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Original article

Clinical outcome of adjuvant radiotherapy for squamous cell carcinoma of the breast; a multicenter retrospective cohort study

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ABSTRACT

Background: Because primary squamous cell carcinoma (SCC) of the breast is a rare disease, the standard therapy has not been established. We examined the clinical outcomes of postoperative adjuvant radiotherapy for breast SCC.

Material and methods: We conducted a multicenter retrospective cohort study. Patients diagnosed with primary breast SCC who received adjuvant radiotherapy as part of their primary definitive treatment were included. Overall survival (OS), breast cancer-specific survival (BCSS), and recurrence-free interval (RFi) were evaluated.

Results: Between January 2002 and December 2017, 25 breast SCC patients received adjuvant radiotherapy as a primary treatment were included. Median follow-up time was 43.5 months. Three (12%), fifteen (60%) and seven (28%) patients had clinical stage I, II and III disease, respectively. Fourteen patients underwent breast-conserving surgery and subsequent adjuvant radiotherapy. Eleven patients underwent mastectomy and post-mastectomy radiotherapy. Ten patients received regional lymph node irradiation. Nine (36%) patients had disease recurrence. The first site of recurrence was locoregional in five, but distant metastasis arose in one. Concurrent local and distant metastasis were seen in two. Six cases of local recurrence occurred within the irradiated site. Seven patients died, and six of the deaths were due to breast cancer. Five-year OS, BCSS, and Rfi were 69%, 70%, and 63%, respectively. In multivariate analysis, age and lymphatic invasion were associated with increased risk of recurrence.

Conclusion: Breast SCC has a high incidence of locoregional recurrence and poor prognosis. Age and lymphatic invasion are significant risk factors for recurrence.

Abbreviations: SCC, squamous cell carcinoma; OS, overall survival; BCSS, breast cancer-specific survival; RFi, recurrence-free interval; ER, estrogen receptor; PgR, progesterone receptor; HER2, human epidermal growth factor receptor 2; EGFR, epidermal growth factor receptor; UICC, the Union for International Cancer Control; CTCAE, the Common Terminology Criteria for Adverse Events; RNI, regional nodal irradiation; AC, doxorubicin and cyclophosphamide; FEC, epirubicin and cyclophosphamide; FAP, 5-FU, cisplatin and doxorubicin; CMF, cyclophosphamide, methotrexate, and 5-fluorouracil; PMRT, post-mastectomy radiotherapy (PMRT); SEER, the Surveillance, Epidemiology and End Results; IDC, invasive ductal carcinoma; EBCTCG, the Early Breast Cancer Trialists' Collaborative Group; PARP, poly (ADP-ribose) polymerase.

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1. Introduction

Squamous cell carcinoma (SCC) is a form of metaplastic carcinoma of the breast. It is commonly considered that the majority of pure breast SCCs originate from squamous metaplasia [1]. The definition of an SCC is a tumor in which 90% or more of the lesion consists of keratinizing SCC in the absence of extramammary primary SCC [1].

Primary SCC of the breast is a rare disease with a prevalence of 0.1% or less of all breast cancers [2,3]. Consequently, most published studies are case reports or small retrospective cohorts from a single institution [4–10].

In relatively old studies, there was no difference in clinical outcome compared to non-squamous carcinoma [6,11], but several studies suggested that SCC of the breast is aggressive and has a poor prognosis, similar to poorly-differentiated adenocarcinoma [5,7,8,12,13]. The prognosis of breast SCC is still controversial. Because of its rarity, the standard therapy for breast SCC has not been established. Adjuvant radiotherapy is a recommended standard treatment for patients who have undergone breast-conserving surgery or mastectomy to reduce the risk of locoregional recurrence and improve breast cancer-specific and overall survival [14,15]. However, there are few studies of radiotherapy in breast SCC. Therefore, the role of adjuvant radiotherapy in SCC of the breast is still unclear. We aimed to evaluate the clinical outcomes of postoperative adjuvant radiotherapy as part of the primary definitive treatment for SCC of the breast.

2. Material and Methods

2.1. Study design and patients

This was a multicenter retrospective cohort study. From January 2002 to February 2017, the database of all consecutive patients diagnosed with primary SCC of the breast who received radiotherapy was searched at five hospitals: the University of Tokyo Hospital, St. Luke's International Hospital, Cancer Institute hospital of JFCR, Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital, and Mitsui Memorial Hospital. Inclusion criteria were patients diagnosed with primary breast SCC who received adjuvant radiotherapy as part of their primary definitive treatment. Exclusion criteria were patients with primary SCC at a second site or those who received radiotherapy for recurrence or with palliative intent.

2.2. Outcome

Medical charts were reviewed to obtain data of patient characteristics, pathological information, clinical stage, type of treatment, including surgical treatment, radiotherapy, chemotherapy, and hormonal therapy, clinical outcome, including locoregional recurrence, distant metastasis, and/or death. Locoregional recurrence was defined as recurrent disease of the ipsilateral breast or thoracic wall (local recurrence) or of the ipsilateral axillary, supraclavicular or internal mammary nodes (regional recurrence). The clinical and pathological stages were classified based on the Union for International Cancer Control (UICC) staging system 7th edition. This study was approved by the Institutional Review Board of the University of Tokyo Hospital (11,970). We evaluated overall survival (OS), breast cancer-specific survival (BCSS), recurrence-free interval (RFi), and type of recurrence: locoregional or distant metastasis, as outcomes. OS was defined as the time from primary surgical treatment to death. BCSS was defined as the time from primary surgical treatment to death from breast cancer. RFi was defined as the time from primary surgical treatment to locoregional recurrence, metastasis, and death from breast cancer, according to DATECAN guidelines [16]. Adverse events following radiotherapy were collected and graded based on the Common Terminology Criteria for Adverse Events (CTCAE) ver. 4.

2.3. Statistical analysis

Kaplan-Meier analysis was used to estimate OS, BCSS, and RFi. The log-rank test was used to assess the differences. Univariable and multivariable Cox proportional hazard models were used to examine factors associated with increased risk of recurrence. The following variables were gathered for analysis: age (continuous variable), stage, breast surgery (breast-conserving surgery or mastectomy), axillary lymph node procedure (axillary lymph node dissection or sentinel node biopsy), chemotherapy, regional nodal irradiation (RNI), hormonal receptor status, lymphatic invasion, vascular invasion, and nuclear grade. The higher stage of the clinical stage and the pathological stage was used as the stage in the analysis. All statistical analyses were performed using SPSS ver.24 software (IBM Corporation, Armonk, NY, USA).

3. Results

3.1. Baseline characteristics

Between January 2002 and December 2017, thirty-two patients were diagnosed with primary breast SCC and received radiotherapy in five hospitals. Seven patients were excluded because radiotherapy was given for recurrence or palliative intent. Twenty-five breast SCC patients who received adjuvant radiotherapy as part of primary treatment were included in the analysis. Median follow-up time was 43.5 months (range, 9–180). The median age of patients was 53 years old (range, 29–83). Patient characteristics are shown in Table 1. Seven patients represented mixed forms of SCC. Eight (32%) of the patients had clinical T3-4 disease; sixteen (64%) patients had nuclear grade 3; ER-positive tumors were found in six (24%) patients, and seventeen patients had triple-negative breast cancer. Nine patients had a tumor of Ki-67 50 or higher. Patients with SCC generally had poorer clinicopathological features. EGFR expression was measured in one patient, and the result showed EGFR positivity.

3.2. Primary treatment

Breast-conserving surgery or mastectomy was performed in 14 (56%) and 11 (44%) patients, respectively. Twenty (80%) patients received chemotherapy as part of their primary treatment. Of them, six patients received chemotherapy in the neoadjuvant setting, while the others received it in an adjuvant setting. The chemotherapy regimen included doxorubicin and cyclophosphamide (AC) with taxane in eight patients, epirubicin and cyclophosphamide (FEC) with taxane in four patients, AC in two patients, FEC in two patients, paclitaxel and epirubicin in one patient, 5-FU, cisplatin and doxorubicin (FAP) in one patient, FEC, taxane, and bevacizumab in one patient, and cyclophosphamide, methotrexate, and 5-fluorouracil (CMF) in one patient. All patients received adjuvant radiotherapy: fifteen (60%) patients underwent whole-breast radiotherapy following breast-conserving surgery and ten (40%) patients received post-mastectomy radiotherapy (PMRT). The details and dose of radiotherapy were shown in Table 2. Regional nodal irradiation was prescribed in ten (40%) patients; eight patients were clinical or pathological stage III, and two patients were pathological stage II. All patients who had four or more axillary lymph node metastases and/or T4 disease received RNI. Patients who had aggressive progression during adjuvant chemotherapy or

Table 1
Baseline patient and tumor characteristics.

	n	%
Clinical T stage		
cT1	3	12
cT2	14	56
cT3	3	12
cT4	5	20
Clinical N stage		
cN0	15	60
cN1	8	32
cN2	2	8
Clinical M stage		
cM0	25	100
Clinical stage		
cStage I	3	12
cStage II	15	60
cStage III	7	28
Pathological T stage		
pT1	2	8
pT2	13	52
pT3	1	4
pT4	3	12
ypT1	1	4
ypT2	2	8
ypT3	1	4
ypT4	2	8
Pathological N stage		
pN0	13	52
pN1	5	20
pN2	1	4
ypN0	3	12
ypN1	2	8
ypN2	0	0
ypN3	1	4
Pathological M stage		
pM0	19	76
ypM0	6	24
Pathological stage		
pStage I	2	8
pStage II	13	52
pStage III	4	16
ypStage I	1	4
ypStage II	2	8
ypStage III	3	12
Estrogen receptor status		
Positive	6	24
Negative	19	76
Progesterone receptor status		
Positive	2	8
Negative	23	92
HER2 status		
Positive	1	4
Negative	22	88
Unknown	2	8
Nuclear grade status		
NG1	2	8
NG2	3	12
NG3	16	64
Unknown	4	16
Ki-67, %		
<50	2	8
≥50	9	36
Unknown	14	56
Lymphatic invasion		
Positive	12	48
Negative	13	52
Vascular invasion		
Positive	9	36
Negative	14	56
Unknown	2	8
Breast surgery		
Breast-conserving surgery	14	56
Mastectomy	11	44
Axially lymph nodes		
Sentinel node biopsy	16	64
Axillary lymph node dissection	9	36
Chemotherapy		
Neoadjuvant	6	24
Adjuvant	14	56
No	5	20
Hormonal therapy		
Yes	5	20
No	19	76
Unknown	1	4

large primary tumor also included RNI at the discretion of the treating physician. Nine of them received RNI at the setting of PMRT, and one patient received RNI in addition to whole-breast radiotherapy following breast-conserving surgery. A hypofractionation regimen (2.66 Gy/fr) was used only for three patients who received whole-breast radiotherapy without RNI. Tumor bed boost (total boost dose of 9–16 Gy) was performed in 12 of 15 whole-breast radiotherapy patients. Internal mammary node irradiation was included in eight of 10 patients who received RNI. Adverse events following radiotherapy were acute dermatitis of grade 1 in 20 patients and grade 2 in two patients. No grade 2 or higher radiation pneumonitis was observed. No grade 3 or higher adverse events related to radiotherapy were observed.

3.3. Clinical outcome

Overall survival, BCSS, and RFi are shown in Fig. 1. The 5-year OS, BSCC and RFi were 69%, 70% and 63%, respectively. Eight (32%) patients experienced disease recurrence, including five locoregional recurrences, two locoregional and distant metastasis recurrence, and one distant metastasis recurrence. In six of seven patients with locoregional recurrence, the recurrence occurred within the irradiated site. The details of all recurrence cases are summarized in Table 3. Six (24%) patients died of recurrent disease, and the remaining two patients who had disease recurrence were still alive at the latest follow-up. One patient without breast cancer recurrence died of ovarian cancer after 13 years follow-up. The median recurrence-free interval of the eight recurrence cases was 12.3 months (range; 4.2–47).

3.4. Risk factors for recurrence

Risk factors for recurrence were examined by univariate and

Table 2
Details of radiotherapy.

	n	%
Radiotherapy		
Whole breast RT	14	56
Whole breast RT + RNI	1	4
PMRT (chest wall + regional lymph node)	9	36
PMRT (chest wall only)	1	4
Total dose, Gy		
48–50 (conventional fractionation, no boost)	13	52
51.56–52.84 (hypofractionation, with boost)	3	12
60–66 (conventional fractionation, with boost)	9	36
Boost dose, Gy		
9 (3 Gy/fr)	1	4
10 (2 Gy/fr)	9	36
12 (2 Gy/fr)	1	4
16 (2 Gy/fr)	1	4
No boost	13	52

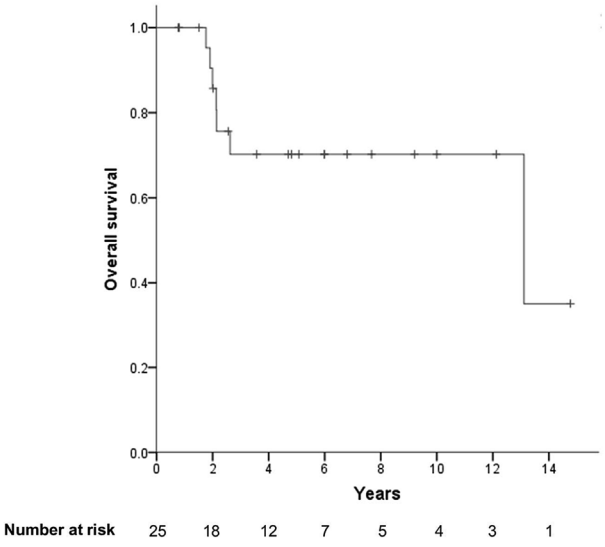
RT; radiotherapy, RNI; regional nodal irradiation, PMRT; post-mastectomy radiotherapy.
Conventional fractionation; 2 Gy/fr, hypofractionation; 2.66 Gy/fr.

multivariate analysis. Factors associated with RFi by univariate analysis were age, RNI, and lymphatic invasion. In multivariate analysis, older age and lymphatic invasion were associated with a significantly increased risk of recurrence ($P = 0.03$, 0.01, respectively) (Table 4).

4. Discussion

Because of rarity of breast SCC, reports on this disease are very limited, and the efficacy of adjuvant radiotherapy is also unknown. In this study, we examined the clinical outcome of breast SCC patients who received adjuvant radiotherapy as a part of their primary treatment. To the best of our knowledge, this is the first and biggest study to evaluate the clinical outcomes of adjuvant radiotherapy to breast SCC in a multicenter cohort study.

Breast SCC is considered aggressive and has a poor prognosis. There are three studies that reported breast SCC survival outcomes using a database. One study based on the Surveillance, Epidemiology and End Results (SEER) database from 1988 to 2001 reported that OS of 125 localized breast SCC patients was 64% at 5 years [5]. Another study using the data in the California Cancer Registry from 1988 to 2006 reported 5-yr OS of 177 breast SCC patients was 68.1%, while it was 83.9% for all other types of invasive ductal carcinoma (IDC) [12]. A third study, based on the national cancer database in the United States between 2004 and 2014, showed that 5-year OS was 62.1% for 686 breast SCC patients and 83% for IDC patients [13]. Several single-institute studies have reported 5-yr OS rates of 40–67.2% [4,5,7,8,10]. The 5-yr OS in our study was 69%, which is



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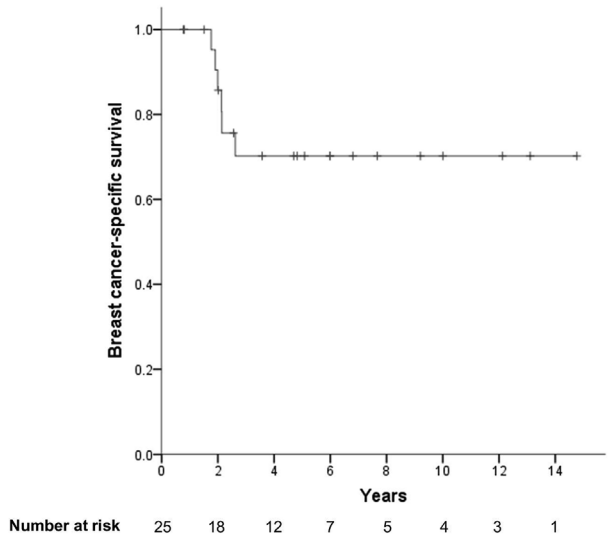

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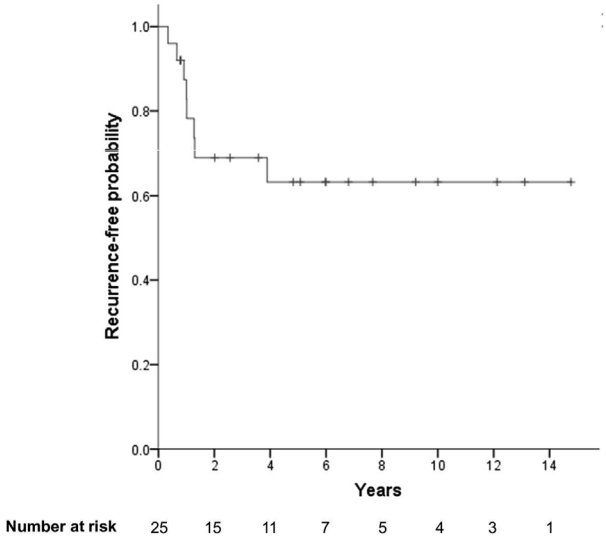

c

Fig. 1. Overall survival (A), breast cancer-specific survival (B), and recurrence-free interval (C) in 25 patients with squamous cell carcinoma of the breast who received adjuvant radiotherapy as a primary treatment.

Table 3
Summary of patients with recurrence.

	Age	Type of recurrence	First recurrent site	In-filed recurrence	Time to recurrence	Clinical stage	Pathological stage	Hormonal receptor	HER2 status	Lymphatic invasion	Vascular invasion	Nuclear grade	Primary treatment		Chemotherapy	Clinical outcome
													Surgery	Radiotherapy		
Case 1	59	Locoregional	Supraclavicular and Rotter lymph nodes	Yes	4.2 months	cT3N1M0	ypT4N3M0	ER-, PgR-	–	+	+	3	Bt + Ax	CW + Sc + IMN	Neoadj FEC[b]	Dead
Case 2	43	Locoregional	Chest wall	Yes	11 months	cT2N1M0	ypT3N1M0	ER+, PgR+[a]	–	+	+	3	Bt + Ax	CW + Sc + IMN	Neoadj FEC + taxane	Dead
Case 3	54	Locoregional	Chest wall	Yes	8.1 months	cT4N1M0	pT4N1M0	ER-, PgR-	+	+	–	3	Bt + Ax	CW + Sc + IMN	Adj CMF[c]	Dead
Case 4	45	Locoregional	Axillary lymph nodes	Yes	16 months	cT4N1M0	pT4N1M0	ER-, PgR-	–	+	–	NA	Bt + Ax	CW + Sc + IMN	Adj AC + taxane	Dead
Case 5	51	Locoregional	Axillary and supraclavicular lymph nodes	Yes	12 months	cT1cN0M0	pT2N1M0	ER-, PgR-	–	+	–	3	Bp + SNB	WB + Sc + IMN + boost	Adj AC + taxane	Alive
Case 6	65	Locoregional and distant metastasis	Skin of breast, lung, pleura, and bone	Yes	47 months	cT2N0M0	pT2N1M0	ER+, PgR-	–	–	–	3	Bp + SNB	WB + boost	Adj AC + taxane	Alive
Case 7	66	Locoregional and distant metastasis	Supraclavicular and neck lymph nodes, lung	No	15 months	cT2N0M0	pT2N0M0	ER-, PgR-	–	+	+	3	Bp + SNB	WB	Adj AC	Dead
Case 8	59	Distant metastasis	Lung, pleura, and bone	No	12 months	cT2N0M0	pT2N0M0	ER-, PgR-	–	+	+	NA	Bt + SNB	CW + Sc + IMN	Adj AC + taxane	Dead

HER2; human epidermal growth factor receptor 2, ER; estrogen receptor, PgR; progesterone receptor, Bt; mastectomy, Ax; axillary lymph node dissection, CW; chest wall, Sc; supraclavicular region, IMN; internal mammary nodes, Neoadj; neo-adjuvant, FEC; epirubicin and cyclophosphamide, CMF; methotrexate, and 5-fluorouracil, AC; doxorubicin and cyclophosphamide, Bp; breast-conserving surgery, SNB; sentinel node biopsy, WB; whole breast.

[a] Negative conversion following NAC.
[b] Progressive disease during neoadjuvant chemotherapy.
[c] Recurrence occurred during adjuvant chemotherapy.

comparable with previous studies. As mentioned in previous studies [12,13], breast SCC seemed to have poor survival outcomes compared to IDC.

All the recurrence occurred within four years with median 12.3 months in our study. In previous studies, disease-specific, progression-free, disease-free, or locoregional recurrence-free survival curves plateaued after four to five years [4,5,7,10]. Breast cancer recurs over time, and the recurrence after 10 years is not uncommon [14,15]. As breast SCC represented early recurrence pattern, the breast SCC recurrence might be different from all other types of breast cancer.

Few studies have focused on the outcomes of radiotherapy on breast SCC. In the single-institute series, six of 19 (32%) breast SCC patients treated with adjuvant radiation therapy had a locoregional recurrence, and four of them experienced locoregional relapse within the irradiated field [5]. Another small study reported that one of four (25%) breast SCC patients who received adjuvant radiotherapy experienced a locoregional relapse [10]. In our study, seven of 25 (28%) patients experienced locoregional recurrence, which arose within the irradiated site in six of them; local recurrence occurred in two patients, and reginal lymph nodes recurrence occurred in four patients.

The locoregional recurrence rate of all other types of breast cancer was basically lower than breast SCC. The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) meta-analysis reported that the 10-year locoregional recurrence was 8% in patients who underwent breast-conserving surgery and radiotherapy, while it was 3% in patients with node-negative cancer and 8.1% in patients with node-positive cancer who received mastectomy and radiotherapy [14,15]. In retrospective studies, the locoregional recurrence rate for all breast cancers was 2.4% in patients who received breast-conserving surgery and whole-breast irradiation [17], and 9.2% in those with locally-advanced breast cancer treated with neo-adjuvant chemotherapy, mastectomy, and radiotherapy [18]. Among node-positive patients treated with breast-conserving surgery, whole-breast irradiation, and systemic therapy on NSABP clinical trials, ipsilateral breast tumor recurrence occurred in 9.7% with a 10-year cumulative incidence of 8.7%, and other locoregional recurrences occurred in 6.2% with 10-year cumulative incidence of 6.0% [19].

SCC is usually negative for estrogen receptor (ER) and progesterone receptor (PR), and few are positive for human epidermal growth factor receptor 2 (HER2) [5–7,20]. A high frequency of epidermal growth factor receptor (EGFR) expression has also been reported [5,20,21]. Most cases of breast SCC are triple-negative breast cancer. In our study, of the 23 patients whose subtypes were confirmed, 17 (74%) represented the triple-negative subtype. The triple-negative biologic subtype corresponded to a higher locoregional recurrence risk compared to other subtypes [22,23]. Breast SCC had a similar or worse locoregional recurrence compared to all forms of triple-negative breast cancer.

As all our patients were treated with radiotherapy, we are unable to compare the locoregional recurrence rate in breast SCC with or without radiotherapy. Because of the higher rate of locoregional relapse within irradiated sites, breast SCC might be radio-resistant. The escalation of radiation dose may thus be the option. In addition to that, multidisciplinary treatment may be required to prevent recurrence. Due to the poor outcomes of patients treated with conventional chemotherapy for breast cancer [5,8], new agents such as EGFR inhibitors and platinum agents have been suggested as adjuvant treatment to improve clinical outcomes [5,24]. The poly (ADP-ribose) polymerase (PARP) inhibitor Olaparib demonstrated improved progression-free survival in patients with HER2-negative metastatic breast cancer and a germline BRCA-mutation [25]. Atezolizumab improved the response rate in patients with

Table 4
Univariate and multivariate analysis of the risk factors for recurrence.

	Univariate	*P*	Multivariate	*P*
	HR (95% CI)		HR (95% CI)	
Age	1.02 (0.97–1.08)	0.45	1.15 (1.01–1.30)	0.03
Stage	2.40 (0.65–8.81)	0.19	2.15 (0.31–14.9)	0.44
Lymph node metastasis	2.63 (0.53–13.0)	0.24		
Breast surgery (breast-conserving surgery vs mastectomy)	2.21 (0.53–9.26)	0.28		
Axillary lymph node (sentinel node biopsy vs axillary lymph node dissection)	1.91 (0.48–7.63)	0.36		
Chemotherapy	27.2 (0.01–70424)	0.41		
Regional lymph node irradiation	5.58 (1.12–27.8)	0.04	4.38 (0.40–47.9)	0.23
Hormonal receptor	0.84 (0.17–4.18)	0.83		
Lymphatic invasion	11.3 (1.36–93.2)	0.03	54.0 (2.34–1250)	0.01
Vascular invasion	1.81 (0.45–7.25)	0.40		
Nuclear grade status	13.4 (0.02–8684)	0.43		

programmed cell death ligand 1 (PD-L1)-positive, locally-advanced or metastatic triple-negative breast cancer [26]. Because most cases of breast SCC represented the triple-negative subtype, these new agents may have some role in treatment of breast SCC. Further research is required to clarify the best treatment approach.

Prognostic factors of breast SCC are little known. There was a report which suggested that a spindle cell component comprising >10% of the tumor was associated with poor locoregional recurrence-free survival in univariate analysis [7]. In our study, age and lymphatic invasion were associated with a significantly increased risk of recurrence. In general, age, tumor size, nodal involvement, histologic grade, lymphovascular invasion, hormone receptors, and HER2 overexpression are well-known prognostic factors of breast cancer [27–32]. Although our sample size may not be large enough to detect statistical significance, age and lymphatic invasion can be identified as significant risk factors. They may be strong predictors of recurrence in breast SCC.

This study has several limitations, including its retrospective nature, small sample size, and the limited results from patients who received adjuvant radiotherapy. Because of small sample size, univariate and multivariate analysis might not have enough power to detect the difference, and the result may not be precise. Patients who did not receive radiotherapy were not included. Central pathology reviews have not been performed. However, because of the rarity of this form of cancer, it is difficult to collect enough cases of breast SCC. A study using a large database can extract data from many patients, but a lack of detailed information may occur. This study was a multi-institutional study, and the largest study to examine the outcome of adjuvant radiotherapy among breast SCC patients.

5. Conclusions

In conclusion, breast SCC had a high incidence of locoregional recurrence, and in-field recurrence occurred especially frequently. Age and lymphatic invasion were significant prognostic factors for recurrence. Patients with these prognostic factors may require multidisciplinary treatment or a new approach to prevent recurrence.

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Ethical approval

This study was approved by the Institutional Review Board of the University of Tokyo Hospital (11970).

Declaration of competing interest

The authors have declared no conflicts of interest.

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