Risk of Ipsilateral Breast Tumor Recurrence in Patients Treated with Tamoxifen or Anastrozole Following Breast-conserving Surgery with or without Radiotherapy

MAKOTO ISHITOBI, SAKI NAKAHARA, YOSHIFUMI KOMOIKE, KAZUYOSHI MOTOMURA, HIROKI KOYAMA and HIDEO INAJI

Department of Breast and Endocrine Surgery, Osaka Medical Center for Cancer and Cardiovascular Diseases, 1-3-3 Nakamichi, Higashinari-ku, Osaka 537-8511, Japan

Abstract. *Background: It is unknown whether anastrozole (Ana) is superior to tamoxifen (Tam) with regard to local control after breast-conserving surgery without radiotherapy (RT). Patients and Methods: Two hundred and ninety-two breast cancer patients who had undergone breast-conserving surgery and been treated with Tam or Ana, with or without RT, were retrospectively analyzed. Ipsilateral breast tumor recurrence (IBTR)-free survival rates were compared according to the treatment drug and RT. Results: In the Tam group, IBTR-free survival rates did not significantly differ according to the use or absence of RT (p=0.08), whereas in the Ana group, a significant difference (5-year IBTR-free survival rate, 98.8% in the RT group vs. 65.7% in the no RT group, p<0.0001) was found. In addition, multivariate analysis showed that RT use was an independent prognostic factor for IBTR-free survival (p=0.01) among the patients treated with Ana. Conclusion: Caution is needed when RT is omitted for patients undergoing breast-conserving surgery and receiving Ana for adjuvant treatment.*

Due to improved disease-free survival, aromatase inhibitors (AI) have become standard adjuvant therapy for postmenopausal women with hormone receptor-positive early breast cancer (1-3). Isolated local recurrences as first events after initial AI administration were significantly fewer than those after tamoxifen (Tam) treatment according to a meta-analysis of randomised trials comparing AI with Tam in an adjuvant setting (4). There seemed to be greater decreases in isolated local recurrence (30%) than in distant recurrence (16%), although this apparent heterogeneity of effect between recurrence sites was not significantly different (p=0.08).

Radiotherapy (RT) is an integral component of the multidisciplinary management of breast cancer. RT significantly reduces locoregional recurrence and improves overall survival for patients undergoing breast-conserving surgery (BCS) (5). BCS without radiation is associated with significantly higher local recurrence rates and possibly a higher mortality risk. Several trials have investigated whether RT could be safely omitted for selected patients showing specific favorable treatment response and disease characteristics (6, 7). Unfortunately, most of these trials were unsuccessful in that RT continued to provide a significant benefit.

Despite robust benefits of RT for local control, previous studies have suggested underutilization as well as disparities in the use of adjuvant RT among patients with breast cancer. Data from the Surveillance, Epidemiology, and End Results registry indicate that about 12% of patients treated with BCS for invasive breast cancer do not receive RT (8). The reasons for omission of RT among women undergoing BCS are unclear, but are probably multifactorial. Patients cite reasons such as inability to find a radiation facility close to home, inability to bear the cost of relocating for radiation treatment at a facility far from home, difficulty finding transportation to and from a radiation facility on a daily basis and extremely advanced age or physical handicap. Accelerated partial breast irradiation may allow some patients with barriers to standard treatment to receive appropriate adjuvant radiation therapy (9) and several trials are now ongoing, but as yet accelerated irradiation is not standard care.

For patients who did not receive RT, AI was selected due to superior local control compared to Tam in several randomised trials. However, there is limited existing evidence regarding local control in breast cancer patients receiving BCS and treated with AI without RT because most

Correspondence to: Makoto Ishitobi, MD, Department of Breast and Endocrine Surgery, Osaka Medical Center for Cancer and Cardiovascular Diseases, 1-3-3 Nakamichi, Higashinari-ku, Osaka 537-8511, Japan. Tel: +81 669721181, Fax: +81 669818055, e-mail: isitobi-ma@mc.pref.osaka.jp

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of the patients in the randomized trials received RT. It is unknown whether AI is superior to Tam with regard to local control without RT. Therefore, a retrospective cohort study was conducted to clarify whether the superiority of local control with AI compared to that with Tam is affected by the presence or absence of RT to the conserved breast.

Patients and Methods

Between January 1997 and March 2005, 1469 patients with stage I or II unilateral breast cancer had undergone BCS at Osaka Medical Center for Cancer and Cardiovascular Diseases. Out of 1469 patients, postmenopausal patients with estrogen receptor (ER)-positive breast cancer who had received adjuvant hormone therapy were selected for this retrospective study. This analysis only included the patients who had received either Tam or AI as monotherapy and had not changed the drugs during adjuvant treatment. Patients who had also received chemotherapy were included. Any patients with prior or synchronous contralateral breast cancer or other prior malignancy were also excluded. Patients with noninvasive breast cancer or more advanced disease were not included in this analysis. To avoid bias due to differences in the lengths of follow-up between the Tam and AI groups, a cut-off time of 5 years after surgery was used to restrict the analyses of any events, and only the patients who had undergone surgery before March 2005 (potentially at least 5 years of follow-up) were included. Five years was selected as the cut-off because ipsilateral breast tumor recurrences (IBTRs) occurring in the early postoperative course have more prognostic significance than those that occur later (10, 11).

Basically, RT was recommended to all the patients who underwent BCS, except for 13 patients with favorable prognostic features, who participated in a prospective trial to evaluate the safety of omitting RT (WORTH trial (12)). Other reasons for omitting RT (n=26) were patient refusal, difficulty in attending radiation sessions, and so on. Radiotherapy was administered to the breast (not including regional lymph nodes) to a total median dose of 50 Gy in 2-Gy fractions. If the surgical margin resulted in microscopically involved tissue, radiotherapy was usually followed by an electron beam boost to the primary tumor bed to a total median dose of 63.2 Gy.

Either Tam at 20 mg or the AI anastrozole (Ana) at 1 mg (which was only available during this study period in Japan) was administered daily for 5 years postoperatively.

Lymphovascular invasion (LVI) was classified as 0 (none), 1 (slight), 2 (moderate) or 3 (extensive). The margin was regarded as positive when an invasive or non-invasive component was within 5 mm from the cut edge of the specimen. Histological grade was determined according to the modified Scarff-Bloom-Richardson criteria (13). ER and progesterone receptor (PgR) status were determined by immunohistochemistry and tumors with 10% or more positively stained tumor cells were classified positive both for ER and PgR.

IBTR-free survival was defined as the time from surgery to IBTR. IBTRs were counted as events only when they were the first sites of failure or occurred concurrently with regional or distant metastasis. In the calculation of IBTR-free survival, occurrence of regional or distant metastasis, contralateral breast cancer, other second primary carcinomas and deaths without evidence of recurrence were treated as censoring events.

Statistical comparisons of clinicopathological factors and the treatment groups were assessed using the Chi-square test or Fisher's exact test. IBTR-free survival curves were calculated using the Kaplan-Meier estimates, with time beginning at the surgery. Comparisons of survival curves were performed by the log-rank test. Clinical and pathological factors were tested by multivariate analysis using the Cox proportional hazards model. All of the statistical tests and *p*-values were two-tailed and *p*-values of <0.05 were considered significant.

Results

A total of 292 patients were included of whom, 182 patients (62.3%) received Tam and 110 patients (37.7%) received Ana. Out of the 292 patients, 253 (86.6%) received postoperative RT. The patient characteristics according to RT in the Tam and Ana groups are listed in Tables I and II, respectively. In both the Tam and Ana groups, there were no significant differences between the two groups receiving or not receiving RT.

According to drug and RT administration, IBTR-free survival curves are shown in Figures 1 and 2. In the Tam group, IBTR-free survival rates did not significantly differ according to RT (5-year IBTR-free survival rate, 99.3% in the RT group *vs*. 94.4% in the no-RT group, $p=0.08$, Figure 1), whereas in the Ana group, IBTR-free survival rates were significantly different according to RT (5-year IBTR-free survival rate, 98.8% in the RT group *vs*. 65.7% in the no RT group, $p<0.0001$, Figure 2). To further evaluate the RT effect among the patients treated with Ana, multivariate analysis including the presence or absence of RT, age (≤60 or >60 years), tumor size (≤20 mm or >20 mm), histological grade (1, 2 or 3), margin status (negative or positive), lymphovascular invasion (0, 1 or 2, 3) and PgR status (negative or positive) was performed. RT use was an independent predictive factor of IBTR-free survival (relative risk 267.7, $p=0.01$, 95% confidence interval 3.6-19937.3).

Discussion

In the patients treated with Tam and Ana, 5-year IBTR rates were 0.7% and 1.2%, respectively, which are considered to indicate excellent local control. These outcomes are comparable to those previously reported (6, 7, 14). In contrast to the excellent local control in patients with RT, the patients treated with adjuvant Ana without postoperative RT had significantly higher IBTR rates, but the patients treated with Tam did not. To date, local control for patients treated with Tam with or without RT has been reported in several randomized trials, and RT significantly reduced IBTR in patients treated with Tam. The lack of RT benefit in our patients treated with Tam may have been due to the low power of the study to detect a treatment effect. Conversely, there are limited IBTR rate data in patients undergoing BCS and treated

Table I. *Patient characteristics according to RT use among patients treated with tamoxifen.*

Tam	RT (+) N=160	RT (–) N=22	*p*-Value RT(+) *vs.* (–)
Age (years)			
≤60	82 (51%)	7 (32%)	0.09
>60	78 (49%)	15 (68%)	
Tumor size (mm)			
≤20	104 (65%)	15 (68%)	0.89
>20	52 (33%)	7 (32%)	
Nodal status			
(–)	118 (74%)	18 (82%)	0.52
(+)	38 (24%)	4 (18%)	
Grade			
1-2	103 (64%)	17 (77%)	0.28
3	54 (34%)	5 (23%)	
PgR			
(–)	54 (34%)	9 (41%)	0.82
(+)	80 (50%)	12 (55%)	
LVI			
0~1	136 (85%)	20 (91%)	0.24
2-3	22 (14%)	1 (5%)	
Margin			
(–)	116 (73%)	17 (77%)	0.25
(+)	43 (27%)	3 (14%)	
Chemotherapy			
(–)	133 (83%)	20 (91%)	0.35
(+)	27 (17%)	2 (9%)	

PgR: Progesterone receptor, LVI: lymphovascular invasion.

Table II. *Patient characteristics according to RT use among patients treated with anastrozole.*

Ana	RT (+) N=93	RT (–) N=17	*p*-Value RT(+) *vs.* (–)
Age (years)			
≤60	52 (56%)	7 (41%)	0.26
>60	41 (44%)	10 (59%)	
Tumor size (min)			
≤20	67 (72%)	12 (71%)	0.74
>20	23 (25%)	5 (29%)	
Nodal status			
(–)	64 (69%)	12 (71%)	0.36
(+)	22 (24%)	2 (12%)	
Grade			
1~2	64 (69%)	11 (65%)	0.86
3	26 (28%)	4 (24%)	
PgR			
(–)	42 (45%)	7 (41%)	0.65
(+)	47 (51%)	6 (35%)	
LVI			
0~1	71 (76%)	13 (76%)	0.49
2~3	19 (20%)	2 (12%)	
Margin			
(–)	71 (76%)	12 (71%)	0.88
(+)	16 (17%)	3 (18%)	
Chemotherapy			
(–)	73 (78%)	16 (94%)	0.13
(+)	20 (22%)	1 (6%)	

PgR: Progesterone receptor, LVI: lymphovascular invasion.

with AI without RT. The Austrian Breast and Colorectal Cancer Study Group-8A randomly assigned 831 women to receive RT±boost (n=414) or not (n=417) after BCS in women with favorable early breast cancer treated by BCS plus Tam or Ana (15). Overall, there were 21 local relapses, with 2 relapses in the RT group (5-year rate 0.4%) *vs.* 19 in the no RT group (5.1%) (p=0.0001, hazard ratio 10.2). There was no difference in locoregional relapse rates between the Tam and Ana groups (16). This trial, however, examined Ana compared with Tam in a switch style. To our knowledge, local control for patients initially treated with adjuvant AI without postoperative RT has not been reported previously.

In the present study, 13.4% of the patients treated with BCS did not receive RT, a similar percentage to that in a previous report using data from the Surveillance, Epidemiology and End Results registry (about 12%) (8). In randomized clinical trials of adjuvant therapy comparing AI with Tam, a lower percentage, 244 (5.4%) out of 4541 patients who underwent BCS, did not receive RT in BIG1-98 (2). It is well known that participants in randomized clinical trials may not be representative of the care received by most patients. In reality, there are various reasons why RT may be omitted in some patients who undergo BCS. Although postoperative RT to the conserved breast is relatively well tolerated, it is not without adverse effects. Therefore, data regarding IBTR rates in patients treated with AI without postoperative RT seem to be important.

The relatively higher IBTR rates in patients treated with Ana without postoperative RT in the present study were not due to bias in patient characteristics because the clinicopathological factors did not significantly differ between the patients treated with Ana without RT and the other patient groups. However, the present study was a nonrandomized, retrospective analysis of a cohort of patients from a single institution. A subtle source of bias in the selection of patients with or without RT cannot be excluded.

In vitro studies have suggested that Tam and AI have different interactions with RT. Although some basic studies have demonstrated reduced radiosensitivity of human tumor cells pretreated with Tam, others have suggested enhanced radiosensitivity (17-19). By contrast, preclinical evidence has suggested that AI may have a radiosensitizing effect (20). Based on this basic research, as well as our own findings, the greater synergistic effect of RT with AI than with Tam could result in superior local control with AI than with Tam.

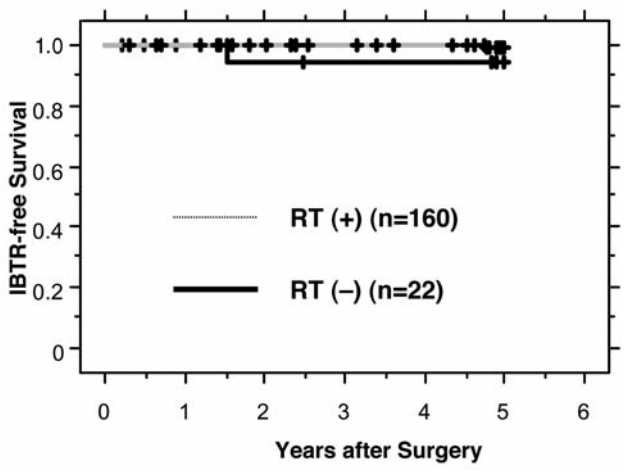

Figure 1. *Ipsilateral breast tumor recurrence-free survival rates according to the presence or absence of radiotherapy use for patients treated with tamoxifen.*

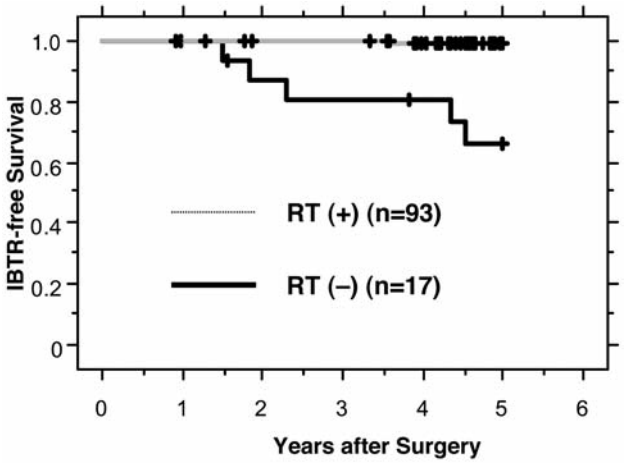

Figure 2. *Ipsilateral breast tumor recurrence-free survival rates according to the presence or absence of radiotherapy use for patients treated with anastrozole.*

This study had several limitations, in particular the small sample size. To avoid the bias of different follow-up periods for the patients treated with Tam and with Ana, only patients who underwent surgery before March 2005 (potentially at least 5 years of follow-up) were selected and the follow-up was censored at 5 years. However, there is a possibility that different chemotherapy regimens affected the IBTR rates.

In conclusion, patients treated with adjuvant Ana without postoperative RT show quite high IBTR rates. Caution is needed when RT is omitted for patients who undergo BCS and receive adjuvant Ana treatment. The results of an ongoing prospective trial to clarify the safety of omitting RT (WORTH trial (12)) are awaited.

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