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ORIGINAL ARTICLE

Interstitial lung disorders following postoperative radiotherapy with concurrent or sequential hormonal therapy for breast cancer: a nationwide database study in Japan

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Abstract

Background Hormonal therapy and radiotherapy are conducted concurrently or sequentially after breast cancer surgery. It remains unclear whether concurrent or sequential treatment is safer in terms of lung complications. Using a Japanese nationwide database, this study aimed to compare the occurrence of severe lung complications between concurrent and sequential treatments.

Methods We identified patients who underwent partial mastectomy for stage 0–III breast cancer from July 2010 to March 2020 and received adjuvant hormonal therapy and radiotherapy concurrently ($n=1851$) or sequentially ($n=18{,}429$). Two propensity score analyses (1:4 matching and overlap weighting) were conducted to compare hospitalization for radiation pneumonitis and pneumonia within 1 year after surgery, and intensive care unit admission and mortality during the hospitalization. We conducted additional analyses stratified by hormonal drugs (aromatase inhibitors and tamoxifen).

Results The propensity score-matched analysis showed no significant differences in occurrence of hospitalization for radiation pneumonitis (0.27 vs. 0.58%, $p=0.10$) and pneumonia (0.16 vs. 0.58%, $p=0.05$) between the concurrent and sequential treatments. The overlap propensity score-weighted analysis also showed no significant differences (0.25 vs. 0.56%, $p=0.08$ and 0.15 vs. 0.44%, $p=0.06$, respectively). Intensive care unit admission and in-hospital mortality did not differ significantly between the two treatments. The stratified analysis showed similar results.

Conclusion Our propensity score analyses revealed no significant differences in severe lung complications between concurrent and sequential hormonal therapy with radiotherapy following breast cancer surgery, regardless of the type of hormonal drugs. Clinicians can provide concurrent or sequential treatment with equivalent attention to early lung complications.

Keywords Adjuvant therapy · Antineoplastic hormonal drugs · Breast cancer · Radiation pneumonitis · Radiotherapy

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Introduction

Adjuvant hormonal therapy and postoperative radiotherapy comprise the standard treatment for patients undergoing breast-conserving surgery for hormone receptor-positive breast cancer [1, 2]. Adjuvant tamoxifen for 5 years, aiming to safely decrease the estrogen level, reduces the 15 years risks of breast cancer recurrence and death [1]. In postmenopausal patients, adjuvant aromatase inhibitor significantly prolongs recurrence-free survival compared with tamoxifen [3, 4]. Radiotherapy after breast-conserving surgery halves the recurrence rate and reduces the breast cancer mortality rate by about one-sixth [2]. These treatments are provided concurrently or sequentially soon after the postoperative pathological results are determined.

Previous studies showed no significant differences in recurrence-free survival or 5 and 10 years overall survival between the concurrent and sequential treatments [5, 6]. However, as short-term complications, several retrospective studies reported that interstitial lung disorders due to radiotherapy occurred in 1% of patients on the concurrent treatment within 1 year [7–10]. In particular, concurrent tamoxifen administration was reported to enhance the risk of irradiation-induced pulmonary fibrosis [11–14]. Nevertheless, a meta-analysis found no significant differences in the occurrence of interstitial lung disorders between the concurrent and sequential treatments [irradiation-related pneumonitis 11/162 (0.7%) vs. 10/163 (0.6%); pulmonary fibrosis 25/416 (0.6%) vs. 18/375 (0.5%)] without adjustment for background characteristics [15]. Consequently, clinicians have to decide on a case-by-case basis whether to provide concurrent or sequential treatment in daily clinical practice without established evidence for severe complications.

Despite the importance for both clinical and research settings, it remains unclear whether concurrent or sequential treatment is safer in terms of lung complications [5, 9]. This study was performed to compare the occurrence of interstitial lung disorders after postoperative radiotherapy between patients receiving concurrent or sequential hormonal therapy for breast cancer, using a nationwide database in Japan.

Methods

Database

This nationwide retrospective cohort study was performed using the Diagnosis Procedure Combination database, which includes hospital administrative claims data and discharge abstracts for approximately 8,000,000 inpatients in more than 1200 hospitals throughout Japan each year. Approximately 300 of the hospitals (including 82 university hospitals) also provide claims data for outpatient clinics that their inpatients visited before and after hospitalization [16]. The need for informed consent in the present study was waived because of the anonymity of the database. The Institutional Review Board at The University of Tokyo approved the study.

The Diagnosis Procedure Combination database includes the following data that are recorded during hospitalization: unique hospital identifier; sex, age, and body mass index at admission; smoking history; main diagnoses and comorbidities at admission and complications after admission recorded with text data in the Japanese language and International Classification of Diseases, Tenth Revision (ICD-10) codes; cancer stage at admission; and interventions and surgical procedures indexed by original Japanese codes. All discharge abstract data for each patient are recorded at the time of discharge by the attending physicians. The database also includes medications and treatments in the outpatient setting and we collected data on hormonal medications (tamoxifen, aromatase inhibitors, and luteinizing hormone-releasing hormone agonists), radiotherapy, and chemotherapy (anthracyclines, taxanes, and molecularly targeted agents). A previous validation study showed good sensitivity and specificity for the diagnosis and procedure records in the database [17].

Patients and outcomes

We retrospectively identified female patients with breast cancer who underwent partial mastectomy from July 2010 to March 2020, and subsequently underwent radiotherapy and hormonal therapy within 6 months after the surgery. We used the Japanese original procedure codes for the surgeries to identify the patients. We excluded (i) patients with stage IV breast cancer (because surgery is not a standard treatment for stage IV breast cancer [18]), (ii) patients who underwent breast reconstruction, (iii) patients with a diagnosis of pulmonary manifestations due to irradiation (ICD-10 codes J70.0, J70.1), interstitial lung disorders (B22.1, J70.2–J70.4, J84.1, J84.9, J99), or systemic connective tissue disorders (M30–M36) before radiotherapy, (iv) patients who received hormonal medication before surgery (i.e., neoadjuvant hormonal therapy), (v) patients who received chemotherapy after surgery (i.e., adjuvant chemotherapy), and (vi) patients who underwent irradiation less than 15 times (because we regarded this as incomplete given that hypofractionated irradiation is generally scheduled for 16 times in Japan [19, 20] and such cases could have included accelerated partial breast irradiation and palliative irradiation for another area).

We divided the eligible patients according to the time when the hormonal agents were initially prescribed: between surgery and completion of radiotherapy (concurrent group); and after completion of radiotherapy (sequential group). In other words, we defined patients who were prescribed postoperative hormonal drugs before the date of radiotherapy completion as the concurrent group.

The primary outcomes were hospitalization for interstitial lung disorders after the treatments (J70.0–J70.4 [pulmonary manifestations due to radiation and drug-induced interstitial lung disorders], J84.1 [interstitial pulmonary diseases with fibrosis], J84.9 [interstitial pulmonary disease, unspecified]) and hospitalization for pneumonia (J13–19 [pneumonia], J80 [adult respiratory distress syndrome], J81 [pulmonary oedema], J96 [respiratory failure]) within 1 year after surgery. The secondary outcomes were intensive care unit admission and mortality during the hospitalization. We only examined outcomes requiring hospitalization because we were able to obtain diagnoses recorded during hospitalization from the database.

We examined the following patient background characteristics: age, body mass index, smoking history (current/past smoker), comorbidities, cancer stage at admission, neoadjuvant chemotherapy, regimen of neoadjuvant chemotherapy (anthracyclines, taxanes, molecularly targeted agents), postoperative hormonal drugs (tamoxifen, aromatase inhibitors, luteinizing hormone-releasing hormone agonists), hypofractionated irradiation, type of hospital (teaching, non-teaching), and hospital volume. Age was categorized into five groups: < 45, 45–54, 55–64, 65–74, and ≥ 75 years. Body mass index was also categorized into five groups: < 18.5, 18.5–21.9, 22.0–24.9, 25.0–29.9, and ≥ 30.0 kg/m^2. Comorbidities were assessed by the Charlson Comorbidity Index [21] and categorized into two groups: 2 and ≥ 3. Hospital volume was defined as the annual number of eligible patients at each hospital and categorized into tertiles (low, medium, and high) with approximately equal numbers of patients in each group.

Statistical analysis

We used two propensity score methods to compare the outcomes between the two groups. First, we conducted 1:4 propensity score matching [22]. We calculated the propensity scores using a logistic regression model that contained the patient background characteristics. Each patient in the concurrent group was matched with four patients in the sequential group having the closest estimated propensity scores within a caliper (≤ 0.2 of the pooled standard deviation of estimated logits) using the nearest-neighbor method with replacement. We calculated the C statistic using the area under the receiver operating characteristic curve to evaluate the ability of the model to predict concurrent treatment. We calculated standardized differences to examine the balance in the baseline variables between the two groups for all patients and the 1:4 propensity score-matched cohort. A standardized difference of 10% denoted a negligible difference between the two groups [23]. After generating the 1:4 propensity score-matched cohort, we used the chi-square test to compare outcomes.

Second, we conducted overlap propensity score weighting, an extension of the propensity score method that balances the covariates between two groups [24–28]. Each patient was weighted by the probability (i.e., propensity score) of that patient being assigned to the opposite group. We compared the proportions of the outcomes between the two groups in the overlap propensity score-weighted cohort using the chi-square test. The method minimizes the asymptotic variance of the nonparametric estimate of the weighted average treatment effect within the class of balancing weights and yields the exact balance between the groups in the means of each covariate included in the model [27, 28]. The weighted population obtained by this method mimics a randomized trial without excluding study participants from the available sample [25].

We further performed two sensitivity analyses to check the robustness of our results. First, we performed analyses stratified by hormonal drugs (tamoxifen and aromatase inhibitors). Second, we conducted an analysis in which we shifted the threshold date of the two groups to 1 week ahead. Specifically, we defined patients who were prescribed postoperative hormonal drugs more than 1 week before the date of radiotherapy completion as the concurrent group because some clinicians may have prescribed hormonal drugs before the completion of radiotherapy and instructed the patients to start the drugs after the radiotherapy was completed. In the sensitivity analyses, we used the same two propensity score methods used in the main analyses.

All hypothesis tests had a two-sided significance level of 0.05. All statistical analyses were conducted using Stata/MP 16.0 (StataCorp, College Station, TX, USA).

Results

We identified a total of 29,255 patients with breast cancer who underwent partial mastectomy from July 2010 to March 2020, and subsequently underwent radiotherapy and hormonal therapy within 6 months after the surgery (Fig. 1). We excluded 8975 patients who met the exclusion criteria: (i) 118 patients with stage IV breast cancer, (ii) 120 patients who underwent breast reconstruction, (iii) 39 patients with a diagnosis of pulmonary manifestations due to irradiation, interstitial lung disorders, or systemic connective tissue disorders before radiotherapy, (iv) 2464 patients who received neoadjuvant hormonal therapy, (v) 5235 patients who received adjuvant chemotherapy, and (vi) 999 patients who underwent irradiation less than 15 times. Of the 20,280 eligible patients, the concurrent group comprised 1,851 patients and the sequential group comprised 18,429 patients. After 1:4 propensity score matching, the concurrent group contained 1849 patients and the sequential group contained 7396 patients. The C-statistic in the propensity score model was 0.64.

Table 1 shows the demographic and clinical characteristics of all patients (n = 20,280), the 1:4 propensity score-matched patients (n = 9245), and the overlap propensity score-weighted patients. Before the propensity score matching, imbalances were noted in cancer stage, tamoxifen use, and hypofractionated irradiation. After the propensity score matching, the patient distributions were closely balanced between the two groups. The overlap propensity score weighting led to an exact balance between the two groups.

Table 2 shows the outcomes in the two groups. In the 1:4 propensity score-matched analysis, no significant differences were found in the occurrence of intestinal lung disorders

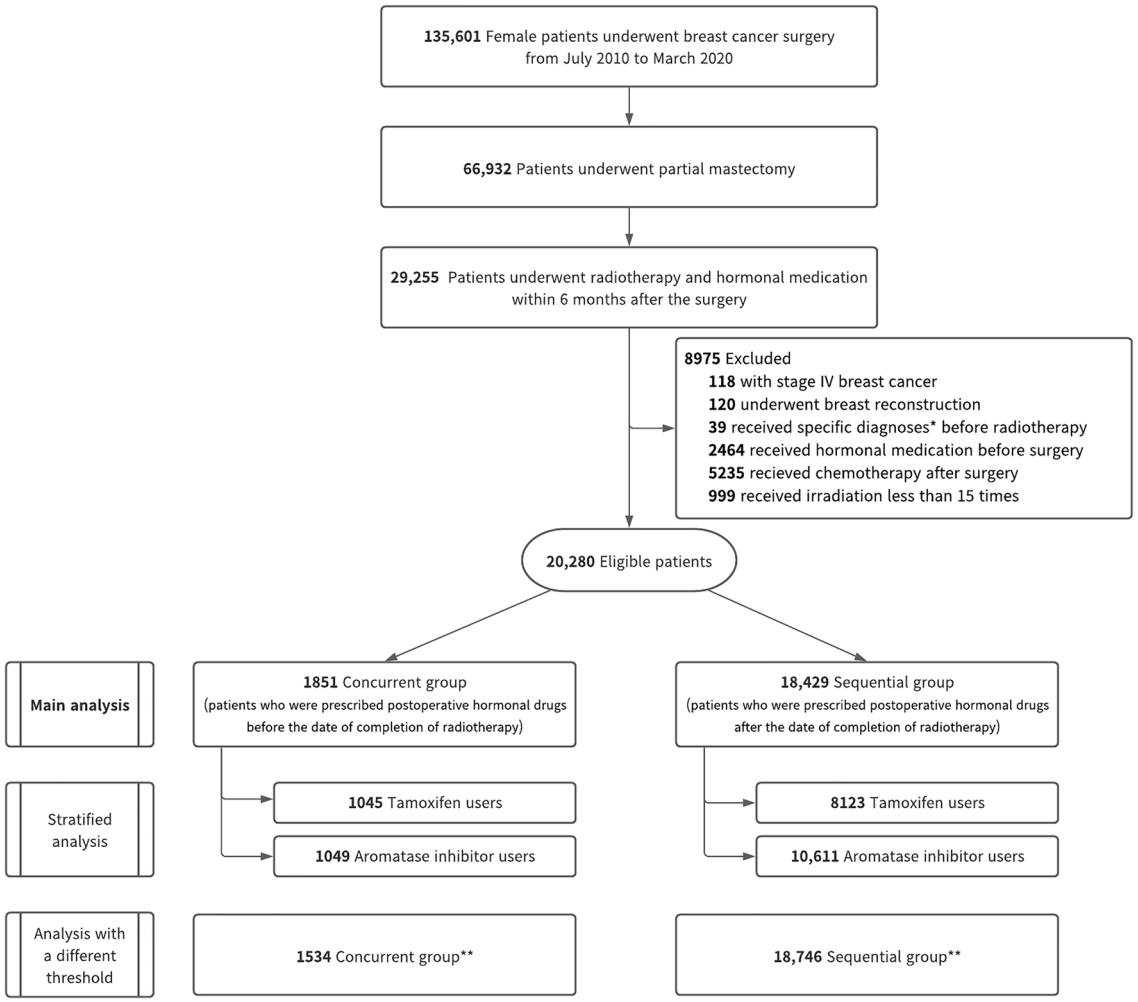

Fig. 1 Patient flowchart. *Specific comorbidity was defined as pulmonary manifestations due to irradiation, interstitial lung disorders, or systemic connective tissue disorders. **These groups were categorized using a different threshold from that in the main analyses. The threshold date was shifted 1 week ahead; that is, the concurrent group was defined as those who were prescribed postoperative hormonal drugs more than 1 week before the date of radiotherapy completion

(0.27 vs. 0.58%, $p=0.10$) or pneumonia (0.16 vs. 0.51%, $p=0.05$) between the two groups. The overlap propensity score-weighted analysis also showed no significant differences between the two groups (0.25 vs. 0.56%, $p=0.08$ and 0.15 vs. 0.44%, $p=0.06$, respectively). There were no significant differences in intensive care unit admission or mortality during the hospitalization in either analysis.

The patient characteristics and results of the sensitivity analyses are shown in Supplemental Tables 1–3 and Tables 3–4. Specifically, Supplemental Table 1 shows the background characteristics of the tamoxifen users, Supplemental Table 2 shows the background characteristics of the aromatase inhibitor users, and Table 3 shows the results of the stratified analysis for these patients. Supplemental Tables 3 and 4 show the background characteristics and the results of the analysis employing a different threshold, respectively. Both sensitivity analyses demonstrated well-balanced background characteristics and consistent results with the main analyses.

Discussion

In the present study, we compared the occurrence of early lung complications between concurrent and sequential adjuvant hormonal therapy with postoperative radiotherapy following breast-conserving surgery, using a nationwide database in Japan. Analyses using propensity score methods showed no significant differences between the groups in hospitalization, intensive care unit admission, and mortality for interstitial lung disorders due to treatment or pneumonia within 1 year after surgery. Analyses stratified by hormonal drugs showed similar results to those of the main analyses. Although we were unable to investigate mild lung

Table 1 Demographic and clinical characteristics

	All patients					Propensity score analysis						
						1:4 matched patients					Overlap weighting[a]	
	Concurrent $n=1851$		Sequential $n=18,429$		ASD[b] (%)	Concurrent $n=1849$		Sequential $n=7396$		ASD[b] (%)	Concurrent	Sequential
Age, years												
< 45	319	(17)	3138	(17)	0.5	319	(17)	1305	(18)	1.0	(18)	(18)
45–54	565	(31)	5169	(28)	5.4	563	(30)	2221	(30)	0.9	(30)	(30)
55–64	409	(22)	4634	(25)	7.2	409	(22)	1722	(23)	2.8	(22)	(22)
65–74	427	(23)	4290	(23)	0.5	427	(23)	1685	(23)	0.7	(23)	(23)
≥ 75	131	(7.1)	1198	(6.5)	2.3	131	(7.1)	463	(6.3)	3.3	(7.0)	(7.0)
Body mass index, kg/m^2												
< 18.5	159	(8.6)	1516	(8.2)	1.3	159	(8.6)	644	(8.7)	0.4	(8.5)	(8.5)
18.5–21.9	697	(38)	6696	(36)	2.7	695	(38)	2783	(38)	0.1	(38)	(38)
22.0–24.9	530	(29)	5249	(28)	0.3	530	(29)	2183	(30)	1.9	(29)	(29)
25.0–29.9	344	(19)	3788	(21)	5.0	344	(19)	1393	(19)	0.6	(19)	(19)
≥ 30	97	(5.2)	1048	(5.7)	2.0	97	(5.2)	325	(4.4)	4.0	(5.0)	(5.0)
Missing data	24	(1.3)	132	(0.7)	5.8	24	(1.3)	68	(0.9)	3.6	(1.2)	(1.2)
Current/past smoker	395	(21)	3645	(20)	3.9	394	(21)	1472	(20)	3.5	(21)	(21)
Charlson comorbidity index ≥ 3	251	(14)	2801	(15)	4.7	251	(14)	949	(13)	2.2	(14)	(14)
Cancer stage at admission												
0	179	(9.7)	1303	(7.1)	9.4	177	(9.6)	727	(9.8)	0.9	(9.5)	(9.5)
I	1,208	(65)	11,993	(65)	0.4	1208	(65)	4864	(66)	0.9	(65)	(65)
II	331	(18)	3836	(21)	7.4	331	(18)	1346	(18)	0.8	(18)	(18)
III	17	(0.9)	278	(1.5)	5.4	17	(0.9)	76	(1.0)	1.1	(1.0)	(1.0)
Missing data	116	(6.3)	1019	(5.5)	3.1	116	(6.3)	383	(5.2)	4.7	(6.1)	(6.1)
Neoadjuvant chemotherapy	99	(5.3)	1164	(6.3)	4.1	99	(5.4)	422	(5.7)	1.5	(5.4)	(5.4)
Chemotherapy regimen												
Anthracyclines	89	(4.8)	1009	(5.5)	3.0	89	(4.8)	393	(5.3)	2.3	(4.8)	(4.8)
Taxanes	94	(5.1)	1102	(6.0)	3.9	94	(5.1)	409	(5.5)	2.0	(5.1)	(5.1)
Molecularly targeted agents	18	(1.0)	68	(0.4)	7.4	18	(1.0)	72	(1.0)	0.0	(0.9)	(0.9)
Postoperative hormonal drugs												
Tamoxifen	1045	(56)	8123	(44)	24.9	1043	(56)	4203	(57)	0.8	(54)	(54)
Aromatase inhibitors	1049	(57)	10611	(58)	1.8	1047	(57)	4153	(56)	1.0	(55)	(55)
LHRH agonists	188	(10)	2346	(13)	8.1	188	(10)	633	(8.6)	5.5	(10)	(10)
Hypofractionated irradiation	385	(21)	2925	(16)	12.8	383	(21)	1428	(19)	3.5	(20)	(20)
Teaching hospital	1769	(96)	17,428	(95)	4.6	1767	(96)	7101	(96)	2.2	(95)	(95)
Hospital volume[c]												
≤ 32	586	(32)	5929	(32)	1.1	586	(32)	2352	(32)	0.2	(31)	(31)
33–66	681	(37)	6134	(33)	7.4	679	(37)	2756	(37)	1.1	(37)	(37)
≥ 67	584	(32)	6366	(35)	6.4	584	(32)	2288	(31)	1.4	(32)	(32)

Data are presented as *n* (%)

Abbreviations: ASD, absolute standardized difference; LHRH, luteinizing hormone-releasing hormone

[a]The percentages show the overlap propensity score-weighted proportions for the two groups

[b]An ASD of ≤ 10% denotes a negligible difference between the two groups

[c]Defined as the annual number of eligible patients at each hospital and categorized into tertiles with approximately equal numbers of patients in each group

Table 2 Comparisons of outcomes between the concurrent and sequential groups

	All patients					Propensity score analysis							
						1:4 matched patients					Overlap weighting[a]		
	Concurrent $n=1851$		Sequential $n=18,429$		p value	Concurrent $n=1849$		Sequential $n=7396$		p value	Concurrent	Sequential	p value
Occurrence requiring hospitalization													
Interstitial lung disorders due to treatment[b]	5	(0.27)	101	(0.55)	0.11	5	(0.27)	43	(0.58)	0.10	(0.25)	(0.56)	0.08
Pneumonia[c]	3	(0.16)	81	(0.44)	0.08	3	(0.16)	38	(0.51)	0.05	(0.15)	(0.44)	0.06
Occurrence during the hospitalization													
Intensive care unit admission	0	(0.00)	9	(0.05)	N.A	0	(0.00)	7	(0.09)	N.A	(0.00)	(0.05)	N.A
Mortality	2	(0.11)	4	(0.02)	0.04	2	(0.11)	10	(0.14)	0.05	(0.10)	(0.05)	0.49

Data are presented as n (%)

[a]The percentages show the overlap propensity score-weighted proportions for the two groups

[b]Defined as ICD-10 codes J70.0–J70.4 (pulmonary manifestations due to radiation and drug-induced interstitial lung disorders; 3 patients vs. 75 patients), J84.1 (interstitial pulmonary diseases with fibrosis; 1 patient vs. 19 patients), and J84.9 (interstitial pulmonary disease, unspecified; 1 patient vs. 23 patients)

[c]Defined as ICD-10 codes J13–J19 (pneumonia; 2 patients vs. 63 patients), J80 (adult respiratory distress syndrome; 0 patients vs. 1 patient), J81 (pulmonary oedema; 0 patients), and J96 (respiratory failure; 2 patients vs. 27 patients)

complications without hospitalization due to the nature of the database, the present study showed the occurrence of critical lung complications that were unable to be treated in the outpatient setting.

Most of the eligible patients in the present study received the sequential treatment ($n=18,429$; 91%). Clinicians tended not to select the concurrent treatment, possibly because the Japanese clinical guideline includes an unfavorable statement for the concurrent treatment; specifically, the guideline states that the concurrent treatment may be considered when deemed necessary despite a risk of moderate lung and skin fibrosis [29]. However, the concurrent group showed a higher proportion of tamoxifen administration than the sequential group, even though concurrent tamoxifen administration was particularly reported to increase the risk of lung fibrosis compared with radiotherapy alone [11–14]. Because the tamoxifen users were younger and had fewer comorbidities than the aromatase inhibitor users (Supplemental Tables 2 and 3), the tamoxifen users and clinicians may not have hesitated to start both treatments as soon as possible. These differences between the two groups were well balanced in the 1:4 propensity score-matched patients and completely balanced in the overlap propensity score-weighted patients.

The present study showed no significant differences between the concurrent and sequential treatments in the occurrence of severe lung complications requiring hospitalization. These findings are consistent with a recent meta-analysis that involved approximately 1000 patients [15]. Although a study on 702 patients in Japan showed that concurrent treatment was associated with symptomatic lung fibrosis [10], the report failed to investigate the occurrence of severe lung complications because of the limited number of patients. The results of the present study involving approximately 20,000 patients suggested that concurrent treatment can be an equivalent option to sequential treatment without increased complications of clinical importance such as intensive care unit admission and mortality. Moreover, the study confirmed that when adjuvant hormonal therapy is combined with postoperative radiotherapy, whether concurrently or sequentially, clinicians need to be equally careful about serious early pulmonary complications.

Previous studies showed that concurrent administration of tamoxifen with radiotherapy increased the risk of lung fibrosis compared with radiotherapy alone and suggested that the combination increased secretion of transforming growth factor-β, which resulted in fibrosis [6, 9, 11–14, 30–32]. However, the stratified analysis in the present study revealed that concurrent tamoxifen administration was not associated with an increased risk of severe lung complications compared with sequential tamoxifen administration. Furthermore, because previous studies reported no significant differences in long-term survival or local recurrence between concurrent and sequential tamoxifen administration [8, 33], concurrent treatment with tamoxifen and radiotherapy can be an equivalent option to sequential treatment.

It is beneficial for patients to know that the two treatment options are equivalent. Previous studies showed patients who are more involved in decision-making had better overall quality of life, and better physical and social functioning than those who are not involved in their cancer care decisions [34, 35]. Moreover, patients were likely to feel tired

Table 3 Comparisons of outcomes between the concurrent and sequential groups stratified by types of hormonal drugs

	All patients					Propensity score analysis							
						1:4 matched patients					Overlap weighting[a]		
	Concurrent		Sequential		*p* value	Concurrent		Sequential		*p* value	Concurrent	Sequential	*p* value
Tamoxifen users	*n* = 1045		*n* = 8123			*n* = 1045		*n* = 4179					
Occurrence requiring hospitalization													
Interstitial lung disorders due to treatment	4	(0.38)	45	(0.55)	0.48	4	(0.38)	34	(0.81)	0.10	(0.38)	(0.58)	0.40
Pneumonia	2	(0.19)	35	(0.43)	0.25	2	(0.19)	12	(0.29)	0.60	(0.18)	(0.48)	0.17
Occurrence during the hospitalization													
Intensive care unit admission	0	(0.00)	3	(0.04)	N.A	0	(0.00)	0	(0.00)	N.A	(0.00)	(0.12)	N.A
Mortality	1	(0.10)	2	(0.02)	0.23	1	(0.10)	11	(0.26)	0.31	(0.28)	(0.13)	0.41
Aromatase inhibitor users	*n* = 1049		*n* = 10,611			*n* = 1045		*n* = 4180					
Occurrence requiring hospitalization													
Interstitial lung disorders due to treatment	3	(0.29)	57	(0.54)	0.28	3	(0.29)	30	(0.72)	0.13	(0.25)	(0.50)	0.23
Pneumonia	3	(0.29)	47	(0.44)	0.46	3	(0.29)	16	(0.38)	0.65	(0.26)	(0.40)	0.46
Occurrence during the hospitalization													
Intensive care unit admission	0	(0.00)	6	(0.06)	N.A	0	(0.00)	1	(0.02)	N.A	(0.00)	(0.05)	N.A
Mortality	2	(0.19)	4	(0.04)	0.04	2	(0.19)	15	(0.36)	0.40	(0.19)	(0.09)	0.45

Data are presented as *n* (%)

[a]The percentages show the overlap propensity score-weighted proportions for the two groups

Table 4 Comparisons of outcomes between the concurrent and sequential groups categorized by a different threshold

	All patients					Propensity score analysis							
						1:4 matched patients					Overlap weighting[b]		
	Concurrent[a] $n=1534$		Sequential[a] $n=18,746$		p value	Concurrent[a] $n=1532$		Sequential[a] $n=6128$		p value	Concurrent[a]	Sequential[a]	p value
Occurrence requiring hospitalization													
Interstitial lung disorders due to treatment	5	(0.33)	101	(0.54)	0.27	5	(0.33)	35	(0.57)	0.24	(0.31)	(0.54)	0.24
Pneumonia	3	(0.20)	81	(0.43)	0.17	3	(0.20)	38	(0.62)	0.05	(0.18)	(0.44)	0.14
Occurrence during the hospitalization													
Intensive care unit admission	0	(0.00)	9	(0.05)	N.A	0	(0.00)	9	(0.15)	N.A	(0.00)	(0.05)	N.A
Mortality	2	(0.13)	4	(0.02)	0.02	2	(0.13)	10	(0.16)	0.78	(0.13)	(0.06)	0.41

[a]The concurrent and sequential groups were categorized using a different threshold from that in the main analyses. The threshold date was shifted 1 week ahead; that is, the concurrent group was defined as those who were prescribed postoperative hormonal drugs more than 1 week before the date of radiotherapy completion

[b]The percentages show the overlap propensity score-weighted proportions for the two groups

after breast cancer surgery [36, 37], and decision-making for themselves was able to reduce such tiredness [34, 35]. Based on the findings of the present study, clinicians can confidently provide patients with an opportunity for decision-making on two equivalent treatment options (concurrent treatment or sequential treatment), and we believe that this opportunity will benefit patients.

Several limitations of the study should be acknowledged. First, there could be both underestimation and overestimation of the occurrence of lung complications. Regarding underestimation, we were only able to investigate readmissions to the same hospital where a patient underwent breast cancer surgery; therefore, we were unable to investigate either hospitalization for lung complications in another hospital or mild lung complications that did not require hospitalization. Indeed, the proportion of lung complications in the present study (approximately 0.5%) was lower than those in previous studies (approximately 1%) [7–10]. In addition, the present study would only show a part of symptomatic radiation pneumonitis. Regarding overestimation, the ICD-10 codes that we used to identify lung complications could have included patients with causes other than treatment for breast cancer to improve the sensitivity of the definition. Because we were unable to find any previous studies on radiation or drug-induced lung disorders that used ICD-10 codes, we needed to define the codes for outcomes through a comprehensive search for codes that would potentially be relevant. However, because the underestimation and overestimation would have occurred equally in both groups, they would not have skewed the present results. Second, we did not acquire information on planned irradiation area; for example, subclavian area, internal mammary area, and surgical margin (i.e., boost irradiation). Third, we were unable to obtain information on skin fibrosis, which was reported to be another complication of the concurrent treatment [15, 31, 38]. However, previous reports showed that hormonal therapy additional to radiotherapy was not associated with poor cosmetic outcomes [9, 32]. Finally, we were unable to compare late lung complications and prognosis at more than 1 year after the initial breast cancer surgery due to the nature of the database. However, previous studies reported no significant differences in the long-term outcomes [8, 13, 15].

In summary, concurrent and sequential treatments of radiotherapy and hormonal therapy following breast cancer surgery were compared in 20,280 patients using a Japanese nationwide database. The study revealed no significant differences in the occurrence of severe lung complications regardless of the type of hormonal drug. Clinicians can provide concurrent treatment as an equivalent option to sequential treatment.

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Declarations

Conflict of interest The authors declare no conflict of interest.

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