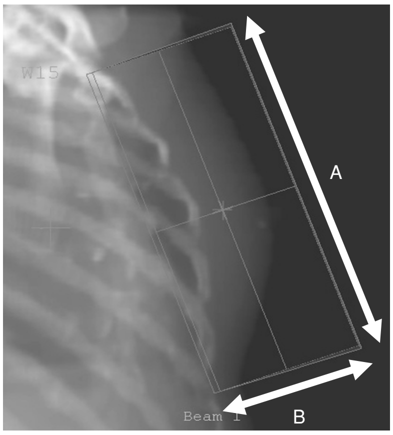

Fig. 1. Digitally reconstructed radiography image of the three-dimensional treatment planning device in the radiation field
A : long axis length of the radiation field (cm), B : short axis length of the radiation field (cm)
At our hospital, the anterior border of the radiation field is set at a distance of 1.5 cm from the skin surface of the nipple base on the CT.

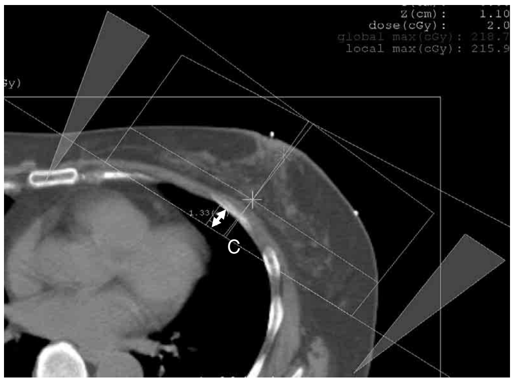

Fig. 2. The furthest distance between the posterior border of the radiation field and the chest wall was measured from the axial image of the treatment planning CT.
C : central lung distance (CLD) (cm).

RESULTS

Cumulative incidence of RP

Of the 423 breasts from 413 patients, 89 breasts from 84 cases (21%) were diagnosed with RP, based on the chest radiograph. According to the evaluation of the grade of pneumonitis using CTC/AE ver. 3.0, there were 77 cases (18.2%) of Grade 1 RP, 10 cases (2.3%) of Grade 2, and 2 cases (0.5%) of Grade 3. The age of patients diagnosed with RP ranged from 25 to 80 years (median : 50). Thirty-six cases had RP in their left breasts and 53 in their right breasts. Fifteen cases (16.8%) had a history of allergic disease and 17 (19.1%) had a smoking history. In 32 cases (35.9%), simultaneous medication was done, in addition to that for breast cancer treatment during radiotherapy. In 26 cases, lesions were found inside the breasts. In 60 cases, the T factor was T1 or less, while in 60 cases, the N factor was N0. According to the staging classification, 49 cases were diagnosed stage I or below. The operative method of 63 cases was lumpectomy. 72 cases were treated with endocrine therapy, of which 34 were treated during the irradiation period. With respect to factors regarding radiotherapy, 82 cases were treated with 4 MV X-rays, whereas 28 cases underwent boost irradiation. The long axis length of the radiation field was 14.6-21.6 cm (median : 17.9 cm) and the short axis length was 3.8-11.1 cm (median : 6.8 cm) ; the CLD was 0.8-3.2 cm (median : 1.8 cm).

Radiation-induced BOOP syndrome

In the present analysis, radiation-induced BOOP syndrome was observed in 12/413 cases (2.9%). All cases of Grade 2 RP or greater developed radiation-induced BOOP syndrome. The age of the patients ranged from 39 to 72 years (median : 50 years old). The clinical symptoms were fever (10 cases), coughing (12 cases), decrease in oxygen saturation (8 cases) and sense of dyspnea (8 cases). The timing of the pathogenesis was 2.5-23.1 months after the end of treatment (median : 3.6 months)., Abnormal shadows were observed on the chest radiographs taken 3 months after the completion of radiotherapy in all cases, except for one case, in which RP occurred after 23.1 months. Bronchoscopy was performed in 8 cases. The total cell number in bronchoalveolar lavage fluid was increased in 7/8 cases. The transbronchial lung biopsy specimens in all 8 cases diagnosed pathologically as organized pneumonia. Of the 12 cases, steroid administration was implemented in 7 cases, resulting in rapid improvement of symptoms. However, recurrence of symptoms due to the decrease or suspension of the steroid administration was observed in 4 cases. The duration of the steroid administration was 5.8-41.4 months (median : 12.3 months) (Table 3).

A 39 year-old woman, in whom RP occurred after

Table 3. Clinical characteristics of 12 patients with radiation-induced BOOP syndrome

Patient	Age (y)	side	Endocrine therapy	Endocrine therapy (drug)	Chemotherapy	dose	CLD (cm)	Short axis (cm)	Ipsilateral V20 Gy (%)	Steroid	Steroid (relapse)	Onset, After RT (month)	Duration of steroid (month)
1	40	right	sequential	Tamoxifen	-	60	2.4	8.2	12.05	+	-	3.2	5.8
2	52	left	sequential	Anastrozole	-	50	2.0	6.6	13.93	+	+	4.4	12
3	46	right	none	-	-	50	2.1	7.3	14.00	-	-	2.7	-
4	53	right	concurrent	Anastrozole	pre+post RT	60	2.0	5.7	7.89	-	-	6.0	-
5	48	left	sequential	Tamoxifen	-	50	1.7	6.7	8.88	+	+	2.5	41.1
6	72	right	sequential	Anastrozole	-	60	2.0	6.4	8.35	+	-	6.9	11.1
7	47	right	sequential	Tamoxifen	-	60	1.9	7.3	9.13	-	-	3.6	-
8	59	left	sequential	Anastrozole	-	50	1.7	6.3	10.56	+	+	3.2	35.8
9	69	right	sequential	Anastrozole	-	60	1.8	8.8	10.05	+	+	3.0	23.8
10	59	left	none	-	-	50	2.3	6.7	12.14	-	-	3.7	-
11	44	right	concurrent	Tamoxifen	-	60	2.1	6.6	8.74	-	-	3.7	-
12	39	left	concurrent	Tamoxifen	-	50	1.7	5.7	9.05	+	-	23.1	12.2

Abbreviations : BOOP=bronchiolitis obliterans organizing pneumonia ; RT=radiotherapy ; CLD=central lung distance

23.1 months, had been taking immunosuppressive agents for a long period due to chronic rheumatoid arthritis. Moreover, radiation treatment planning CT did not show any lesions in her lung fields, and chest radiography taken 3 months after radiotherapy did not reveal any obvious abnormal shadows. Administration of the immunosuppressive agents was partially suspended 20 months after the completion of the radiotherapy. Moreover, an increased density area that was corresponding to the irradiation field, appeared in the lung field on the CT images at 22 months after radiotherapy. However, she complained of no symptoms at that time. Fever and coughing appeared 23 months after the completion of radiotherapy. Chest radiography revealed an infiltrative shadow expanding outside the radiation field. She was diagnosed with organized pneumonia using a bronchoscope, and was clinically diagnosed with radiation-induced BOOP syndrome. Therefore, we started steroid administration and her symptoms improved rapidly. Although this case did not match the criteria proposed by Crestani in terms of the timing of the pathogenesis (11), we extrapolated that RP can occur more than 1 year after irradiation provided that there are special conditions, such as the use of immunosuppressive agents, as in this case (Fig. 3).

Risk factors for RP

The univariate analysis detected significant differences in the following factors for incidence of RP of Grade 1 or greater : chemotherapy after radiotherapy ($p=0.005$), chemotherapy in all the periods including before and after radiotherapy ($p=0.001$), short axis of the radiation field (> 6.8 cm ; $p=0.002$), CLD (> 1.8 cm ; $p=0.002$), N factors (≥ N1 ;

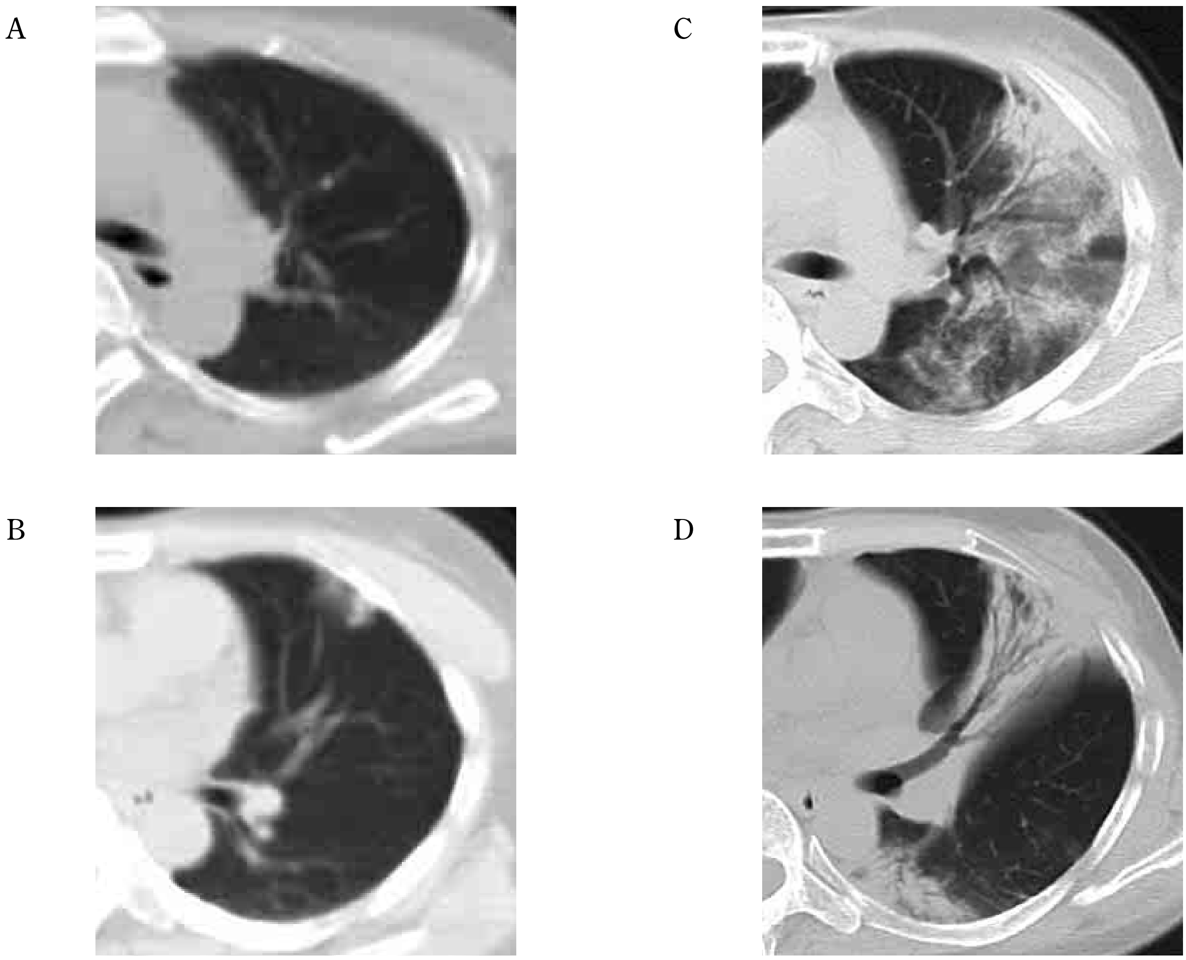

Fig. 3. A 39-year-old woman had been continuously taking immunosuppressive agents for the treatment of chronic rheumatoid arthritis. No abnormalities were recognized from the treatment planning CT before irradiation or from the chest radiograph taken 3 months after irradiation. Partial suspension of immunosuppressive agent administration 20 months after irradiation led to the detection of a localized concentration increasing region by chest CT conducted 22 months after irradiation. No symptoms were indicated at this point. Chest CT conducted 23 months after irradiation, however, revealed a clinical symptom consisting of infiltrative shadows and ground-glass opacity expanding outside the radiation field. They were diagnosed as organized pneumonia by bronchoscopy (A, B : CT performed 20 months after irradiation, C, D : CT performed 23 months after irradiation).

p=0.029), and use of AIs (*p*=0.028) (Table 4, 5). The cases of Grade 2 or greater were analyzed in the same manner. The univariate analysis detected significant differences only in CLD (>1.8 cm ; *p*=

Table 4. Univariate analysis of patient factors associated with Radiation pneumonitis

Factor		RP (n=89)	RR	*p*-value	95% CI
Age	< 50 y	33(191)	0.76	0.20	0.49-1.2
	> 51 y	56(232)	1		
Side	left	36(201)	0.73	0.15	0.48-1.1
	right	53(222)	1		
Tumor factor	T0,Tis,T1	60(301)	0.84	0.43	0.54-1.3
	T2,T3,T4	29(122)	1		
Node factor	N0	62(331)	0.60	0.03	0.39-0.95
	N1,N2,N3	27(92)	1		
Clinical stage	< I stage	49(263)	0.73	0.14	0.48-1.1
	≧ IIA stage	40(160)	1		
Location (region)	inner side	26(161)	0.65	0.06	0.41-1.0
	outer side	63(259)	1		
	unknown	0(3)			
Operation	lumpectomy	63(316)	0.76	0.24	0.48-1.2
	quadrantectomy	26(105)	1		
Allergic disease	(+)	15(73)	0.96	0.89	0.55-1.7
	(-)	74(350)	1		
Usage of other medication unrelated to breast cancer	(+)	32(126)	1.23	0.34	0.80-1.9
	(-)	57(297)	1		
Smoking status	(+)	17(64)	1.14	0.70	0.65-1.9
	(-)	66(283)	1		
	unknown	0(76)			
Chemotherapy	(+)	44(143)	1.98	< 0.01	1.3-3.0
	(-)	45(280)	1		
chemotherapy (pre-RT)	(+)	14(54)	1.27	0.41	0.72-2.3
	(-)	75(369)	1		
chemotherapy (post-RT)	(+)	32(100)	1.87	< 0.01	1.2-2.9
	(-)	57(323)	1		
Endocrine therapy	(+)	72(313)	1.39	0.23	0.82-2.4
	(-)	17(98)	1		
	unknown	0(12)			
antiestrogen drug	(+)	26(148)	0.79	0.32	0.50-1.3
	(-)	63(275)	1		
aromatase inhibitor	(+)	45(164)	1.59	0.03	1.1-2.4
	(-)	44(259)	1		
(Concurrent endocrine therapy)	concurrent	34(130)	1.34	0.20	0.85-2.1
	sequential	38(183)	1		
antiestrogen drug	concurrent	10(47)	1.08	0.81	0.56-2.1
	other	79(376)	1		
aromatase inhibitor	concurrent	24(83)	1.59	0.05	0.99-2.5
	other	65(340)	1		

Abbreviations : RP=radiation pneumonitis ; RT=radiotherapy ; CLD=central lung distance ; RR=relative risk ; CI=confidence interval.

Table 5. Univariate analysis of radiotherapy factors associated with Radiation pneumonitis

Factor		RP (n=89)	RR	*p*-value	95% CI
Energy	4 MVX	82(405)	0.58	0.17	0.27-1.3
	6 MVX	7(18)	1		
Radiation dose	50 Gy	61(309)	0.76	0.23	0.49-1.2
	60 Gy	25(114)	1		
Field length (long axis) (mean : 17.9 cm)	14.6-17.9	45(212)	1.01	0.97	0.67-1.5
	18.0-21.6	44(211)	1		
Field length (short axis) (mean : 6.8 cm)	3.8-6.8	33(217)	0.51	< 0.01	0.33-0.79
	6.8-11.1	56(206)	1		
CLD (mean : 1.8 cm)	0.8-1.8	42(222)	0.51	< 0.01	0.35-0.80
	1.9-3.1	47(112)	1		
Ipsilateral lung V_{20Gy} (mean : 9.6%)	1.8-9.6 (%)	36(213)	0.67	0.13	0.48-1.1
	9.7-18.8 (%)	53(210)	1		
Ipisilateral lung V_{10Gy} (mean : 12.2%)	2.9-12.2 (%)	37(214)	0.69	0.09	0.45-1.1
	12.3-22.3 (%)	52(209)	1		
Bilateral lung V_{20Gy} (mean : 4.9%)	0.8-4.9 (%)	38(213)	0.75	0.17	0.49-1.1
	4.9-14.2 (%)	51(210)	1		
Bilateral ling V_{10Gy} (mean : .2%)	1.3-6.2 (%)	39(213)	0.77	0.23	0.51-1.2
	6.3-17.5 (%)	50(210)	1		

Abbreviations : RP=radiation pneumonitis ; RT=radiotherapy ; CLD=central lung distance ; RR=relative risk ; CI=confidence interval.

0.043) and in the operative method (lumpectomy ; $p=0.007$). Other than these factors, the patients who underwent chemotherapy ($p=0.090$) and the patients who received radiation dose of 60 Gy ($p=0.080$) tended to appear RP, but it was not statistically significant (Table 6, 7).

Table 6. Univariate analysis of patient factors associated with RP of Grade 2 or greater, diagnosed as radiation-induced BOOP syndrome

Factor		BOOP (n=12)	RR	p-value	95% CI
Age	< 50 y	6(191)	1.30	0.65	0.42-4.0
	> 51 y	6(232)	1		
Side	left	5(201)	0.77	0.66	0.24-2.4
	right	7(222)	1		
Tumor factor	T0,Tis,T1	9(301)	1.25	0.74	0.34-4.6
	T2,T3,T4	3(122)	1		
Node factor	N0	11(331)	3.20	0.27	0.41-24.8
	N1,N2,N3	1(92)	1		
Clinical stage	< I stage	9(263)	1.87	0.35	0.51-6.9
	≧ IIA stage	3(160)	1		
Location (region)	inner side	3(161)	0.54	0.35	0.15-2.0
	outer side	9(259)	1		
	unknown	0(3)			
Operation	lumpectomy	5(316)	0.21	< 0.01	0.07-0.65
	quadrantectomy	7(105)	1		
	other	0(2)			
Allergic disease	(+)	4(73)	2.35	0.16	0.71-7.8
	(-)	8(350)	1		
Usage of other medication unrelated to breast cancer	(+)	3(126)	0.73	0.63	0.20-2.7
	(-)	9(297)	1		
Smoking status	(+)	1(64)	0.38	0.36	0.05-3.0
	(-)	11(283)	1		
	unknown	0(76)			
Chemotherapy	(+)	1(143)	0.17	0.09	0.02-1.3
	(-)	11(280)	1		
chemotherapy (pre-RT)	(+)	1(54)	0.63	0.66	0.08-4.9
	(-)	11(369)	1		
chemotherapy (post-RT)	(+)	1(100)	0.27	0.21	0.04-2.1
	(-)	11(323)	1		
Endocrine therapy	(+)	10(313)	1.55	0.54	0.34-7.1
	(-)	2(98)	1		
	unknown	0(12)			
antiestrogen drug	(+)	5(148)	1.32	0.63	0.42-4.2
	(-)	7(275)	1		
aromatase inhibitor	(+)	5(164)	1.06	0.92	0.34-3.3
	(-)	7(259)	1		
(Concurrent endocrine therapy)	concurrent	4(130)	1.02	0.98	0.29-2.6
	sequential	6(183)	1		
antiestrogen drug	concurrent	2(47)	1.70	0.50	0.37-7.7
	other	10(376)	1		
aromatase inhibitor	concurrent	2(83)	0.82	0.80	0.18-3.7
	other	10(340)	1		

Abbreviations : BOOP=bronchiolitis obliterans organizing pneumonia ; RT=radiotherapy ; CLD=central lung distance ; RR=relative risk ; CI=confidence interval.

Table 7. Univariate analysis of radiotherapy factors associated with RP of Grade 2 or greater, diagnosed as radiation-induced BOOP syndrome

Factor		BOOP (n=12)	RR	p-value	95% CI
Energy	4 MVX	12(405)			
	6 MVX	0(18)			
Radiation dose	50 Gy	6(309)	0.36	0.08	0.12-1.1
	60 Gy	6(114)	1		
Field length (long axis) (mean : 17.9 cm)	14.6-17.9	6(212)	1.00	0.99	0.32-3.1
	18.0-21.6	6(211)	1		
Field length (short axis) (mean : 6.8 cm)	3.8-6.8	8(217)	1.76	0.36	0.53-5.9
	6.8-11.1	4(206)	1		
CLD (mean : 1.8 cm)	0.8-1.8	4(222)	0.29	0.04	0.09-0.96
	1.9-3.1	8(112)	1		
Ipsilateral lung V_{20Gy} (mean : 9.6%)	1.8-9.6 (%)	7(213)	1.02	0.97	0.32-3.2
	9.7-18.8 (%)	5(210)	1		
Ipisilateral lung V_{10Gy} (mean : 12.2%)	2.9-12.2 (%)	6(214)	1.01	0.99	0.33-3.1
	12.3-22.3 (%)	6(209)	1		
Bilateral lung V_{20Gy} (mean : 4.9%)	0.8-4.9 (%)	6(213)	1.04	0.95	0.33-3.2
	4.9-14.2 (%)	6(210)	1		
Bilateral ling V_{10Gy} (mean : 6.2%)	1.3-6.2 (%)	6(213)	1.04	0.95	0.33-3.2
	6.3-17.5 (%)	6(210)	1		

Abbreviations : BOOP=bronchiolitis obliterans organizing pneumonia ; RT=radiotherapy ; CLD=central lung distance ; RR=relative risk ; CI=confidence interval.

The multivariate analysis detected significant differences in the following factors for incidence of Grade 1 or greater RP : short axis length (>6.8 cm ; p=0.024) and CLD (>1.8 cm ; p=0.021) (Table 8). The multivariate analysis of the RP cases of Grade 2 or greater detected a significant difference only in CLD (>1.8 cm ; p=0.027) (Table 9).

Table 8. Multivariate analysis of factors associated with RP

Factor		RP (n=89)	RR	p-value	95% CI
Node factor	N0	62(331)	1.08	0.78	0.61-1.9
	N1,N2,N3	27(92)	1		
Location (region)	inner side	26(161)	0.76	0.25	0.48-1.2
	outer side	63(259)	1		
	unknown	0(3)			
Chemotherapy	(+)	44(143)	1.70	0.16	0.81-3.6
	(-)	45(280)	1		
chemotherapy (post-RT)	(+)	32(100)	1.32	0.45	0.65-2.7
	(-)	57(323)	1		
aromatase inhibitor	(+)	45(164)	1.39	0.24	0.80-2.4
	(-)	44(259)	1		
aromatase inhibitor	concurrent	24(83)	1.31	0.41	0.69-2.5
	other	65(340)	1		
Field length (short axis) (mean : 6.8 cm)	3.8-6.8	33(217)	0.60	0.02	0.39-0.94
	6.8-11.1	56(206)	1		
CLD (mean : 1.8 cm)	0.8-1.8	42(222)	0.58	0.02	0.36-0.92
	1.9-3.1	47(112)	1		
Ipsilateral lung V_{20Gy} (mean : 9.6%)	1.8-9.6 (%)	36(213)	0.89	0.63	0.56-1.4
	9.7-18.8 (%)	53(210)	1		

Abbreviations : RP=radiation pneumonitis ; RT=radiotherapy ; CLD=central lung distance ; RR=relative risk ; CI=confidence interval.

Table 9. Multivariate analysis of factors associated with Grade2 or greater pneumonitis, diagnosed as radiation-induced BOOP syndrome

Factor		BOOP (n=12)	RR	*p*-value	95% CI
Chemotherapy	(+)	1(143)	0.17	0.09	0.02-1.3
	(-)	11(280)	1		
Radiation dose	50 Gy	6(309)	0.44	0.17	0.14-1.4
	60 Gy	6(114)	1		
Field length (short axis) (mean : 6.8 cm)	3.8-6.8	8(217)	1.55	0.49	0.45-5.3
	6.8-11.1	4(206)	1		
CLD (mean : 1.8 cm)	0.8-1.8	4(222)	0.24	0.03	0.07-0.85
	1.9-3.1	8(112)	1		
Ipsilateral lung V_{20Gy} (mean : 9.6%)	1.8-9.6 (%)	7(213)	1.64	0.43	0.48-5.6
	9.7-18.8 (%)	5(210)	1		

Abbreviations : BOOP=bronchiolitis obliterans organizing pneumonia ; RT=radiotherapy ; CLD=central lung distance ; RR=relative risk ; CI=confidence interval.

DISCUSSION

The frequency of pulmonary damage caused by radiotherapy following breast cancer surgery, including RP occurring at an early time after irradiation and fibrosis occurring at a late time, varies greatly from 0.9% to 85%, depending on reports. Naturally, the detection rates differ between chest radiography and chest CT. According to a previous report, CT evaluation 3 months after radiotherapy showed a frequency of Grade 1 or greater RP of 37% (14). HR-CT evaluation, 4 months after radiotherapy, also detected changes in pulmonary parenchyma within radiation fields in 85% of cases(7). In general, the frequency of RP evaluated by chest radiograph is 0.9-47%. In the present study, 21% of patients showed RP on the chest radiograph at 3 months after completion of radiotherapy. The previous reports, however, also involve local-regional radiotherapy on supraclavicular and axilla fields, as well as chest-wall irradiation after mastectomy and differ slightly from our study with respect to the subjects (2, 6, 14, 16, 17). BOOP was reported in 1985 by Epler, *et al.* It presents symptoms such as coughing, sense of dyspnea, fever and chest pain. On images, it shows patchy consolidation accompanied by ground-glass opacities. Histological characteristics include polypoid masses of granulation tissue in the lumens of small airways, alveolar ducts and some alveoli. Although it can be classified into idiopathic and secondary, the majority of cases are usually idiopathic. The frequency of radiation-induced BOOP syndrome following breast-conserving surgery of breast cancer has been reported as 2.3% (15), 2.4% (13) and 2.5% (12). In the present study, a similar incidence of 2.9% was obtained as a result. It included one atypical case among the 12 cases in which clinically problematic RP of Grade 2 or greater presented. Apart from this case, however, clinical symptoms requiring treatment did not appear before the period of 2.5-6.9 months after radiotherapy. In all cases, slight abnormal shadows can be detected on the chest radiographs at the 3-month after radiotherapy. It is considered that RP and radiation-induced BOOP syndrome are two different clinical conditions. RP results from the direct influence of irradiation, whereas radiation-induced BOOP syndrome is believed to be caused by autoimmunization induced indirectly by irradiation (10-13, 18, 19). Nevertheless, at the onset of radiation-induced BOOP syndrome, infiltrative shadows resembling ground-glass opacity, in areas corresponding to radiation fields, begin to appear. They then develop into infiltrative shadows expanding outside the radiation field areas. In the present study, there were hardly any clinical symptoms 3 months after radiotherapy. However, the next follow-up observations indicated 7 cases of exacerbated symptoms of Grade 2 or greater, despite the fact that the CT taken at 3 months after radiotherapy was only able to detect localized shadows within the radiation field. This led us to believe that conducting an evaluation 3 months after radiotherapy was crucial.

There have been several reports analyzing the factors concerning pathogenesis of RP and radiation-induced BOOP syndrome caused by irradiation following breast cancer surgery. There have been 4 reports investigating radiation-induced BOOP syndrome caused by irradiation after conserving surgery (12, 13, 15, 20). However, no reports have been published investigating the effects of patient background and treatment regimens on the pathogenesis of Grade 1 RP. In the present study, we only analyzed cases in which whole breast irradiation had been performed and in which all radiotherapy technical factors had been evaluated. As for the relationship between patient characteristics and RP, although patient age has often been cited as a risk factor (2, 14, 20-24), no such relationship was established in the present study. In agreement with previous reports, smoking history and the simultaneous use of other medication were not identified as factors influencing risk of RP (3, 20, 25). The use of radiotherapy and chemotherapy simultaneously increases the risk of RP (9, 17), however, the risk induced by the use of chemotherapy in stages varies greatly among reports (15, 20, 26, 27). Our univariate analysis also suggested that adjuvant chemotherapy increases the risk of RP.

There are numerous reports indicating the involvement of anti-estrogen agents in the pathogenesis of RP, especially tamoxifen (15, 21, 22, 28, 29). In the present study, however, anti-estrogen agents were not a significant variable for RP, whereas a correlation was found with the use of AIs. Increasing of RP patients who have used AIs might be related to age because AIs are generally used in postmenopausal women. With regard to radiotherapy factors, breast and regional irradiation including supraclavicular and axilla (local-regional radiotherapy) is considered to result in a higher frequency of RP compared with whole breast irradiation (local radiotherapy) (2, 6, 14, 16, 17). Lind, *et al.* have reported that the risk of RP was significantly higher in local-regional radiotherapy (4.1%) compared with local radiotherapy (0.9%) (16). Kahan (14), likewise, has reported that the incidence of RP and fibrosis were 2.5 times higher in regional irradiation. V_{20Gy} was reported to correlate with lung volume ; the more V_{20Gy} increased, the higher the incidence of RP (2, 14, 23). So we investigated only cases of breast irradiation, the frequency of RP had no significant statistically correlation with V_{20Gy} as well as V_{10Gy} in the present study. Previous reports, on the other hand, took into consideration the regional irradiation, leading to the speculation that significant differences were obtained due to the high influence of the regional irradiation. There have also been several reports indicating the involvement of CLD with RP (8, 9). Fernando, *et al.* (9) have reported the frequency of RP as 4.6% in cases where CLD was 3 cm or more. The present study also showed that CLD of 1.9 cm or more increased the risk of RP and radiation-induced BOOP syndrome. Another result of the present study was that the short axis length of the radiation field correlated with RP in the univariate and multivariate analyses. Although there have been reports examining the long axis length of radiation fields (15), it is difficult to compare the short axis with other analyses owing to different operational criteria among institutions. Nevertheless, RP is considerably affected by the lung volume to be irradiated, in the same way as CLD. The radiation dose exhibited no significant difference, albeit a tendency to correlate with the radiation-induced BOOP syndrome was observed. There are numerous reports investigating risk factors for the RP and radiation-induced BOOP syndrome. Though, in our study, there are no significant differences with previously suggested factors, such as age and the simultaneous use of hormonal treatment. In multivariate analysis, setting of the radiation field, such as CLD and short axis length of the radiation field, was an important factor. As for the timing of the RP, RP and radiation-induced BOOP syndrome that required treatment were detected on the chest radiography 3 months after the treatment, suggesting that evaluation at this stage is crucial. These results are suggesting that we need to give careful attention to occurrence of RP in around 3 months after completion of RT.

CONCLUSIONS

In the tangential irradiation of whole breast after breast conserving surgery, the significant risk factors of RP are CLD (>1.8 cm) and the short axis length of the radiation field, as determined by multivariate analysis. The pathogenesis of radiation-induced BOOP syndrome significantly correlated with CLD. Therefore, the lung volume within the radiation field proved to be a significant risk factor for RP and radiation-induced BOOP syndrome. Regarding follow-up after irradiation, the evaluation of chest radiography 3 months after the end of irradiation is postulated to be crucial.

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