Treatment Sequence of Aromatase Inhibitors and Radiotherapy and Long-term Outcomes of Breast Cancer Patients

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Abstract. *Background: The optimal sequence of radiotherapy (RT) and hormone therapy using aromatase inhibitors (AI) in patients with breast cancer treated with breast-conserving surgery is unclear. Several short-term analyses have shown that there are no differences in breast cancer outcomes according to the treatment sequence. However, long-term outcomes have not been reported. Patients and Methods: We retrospectively analyzed disease-free survival events in 315 consecutive breast cancer patients who underwent breast-conserving surgery, RT, and received adjuvant AI at our Institute between 2001 and 2009. We compared the outcomes between treatment sequences of AI and RT (concurrent vs. sequential). Results: With a median follow-up of 5.6 years, no significant differences between the 2 groups in terms of disease-free survival (unadjusted p=0.6; adjusted p=0.5) were observed. Conclusion: Similarly to previous short-term reports, AI administration after RT and AI concurrently with RT are both reasonable treatment options for early-stage breast cancer patients treated with breast-conserving surgery.*

Breast-conserving surgery, radiotherapy (RT) for the affected breast, and adjuvant hormone therapy using tamoxifen or aromatase inhibitors (AI) are standard treatments for post-menopausal early breast cancer patients with hormone receptor-positive tumors (1, 2). However, the optimal sequence of radiotherapy and hormone therapy remains unclear (3). Until now, there have been several reports on the association of the sequencing of tamoxifen and radiotherapy with long-term patient outcomes (4-6). In these reports, there were no differences in long-term outcomes with treatment sequences of tamoxifen and RT (4-6). However, in cases of AI, only short-term (*i.e.*, less than 3 years) outcomes have been reported (7-9), and not long-term outcomes. It is clinically important to evaluate longer-term outcomes of hormone receptor-positive breast cancer patients because these patients have a marked risk of recurrence for a prolonged period (10, 11).

Previously, we reported on treatment sequences of AI and RT in post-menopausal breast cancer patients with a median follow-up time of 2.9 years (7). In the present study, we report updated data with a median follow-up time of 5.6 years.

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Patients and Methods

Patients and inclusion criteria. We previously reported 264 consecutive women with breast cancer treated with breast-conserving surgery, RT, and AI at the Osaka Medical Center for Cancer and Cardiovascular Disease between October 2001 and August 2008 (7). In the present analysis, the patient population was expanded to include those who underwent surgery until December 2009, and we updated the follow-up data until March 2014. Inclusion criteria were as follows: (i) post-menopausal patients with clinical stage I or II breast cancer; (ii) patients treated with breast-conserving surgery; (iii) tumors were estrogen and/or progesterone receptor-positive; (iv) patients who received postoperative RT for the affected breast at a total median dose of 50 Gy in 2-Gy fractions or 63.2 Gy as a boost if there was a microscopically involved surgical margin; and (v) patients who received adjuvant AI (anastrozole: 1 mg, letrozole: 2.5 mg, or exemestane: 25 mg) daily for 5 years postoperatively. Exclusion criteria were as follows: (a) prior malignancy other than breast cancer; (b) ductal carcinoma *in situ*; and (c) patients who received neoadjuvant therapy at the initial treatment. In total, 315 patients were included in this analysis. The median follow-up was 5.6 years.

According to the treatment sequence of AI and RT, patients were divided into a concurrent or sequential group. Patients who received AI during RT followed by continued AI were defined as the concurrent group, and those who received RT followed by AI as the sequential group.

Table I. *Patients' characteristics (N=315).*

		Concurrent (N=158) No. of patients (%)	Sequential (N=157) No. of patients (%)	*p*-Value
Age, years	Median	61	61	0.7
	Range	48-81	49-80	
Follow-up periods	Median	5.1	6.9	0.0001
	Range	1.6-11.0	0.9-11.8	
p-T stage	1	96 (61)	85 (54)	0.3
	2	60 (38)	68 (43)	
	Unknown	2 (1)	4 (3)	
Grade	1	47 (30)	38 (24)	0.3
	2	82 (52)	76 (48)	
	3	28 (18)	40 (25)	
	Unknown	1 (1)	3 (2)	
Histological type	Invasive ductal	148 (94)	148 (94)	0.8
	Other	10 (6)	9 (6)	
No. of positive lymph nodes	0	124 (78)	116 (74)	0.4
	1 to 3	21 (13)	29 (18)	
	4 or more	9 (6)	6 (4)	
	Unknown	4 (3)	6 (4)	
Lymphovascular invasion	Negative	89 (56)	75 (48)	0.2
	Positive	68 (43)	79 (50)	
	Unknown	1 (1)	3 (2)	
Surgical margin status	Negative	151 (96)	141 (90)	0.07
	Positive	7 (4)	15 (10)	
	Unknown	0 (0)	1 (1)	
Estrogen receptor status	Positive	155 (98)	147 (94)	0.05
	Negative	2 (1)	8 (5)	
	Unknown	1 (1)	2 (1)	
Progesterone receptor status	Positive	112 (71)	94 (60)	0.04
	Negative	44 (28)	61 (39)	
	Unknown	2 (1)	2 (1)	
HER-2 status	Positive	12 (8)	5 (3)	0.08
	Negative	144 (91)	150 (96)	
	Unknown	2 (1)	2 (1)	
Adjuvant chemotherapy	Yes	27 (17)	30 (19)	0.6
	No	131 (83)	127 (81)	

Post-operative management. Patients received a physical examination every 3-6 months for 5 years after surgery and annually thereafter. Mammograms were performed annually after surgery. The estrogen and progesterone receptor statuses were determined by immunohistochemistry, and tumors with 10% or more positively stained tumor cells were classified as positive. The HER-2 status was considered positive if immunohistochemistry was 3+ or fluorescence *in situ* hybridization (HER-2/neu to chromosome 17 ratio) was >2.0.

As previously analyzed (7), grade 3, 4, or 5 pneumonitis, rib fracture, and axillary vein thrombosis were evaluated according to the Radiation Therapy Oncology Group Late Toxicity Criteria (12). Grade 3, 4, or 5 arm edema was assessed according to the National Cancer Institute Common Toxicity Criteria, version 3.0 (13).

Statistical analyses. Patients' characteristics according to the treatment sequence of AI and RT were compared using the chi-square test or Student's *t*-test. Disease-free survival (DFS) was defined as the period from the date of surgery to that of recurrence or death, and was calculated by the Kaplan-Meier method. The log-rank test was used to evaluate differences in DFS among the various patient sub-groups. Multivariate analyses for DFS were performed using the Cox proportional hazards model. In the calculation of DFS, occurrences of local, regional, or distant metastases, contralateral breast cancer, and deaths without evidence of recurrence were treated as events.

All statistical tests and *p*-values were two-tailed, and *p*-values <0.05 were considered significant. All statistical tests were performed with the IBM SPSS Statistics 21 software (IBM Japan, Nihonbashi Hakozaki-cho, Tokyo, Japan).

Results

In Table I, patients' characteristics according to treatment sequence are shown. Out of the 315 patients, 158 (50%) were defined as the concurrent group and 157 (50%) were defined as the sequential group. Out of the 315 patients, 301 (96%), 14 (4%), and 0 (0%) were administered anastrozole, letrozole, and exemestane, respectively. Ten

Table II. *Disease-free survival events according to treatment sequence (N=315).*

Events	Concurrent (N=158) No. of patients (%)	Sequential (N=157) No. of patients (%)	*p*-Value
Local recurrence	1 (1)	3 (2)	0.3
Regional recurrence	3 (2)	2 (1)	0.7
Distant recurrence	5 (3)	10 (6)	0.2
Contralateral breast cancer	2 (1)	3 (2)	0.6
Death without evidence of recurrence	3 (2)	0 (0)	0.08

patients (3%) switched from AI to tamoxifen because of adverse events. Between the concurrent and sequential groups, frequencies of the following factors were significantly different: follow-up period and progesterone receptor status.

The median follow-up period was 5.1 (range=1.6-11.0) years in the concurrent group and 6.9 (range=0.9-11.8) years in the sequential group. Fourteen (9%) patients had DFS events in the concurrent group, and 18 (12%) patients had such events in the sequential group. Detailed DFS events are shown in Table II. There was a non-significant tendency toward a difference in death without evidence of recurrence between the 2 groups (p=0.08 by chi-square test). All non-breast cancer deaths occurred in the concurrent group. The causes of death were cardiac dysfunction (n=1) and aspiration pneumonia (n=2). There were no differences in DFS rates according to treatment sequence (p=0.6 by log-rank test). The 5-year DFS was 94% in both sequential and concurrent groups (Figure 1). Multivariate analyses using tumor size (pT1 *vs*. pT2), lymph nodal status (positive *vs*. negative), histological grade (1 *vs*. 2 or 3), estrogen receptor status (positive *vs*. negative), progesterone receptor status (positive *vs*. negative), HER-2 status (positive *vs*. negative), and treatment sequence (concurrent *vs*. sequential) also demonstrated no significant differences according to the treatment sequence (hazard ratio, 1.3 [95% confidence interval, 0.6 to 2.7], p=0.5).

To exclude confounding factors, we further performed statistical analyses excluding 65 patients with positive axillary nodes or 57 patients who received adjuvant chemotherapy. Again, there was no significant difference between the 2 groups in DFS by uni- or multivariate analyses (data not shown).

Similarly to previously reported results with a shorter follow-up (7), severe adverse events were very rare in both groups. Grade 3 to 5 rib fracture and axillary vein thrombosis did not occur in either group. Grade 3 pneumonitis occurred in 1 patient (1%) of the concurrent group and none of the sequential group. Grade 3 arm edema occurred in 2 patients in each group.

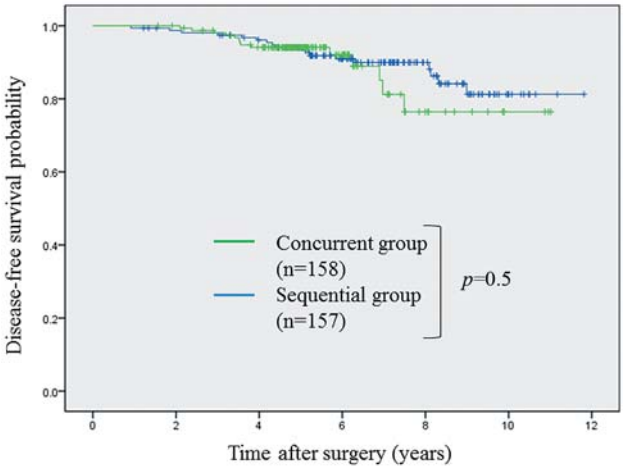

Figure 1. *Disease-free survival curves according to treatment sequence.*

Discussion

In the present study, there was no association between long-term outcomes and the sequence of AI and RT, which is in agreement with previous reports (7-9). We have previously (7) demonstrated that there was no difference in DFS between the concurrent group (n=113) and sequential group (n=151), with a median follow-up of 2.9 years. Azria *et al*. (8) reported a randomized phase II study with assigned groups to letrozole and RT concurrently (n=75) or letrozole after RT (n=75) involving hormone receptor-positive post-menopausal patients treated with breast-conserving surgery. With a median follow-up of 26 months, no significant differences in patient outcomes were noted between the 2 groups. Vladimir *et al*. (9) reported a retrospective analysis of their experiences at the Allegheny General Hospital. Fifty-seven patients received anastrozole and RT concurrently and 126 patients received hormone therapy (anastrozole or tamoxifen) after completion of RT. Out of these, 1 and 5 local failures occurred with a median follow-up of 28 and

30.8 months, respectively. In these studies (7-9), the median follow-up times were less than 3 years, which may be too short to evaluate the prognosis of patients with hormone receptor-positive breast cancer. The peak of the annual hazard risk of recurrence was 2-3 years after surgery (10). However, the hazard of recurrence for hormone receptor-positive patients was relatively constant (10, 11). Therefore, it is clinically important to assess longer-term outcomes in this patient population. Our study cohort comprised of a larger patient population and longer follow-up period compared with previous reports (7-9). However, because patients with hormone receptor-positive tumors show recurrence beyond 5 years (11), much longer follow-up periods are required to validate our results.

Because of the retrospective nature of this study, there were several statistical differences in clinical and pathological factors between the 2 groups. Although adjustment was realized using multivariate analyses, it could not be ruled out that several biases remained unadjusted for between the 2 groups.

In conclusion, AI administration after RT and AI concurrently with RT are both reasonable treatment options. Further studies with a longer follow-up are warranted.

References

1 Goldhirsch A, Winer EP, Coates AS, Gelber RD, Piccart-Gebhart M, Thürlimann B and Senn HJ; Panel members: Personalizing the treatment of women with early breast cancer: highlights of the St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2013. Ann Oncol *24*: 2206-2223, 2013.

2 Dowsett M, Cuzick J, Ingle J, Coates A, Forbes J, Bliss J, Buyse M, Baum M, Buzdar A, Colleoni M, Coombes C, Snowdon C, Gnant M, Jakesz R, Kaufmann M, Boccardo F, Godwin J, Davies C and Peto R: Meta-analysis of breast cancer outcomes in adjuvant trials of aromatase inhibitors versus tamoxifen. J Clin Oncol *28*: 509-518, 2010.

3 Chargari C, Toillon RA, Macdermed D, Castadot P and Magné N: Concurrent hormone and radiation therapy in patients with breast cancer: what is the rationale? Lancet Oncol *10*: 53-60, 2009.

4 Pierce LJ, Hutchins LF, Green SR, Lew DL, Gralow JR, Livingston RB, Osborne CK and Albain KS: Sequencing of tamoxifen and radiotherapy after breast-conserving surgery in early-stage breast cancer. J Clin Oncol *23*: 24-29, 2005.

5 Ahn PH, Vu HT, Lannin D, Obedian E, DiGiovanna MP, Burtness B and Haffty BG: Sequence of radiotherapy with tamoxifen in conservatively managed breast cancer does not affect local relapse rates. J Clin Oncol *23*: 17-23, 2005.

6 Harris EE, Christensen VJ, Hwang WT, Fox K and Solin LJ: Impact of concurrent versus sequential tamoxifen with radiation therapy in early-stage breast cancer patients undergoing breast conservation treatment. J Clin Oncol *23*: 11-16, 2005.

7 Ishitobi M, Komoike Y, Motomura K, Koyama H, Nishiyama K and Inaji H: Retrospective analysis of concurrent *vs*. sequential administration of radiotherapy and hormone therapy using aromatase inhibitor for hormone receptor-positive postmenopausal breast cancer. Anticancer Res *29*: 4791-4794, 2009.

8 Azria D, Belkacemi Y, Romieu G, Gourgou S, Gutowski M, Zaman K, Moscardo CL, Lemanski C, Coelho M, Rosenstein B, Fenoglietto P, Crompton NE and Ozsahin M: Concurrent or sequential adjuvant letrozole and radiotherapy after conservative surgery for early-stage breast cancer (CO-HO-RT): a phase 2 randomised trial. Lancet Oncol *11*: 258-265, 2010.

9 Valakh V, Trombetta MG, Werts ED, Labban G, Khalid MK, Kaminsky A and Parda D: Influence of concurrent anastrozole on acute and late side effects of whole breast radiotherapy. Am J Clin Oncol *34*: 245-248, 2011.

10 Saphner T, Tormey DC and Gray R: Annual hazard rates of recurrence for breast cancer after primary therapy. J Clin Oncol *14*: 2738-2746, 1996.

11 Early Breast Cancer Trialists' Collaborative Group (EBCTCG), Davies C, Godwin J, Gray R, Clarke M, Cutter D, Darby S, McGale P, Pan HC, Taylor C, Wang YC, Dowsett M, Ingle J and Peto R: Relevance of breast cancer hormone receptors and other factors to the efficacy of adjuvant tamoxifen: patient-level meta-analysis of randomised trials. Lancet *378*: 771-784, 2011.

12 Cox JD, Stetz J and Pajak TF: Toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC). Int J Radiat Oncol Biol Phys *31*: 1341-1346, 1995.

13 Trotti A, Colevas AD, Setser A, Rusch V, Jaques D, Budach V, Langer C, Murphy B, Cumberlin R, Coleman CN and Rubin P: CTCAE v3.0: development of a comprehensive grading system for the adverse effects of cancer treatment. Semin Radiat Oncol *13*: 176-181, 2003.

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