TITLE PAGE

Analysis of factors associated with radiation-induced bronchiolitis obliterans organizing pneumonia (BOOP) syndrome after breast-conserving therapy

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ABSTRACT

Purpose: To evaluate factors associated with radiation-induced bronchiolitis obliterans organizing pneumonia (BOOP) syndrome after breast-conserving therapy.

Methods and Materials: We retrospectively analyzed 702 women patients with breast cancer who received radiation therapy after breast-conserving surgery at 7 institutions between July 1995 and December 2006. In all patients, the whole breast was irradiated with 2 tangential photon beams. The criteria used for the diagnosis of radiation-induced BOOP syndrome were as follows: (1) radiation therapy to the breast within 12 months; (2) general and/or respiratory symptoms lasting for at least 2 weeks; (3) radiographs showing lung infiltrations outside the radiation port; and (4) no evidence of a specific cause.

Results: Radiation-induced BOOP syndrome was seen in 16 patients (2.3%). Eleven patients (68.8%) were administered steroids. The duration of steroid administration ranged from 1 week to

3.7 years (median, 1.1 years). Multivariate analysis revealed that age (≧50years; odds ratio [OR], 8.88; 95% confidence interval [95% CI], 1.16–67.76; $p = 0.04$) and concurrent endocrine therapy (OR, 3.05; 95% CI, 1.09–8.54; $p = 0.03$) were significantly associated with BOOP syndrome. Of the 161 patients whose age was 50 years and older and who received concurrent endocrine therapy, 10 (6.2%) developed BOOP syndrome.

Conclusions: Age (≧50years) and concurrent endocrine therapy can promote the development of radiation-induced BOOP syndrome after breast-conserving therapy. The physicians should carefully follow up patients who received breast-conserving therapy, especially those who are older than 50 years and received concurrent endocrine therapy during radiation therapy.

KEY WORDS

Breast cancer, Breast-conserving surgery, Radiation therapy, Radiation-induced BOOP syndrome, Endocrine therapy

INTRODUCTION

Breast-conserving therapy (BCT) has become the standard of care for early-stage breast cancer. Postoperative radiation therapy significantly reduces the local recurrence rate. The recent update of the EBCTCG (Early Breast Cancer Trialists' Collaborative Group) meta-analysis revealed that higher local control rate translated into an improved survival in patients receiving radiation therapy as part of their BCT (1).

Bronchiolitis obliterans organizing pneumonia (BOOP) syndrome is known as lung injury occurring after radiation therapy to the breast. It is characterized by lung infiltrates outside the radiation port (2–4). Radiation-induced BOOP syndrome is different from radiation pneumonitis (RP). RP tends to occur shortly after the completion of radiation therapy (5) and is generally limited to the irradiated field; further, migration of shadows is not observed in RP (6). Radiation-induced BOOP syndrome after BCT is rare (3, 4), but steroids are often administered over a prolonged period, and their side effects lead to complications (2–4).

To date, only 2 small studies have analyzed the factors associated with radiation-induced BOOP syndrome after BCT (3, 4); the analysis, however, could not identify any factor. Therefore, we

retrospectively analyzed 702 female patients with breast cancer who had undergone BCT, and attempted to analyze the factors associated with radiation-induced BOOP syndrome after BCT.

METHODS AND MATERIALS

Study design

Between July 1995 and December 2006, 1074 consecutive patients with breast cancer received radiation therapy after breast-conserving surgery at 7 institutions*. Of the 1074 patients, 702 patients met the following criteria and were thus eligible for this study: (1) radiation therapy was accomplished; (2) radiation therapy was planned by a full-time radiation oncologist; and (3) the follow-up period from radiation therapy was more than 12 months. The medical records, radiation therapy documentation, and portal or simulation images of the 702 patients were examined. Chest roentgenograms were obtained for patients with respiratory or somatic symptoms. If an abnormal shadow was detected on the chest roentgenogram, computed tomography (CT) scanning was performed.

The observation period ranged from 12.0 to 128.0 months (median, 34.0 months).

The characteristics of the 702 eligible patients are shown in Table 1. All patients were women. Data on smoking habits were incomplete.

The details of radiation therapy are shown in Table 2. In all patients, the whole breast was irradiated with 2 tangential photon beams. For the treatment of the supraclavicular region, an anterior photon beam was used. For the boost irradiation to tumor bed, an electron beam was used.

The details of the adjuvant therapy administered are shown in Table 3. The regimen that was administered for more than 1 month and for the longest period of time ranging from 1 year before to 1 year after radiation therapy was selected in the items of chemotherapy and endocrine therapy. The regimen that was administered for more than 1 month and for the longest period of time during radiation therapy was selected in the items of concurrent chemotherapy and concurrent endocrine therapy.

The diagnosis of radiation-induced BOOP syndrome was based on the criteria proposed by Crestani et al. (4): (1) radiation therapy to the breast within 12 months; (2) general and/or respiratory symptoms lasting for at least 2 weeks; (3) radiographic lung infiltrations outside the radiation port; and (4) no evidence of a specific cause.

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Statistical analyses

Factors associated with radiation-induced BOOP syndrome were analyzed by logistic regression. Age (<50 or ≧50 years), the side affected, asthma, diabetes, drug allergy, chemotherapy, concurrent chemotherapy, endocrine therapy, concurrent endocrine therapy, concurrent endocrine therapy without chemotherapy and trastuzumab, concurrent endocrine therapy with chemotherapy before radiation therapy, endocrine therapy after radiation therapy, radiation therapy method, photon energy (4–6 MV or 10 MV), wedge filter, central lung distance (<3 or ≧3 cm), field length (<20 or ≧20 cm), irradiation to the supraclavicular region, boost to tumor bed, and overall radiation therapy time (<36 or ≧36 days) were evaluated as categorical data. The odds ratios (OR) and their 95% confidence intervals (95% CI) were also estimated. Values of p less than 0.05 were considered significant. Data processing and statistics were carried out using SPSS software, version 11.0 (SPSS, Chicago, IL).

RESULTS

Incidence of BOOP syndrome

Sixteen patients developed BOOP syndrome (Table 4). The incidence of BOOP syndrome was 2.3%.

Their age ranged from 44 to 74 years (median, 60 years). Five had right breast cancer and 11 had left breast cancer. Of the 16 patients, no patients had collagen vascular disease, 1 had asthma, 1 had diabetes, and 1 had drug allergy. For whole-breast irradiation, 14 patients received 50 Gy in 25 fractions; 1 patient, 50 Gy in 20 fractions; and 1 patient, 48 Gy in 24 fractions. The photon energy was 4 MV in 11 patients, 6 MV in 4 patients, and 10 MV in 1 patient. The radiation methods were the opposed pair method in 9 patients, the nonopposed pair method in 4 patients, and the half-beam method in 3 patients. A wedge filter was used in 14 patients. The central lung distance ranged from 1.3 to 3.6 cm (median, 2.1 cm); the field length, from 15 to 21 cm (median, 18 cm). No patients underwent irradiation to the supraclavicular region. One patient underwent boost irradiation to tumor bed. Overall radiation therapy time was from 33 to 47 days (median, 36.5 days). Four

patients received chemotherapy. Fifteen patients received endocrine therapy, and 10 patients received endocrine therapy concurrent with radiation therapy. No patients received trastuzumab.

Clinical courses of patients with BOOP syndrome

The interval from the completion of radiation therapy to occurrence of any symptoms ranged from 2.3 to 7.9 months (median, 3.8 months). The clinical symptoms in the 16 patients were cough (16 patients), fever (7 patients), sputum (5 patients), and dyspnea (3 patients). In 10 patients, abnormal pulmonary findings were observed in the unilateral diseased area; in 6 patients, in the bilateral diseased area. Eleven patients (68.8%) were administered steroids. The duration of steroid administration ranged from 1 week to 3.7 years (median, 1.1 years). In 2 patients with a longer duration of steroid administration, cataract developed as a side effect. All the 16 patients improved, but relapses occurred in 8 patients. Finally, these 8 patients also improved, and steroids were not administered to any patients at the time of this study.

Univariate analysis of factors associated with BOOP syndrome

Table 5 shows the results of the univariate analysis for the effect of various factors on the incidence of BOOP syndrome. Age (≧50 years; OR, 9.04; 95% CI, 1.19–68.87; p = 0.03) and concurrent endocrine therapy (OR, 3.12; 95% CI, 1.12–8.68; p = 0.03) were significantly associated with BOOP syndrome. The association between concurrent endocrine therapy without chemotherapy or trastuzumab and BOOP syndrome was borderline significant (OR, 2.24; 95% CI, 0.89–6.64; p = 0.08). Of 161 patients whose age was 50 years and older and who received concurrent endocrine therapy, 10 (6.2%) developed BOOP syndrome.

Multivariate analysis of factors associated with BOOP syndrome

We performed multivariate analysis to analyze factors that were found to be significantly associated with BOOP syndrome in the univariate analysis. Table 6 shows the results of the multivariate analysis for the effect of factors on the incidence of BOOP syndrome. In multivariate analysis, as in univariate analysis, age (≧50 years; OR, 8.88; 95% CI, 1.16–67.76; p = 0.04) and concurrent endocrine therapy (OR, 3.05; 95% CI, 1.09–8.54; p = 0.03) were significantly associated with BOOP syndrome.

DISCUSSION

BOOP was reported for the first time in 1985 by Epler et al. Cough, flu-like symptoms, or dyspnea is observed. Clinically, radiographs show an unusual pattern of patchy consolidations with ground-glass opacities. Histologic characteristics include polypoid masses of granulation tissue in the lumens of small airways, alveolar ducts, and some alveoli (7). Most cases of BOOP are idiopathic, but the histologic reaction pattern of BOOP can be seen in association with connective tissue disease, drugs, infection, and aspiration (8). BOOP also occurs after radiation therapy, and radiation-induced BOOP syndrome is different from radiation pneumonitis (RP). RP usually occurs within 3 months after the completion of radiation therapy (5), but radiation-induced BOOP syndrome often occurs after more than 4 months (2–4, 9), as was the case in our study. In radiation-induced BOOP syndrome, shadows extend beyond the radiation port and often migrate (2–4, 9). Although in RP, shadows occasionally extend beyond the radiation port, these are less marked than those within the radiation port (6). RP is a direct effect of irradiation, but radiation-induced BOOP syndrome has been suggested to be an indirect effect of irradiation, that is,

autoimmune processes play important roles in its development (3, 5, 10, 11).

The incidence of radiation-induced BOOP syndrome after BCT was reported to be 2.5% (3) and 2.4% (4). It was 2.3% in our study, which is similar to that reported previously.

Dramatic improvement is achieved by administration of corticosteroids in radiation-induced BOOP syndrome, but relapses often occur while tapering the dose or after suspending the treatment. Therefore, steroids are administered over a prolonged period, and their side effects lead to complications (2–4). In our study, of the 16 patients, 11 (68.8%) were administered steroids, and the duration of the steroid administration ranged from 1 week to 3.7 years (median, 1.1 years). Two patients who were administered steroids for longer durations developed cataract as a side effect.

Only 2 reports have analyzed the factors associated with radiation-induced BOOP syndrome after BCT (3, 4). Although no factors associated with radiation-induced BOOP syndrome were found in those reports, the number of patients was small, with 157 cases (3) and 206 cases (4). Further, radiation therapy factors, such as the central lung distance and field length, were not analyzed, with the exception of the total dose (3). We performed this study based on the hypothesis that radiation therapy factors as well as patient characteristics and adjuvant therapy might be

associated with radiation-induced BOOP syndrome. Therefore, when we analyzed 702 cases, concurrent endocrine therapy and age (≧50 years) were found to be significantly associated with radiation-induced BOOP syndrome. Although the association between concurrent endocrine therapy without chemotherapy and trastuzumab and radiation-induced BOOP syndrome was only borderline significant (p = 0.08), this result may be because the number of patients who received this type of therapy was small (n = 173).

In our study, of the 16 patients who developed BOOP syndrome, 10 received endocrine therapy concurrently with radiation therapy: 4 received tamoxifen, 4 received anastrozole, and 2 received toremifene. In some studies, tamoxifen was significantly associated with lung fibrosis or pulmonary changes in radiography after radiation therapy to the breast (12–14). Colletta et al. reported that toremifene induced human fetal lung fibroblasts to secrete transforming growth factor beta (TGF-beta) (15), which has been implicated in the pathogenesis of pulmonary fibrosis (16). These previous findings may be related with the result in our study. However, in other studies, tamoxifen was not found to be associated with pneumonitis or pulmonary changes observed in the radiograph after administering radiation therapy to the breast (17, 18).

Age was significantly associated with RP after radiation therapy to the breast in many studies (12, 13, 19–21). It was reported that patients whose age is 50 years and older (13) and 58 years and older (12) are at a higher risk for developing RP.

In some studies, chemotherapy (17, 22, 23), central lung distance (23, 24), and irradiation to the supraclavicular region (17, 20, 22) were significantly associated with RP after radiation therapy to the breast. In our study, these factors were not associated with radiation-induced BOOP syndrome. The result demonstrated that the central lung distance, field length, and irradiation to the supraclavicular region were not associated with radiation-induced BOOP syndrome. This supports the notion that radiation-induced BOOP syndrome is not a direct effect of irradiation.

This study had certain limitations. It was retrospectively designed, and the number of subjects with BOOP syndrome was only 16. It is necessary to perform a large-scale prospective study.

CONCLUSIONS

Age (≧ 50 years) and concurrent endocrine therapy can promote the development of radiation-induced BOOP syndrome after breast-conserving therapy. The physicians should

carefully follow up patients who received breast-conserving therapy, especially those who are older than 50 years and received concurrent endocrine therapy during radiation therapy.

Table 1. Patient characteristics (n = 702)

Characteristics	
Age (years)	26-85 (median 54)
Side right/left/bilateral	340/355/7
Collagen vascular disease Yes/No	1*/701
Asthma Yes/No	21/681
Diabetes Yes/No	38/664
Drug allergy Yes/No	70/632
Clinical stage (UICC)	
0	30
Ⅰ	383
ⅡA	197
ⅡB	60
ⅢA	18
ⅢB	6
ⅢC	5
Ⅳ	3
Histologic type	
Non-invasive ductal carcinoma	30
Invasive ductal carcinoma	618
Others	54

* Chronic articular rheumatism

Table 2. Radiation therapy details

Characteristics	
Whole breast irradiation	
Dose and fractions	
46 Gy in 23 fractions	1
48 Gy in 24 fractions	1
48.4 Gy in 22 fractions	1
50 Gy in 25 fractions	693
50 Gy in 20 fractions	2
50.4 Gy in 28 fractions	1
52 Gy in 26 fractions	2
60 Gy in 30 fractions	1
Photon energy 4 MV/6 MV/10 MV	414/190/98
Method Opposed pair/Nonopposed pair/Half-beam	325/306/71
Wedge filter Yes/No	515/187
Central lung distance (cm)	0.1–4.9 (median 1.9)
Field length (cm)	13–26 (median 18)
Irradiation to the supraclavicular region Yes/No	12/690
Boost to tumor bed Yes/No	76/626
Dose and fractions	
6 Gy in 2 fractions	1
9 Gy in 3 fractions	1
10 Gy in 5 fractions	74
Electron energy (MeV)	6–18 (median 10)
Area (cm^2)	19.6–112 (median 50)
Overall radiation therapy time (days)	29–88 (median 36)

Table 3. Adjuvant therapy details

Characteristics	
Chemotherapy Yes/No	247/455
Anthracycline-based regimens	78
Taxane-based regimens	59
CMF	59
Others	51
Concurrent chemotherapy Yes/No	22/680
CMF	10
Doxifluridine	5
Others	7
Endocrine therapy Yes/No	542/160
Tamoxifen	278
Anastrozole	174
Toremifene	31
Others	59
Concurrent endocrine therapy Yes/No	249/453
Tamoxifen	152
Anastrozole	66
Toremifene	13
Others	18
Trastuzumab Yes/No	10/692

Abbreviations: CMF = cyclophosphamide, methotrexate, 5-fluorouracil

Table 4. Clinical characteristics of 16 patients with BOOP syndrome

No.	Age	Drug before RT	Drug concurrent with RT	Drug after RT	CLD	Field length	Period before onset, after RT	Location of pulmonary findings	Duration of steroid administration
1	51 years	Tamoxifen	Tamoxifen	Tamoxifen	2.0 cm	20 cm	2.3 months	Unilateral	1.1 years
2	65 years	—	Anastrozole	Anastrozole	2.9 cm	18 cm	2.5 months	Bilateral	3.7 years
3	74 years	CMF	—	—	1.6 cm	17 cm	3.4 months	Bilateral	—
4	60 years	—	Tamoxifen	Tamoxifen,	1.8 cm	15 cm	3.4 months	Unilateral	4.6 months
5	60 years	—	—	Anastrozole	2.5 cm	17 cm	3.4 months	Unilateral	1.7 years
6	58 years	—	Anastrozole	Anastrozole	2.1 cm	18 cm	3.6 months	Bilateral	1.2 years
7	67 years	Anthracycline	—	Anastrozole	1.8 cm	18 cm	3.6 months	Unilateral	1.1 years
8	58 years	—	Toremifene	Toremifene	3.6 cm	19 cm	3.8 months	Unilateral	—
9	57 years	—	Tamoxifen	Tamoxifen	2.1 cm	19 cm	3.8 months	Bilateral	—
10	68 years	—	Anastrozole	Anastrozole	1.3 cm	19 cm	4.6 months	Bilateral	—
11	44 years	—	—	Tamoxifen	2.2 cm	17 cm	4.8 months	Unilateral	—
12	50 years	—	—	Tamoxifen	2.6 cm	19 cm	4.8 months	Unilateral	3 weeks
13	61 years	—	—	Tamoxifen	2.1 cm	20 cm	5.3 months	Unilateral	1 week
14	52 years	Tamoxifen	Tamoxifen	Tamoxifen	2.0 cm	16 cm	6.8 months	Unilateral	11 months
15	64 years	Anastrozole, taxane	Anastrozole	Anastrozole	1.6 cm	18 cm	7.1 months	Unilateral	1 month
16	60 years	—	Toremifene	Toremifene	2.1 cm	21 cm	7.9 months	Bilateral	3.2 years

Abbreviations: RT = radiation therapy; CLD = central lung distance; CMF = cyclophosphamide, methotrexate, 5-fluorouracil
taxane = taxane-based regimens; anthracycline = anthracycline-based regimens

Table 5. Univariate analysis of factors associated with BOOP syndrome

Parameters	BOOP n = 16	No BOOP n = 686	OR	95% CI	*p*
Age: ≧50 years	15 (94%)	428 (62%)	9.04	1.19–68.87	0.03
Side: left	11 (69%)	344 (50%)	2.14	0.74–6.23	0.16
Asthma	1 (6%)	20 (3%)	2.22	0.28–17.64	0.45
Diabetes	1 (6%)	37 (5%)	1.17	0.15–9.10	0.88
Drug allergy	1 (6%)	69 (10%)	0.60	0.08–4.58	0.62
Chemotherapy	5 (31%)	242 (35%)	0.83	0.29–2.43	0.74
Concurrent chemotherapy	0 (0%)	22 (3%)	0	—	0.98
Endocrine therapy	15 (94%)	527 (77%)	4.53	0.59–34.53	0.15
Concurrent endocrine therapy	10 (63%)	239 (35%)	3.12	1.12–8.68	0.03
Concurrent endocrine therapy without chemotherapy and trastuzumab	7 (44%)	166 (24%)	2.44	0.89–6.64	0.08
Concurrent endocrine therapy with chemotherapy before RT	1 (6%)	32 (5%)	1.36	0.17–10.64	0.77
Endocrine therapy after RT	15 (94%)	522 (76%)	4.71	0.62–35.96	0.13
OPM vs. (NOPM or HBM)	9 (56%)	316 (46%)	1.51	0.55–4.09	0.42
Energy of photon : 4-6-MV	15 (94%)	589 (86%)	2.47	0.32–18.92	0.38
Wedge filter	14 (88%)	472 (73%)	2.59	0.58–11.48	0.21
Central lung distance: ≧3cm	1 (6%)	33 (5%)	1.32	0.17–10.29	0.79
Field length: ≧20cm	3 (19%)	204 (30%)	0.55	0.15–1.93	0.35
Irradiation to the supraclavicular region	0 (0%)	12 (2%)	0	—	0.98
Boost to tumor bed	1 (6%)	75 (11%)	0.54	0.07–4.17	0.56
Overall RT time: ≧36days	13 (81%)	523 (76%)	1.35	0.38–4.80	0.64

Abbreviations: OR = odds ratio; CI = confidence interval; vs. = versus; RT = radiation therapy;
OPM = opposed pair method; NOPM = nonopposed pair method; HBM = half-beam method

Table 6. Multivariate analysis of factors associated with BOOP syndrome

Parameters	OR	95% CI	*p*
Age : ≧50years	8.88	1.16–67.76	0.04
Concurrent endocrine therapy	3.05	1.09–8.54	0.03

Abbreviations: OR = odds ratio; CI = confidence interval

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