SPANDIDOS PUBLICATIONS

# Impact of radiation therapy on breast-conserving therapy for breast cancer in Japanese women: A retrospective analyses of multi-institutional experience. Kansai Breast Cancer Radiation Therapy Study Group

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**Abstract.** Whole breast radiation therapy (RT) after breast-conserving surgery is sometimes omitted in Japan; however, its impact on the outcome has not been properly evaluated. A multi-institutional retrospective study was conducted to clarify the impact of RT on local control after breast-conserving therapy (BCT). Data were collected from 3576 patients from 37 participating hospitals, of whom 1763 were eligible for analyses. Five hundred and five patients had ipsilateral breast tumor recurrence (IBTR) and 1258 patients did not. Details of IBTR were available for 245 of 505 patients who had IBTR, the location of IBTR was within or adjacent to the original tumor bed in 168 patients (68.6%). IBTR was salvaged with partial mastectomy in 119 patients (48.6%). Second recurrence in the ipsilateral breast was observed in 27 patients (11.0%). Univariate analyses demonstrated that administration of RT, the resection margin status, hormone responsiveness, T stage, N stage and stage were significantly related to IBTR. Multivariate analysis demonstrated that administration of RT, T stage and N stage were significantly correlated to IBTR. Among them, administration of RT had the largest impact on RT and it decreased the risk of IBTR by 77.3%. Omission of RT had the most significant impact on IBTR. RT should be given as a standard component of BCT.

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*Key words:* breast cancer, breast-conserving therapy, radiation therapy, ipsilateral breast recurrence

## Introduction

The incidence of breast cancer in Japanese women has become the highest among various cancers and it was estimated that 40675 women were newly diagnosed with breast cancer in 2001. The ratio of patients who undergo breast-conserving surgery (BCS) is also increasing and BCS has become the most frequently employed method of initial surgery for breast cancer in Japan (1). According to the NIH consensus statement, breast-conserving therapy (BCT) comprises of BCS and adjuvant radiation therapy (RT). The role of RT in BCT has been well established as a result of at least 8 randomized controlled trials and meta-analyses of these trials (2-10). Moreover, the subgroup of patients who do not receive a benefit from RT after BCS has not been defined in spite of various attempts to find such a subgroup. In Japan, however, ~20% of patients who undergo BCS do not receive RT (1). This number is larger than in the USA (11). One reason for not receiving RT in Japan is that some surgeons believe that RT is not necessary if the tumor was resected with an ample pathologically negative margin and that RT is harmful and deteriorates the cosmetic outcome. To clarify the impact of RT on ipsilateral breast tumor recurrence (IBTR) in such practice in Japan, we collected data from participating institutions of the Kansai Breast Cancer Radiation Therapy Study Group (KBCRTSG) and analyzed them retrospectively.

## Patients and methods

*Study design*. This study was conducted as a multi-institutional retrospective review. The primary endpoint was IBTR, including those preceded by any form of regional and distant recurrence.

*Patients*. Between August 2004 and February 2005, data from 3576 patients were collected from 37 participating hospitals in

Table I. Patient characteristics.

| | Patients with IBTR (n=505) | Patients without IBTR (n=1258) | P-value |
|---|---|---|---|
| Age | 49.8±12.2 | 49.8±9.9 | N.S. |
| Method of surgery | | | P=0.082 |
| Quadrantectomy | 129 | 211 | |
| Wide excision | 362 | 572 | |
| Tumorectomy | 8 | 3 | |
| Other | 0 | 2 | |
| Unknown | 6 | 470 | |
| T stage[a] | | | P=0.017 |
| T0 | 4 | 0 | |
| T1 | 169 | 402 | |
| T2 | 153 | 256 | |
| T3 | 3 | 1 | |
| Unknown | 176 | 599 | |
| N stage[a] | | | P=0.000 |
| N0 | 193 | 570 | |
| N1 | 121 | 159 | |
| N2 | 26 | 15 | |
| N3 | 0 | 1 | |
| Unknown | 165 | 513 | |
| Stage[a] | | | P=0.000 |
| Stage 0 | 5 | 0 | |
| Stage 1 | 142 | 349 | |
| Stage 2a | 119 | 233 | |
| Stage 2b | 73 | 71 | |
| Stage 3a | 27 | 7 | |
| Unknown | 139 | 658 | |
| Margin status | | | P=0.000 |
| >5 mm | 302 | 750 | |
| ≤5 mm | 139 | 219 | |
| Unknown | 63 | 289 | |
| Hormone receptor stastus | | | P=0.000 |
| Positive | 236 | 715 | |
| Negative | 184 | 289 | |
| Unknown | 85 | 254 | |
| Radiation therapy | | | P=0.000 |
| Yes | 356 | 1146 | |
| No | 148 | 69 | |
| Unknown | 1 | 43 | |

IBTR, Ipsilateral Breast Tumor Recurrence. [a]General rules for clinical and pathological recording of breast cancer. 14th edition, The Japanese Breast Cancer Society.

KBCRTSG. The data format was developed by the steering committee of KBCRTSG and includes patient characteristics, including clinicopathological findings, method of BCT and outcome.

Table II. Details of IBTR.

| | Patients with detailed information of IBTR (n=245) | |
|---|---|---|
| Location of IBTR | | |
| TR/MM[a] | 168 | 68.6% |
| Other than TR/MM | 65 | 26.5% |
| Unknown | 12 | 4.9% |
| Type of IBTR | | |
| Nodular | 209 | 85.3% |
| Diffuse | 32 | 13.1% |
| Nodular/diffuse | 3 | 1.2% |
| Method of salvage | | |
| Partial mastectomy | 119 | 48.6% |
| With RT | 36 | 14.7% |
| Total mastectomy | 102 | 41.6% |
| With RT | 3 | 1.2% |
| Unknown surgery | 6 | 2.4% |
| With RT | 2 | 0.8% |
| No surgery | 18 | 7.3% |
| With RT | 2 | 0.8% |
| Re-IBTR | | |
| No | 193 | 78.8% |
| Yes | 27 | 11.0% |
| Unknown | 25 | 10.2% |

[a]True recurrence/marginal miss: Recurrence within or adjacent to original tumor bed.

Eligibility criteria for this study were as follows: i) Japanese female, ii) received BCS alone or BCT, including RT, at participating hospitals of KBCRTSG, iii) has outcome data regarding both local and systemic control and iv) longer than 5-year follow-up for patients without IBTR.

Thus, 1813 cases without IBTR were excluded due to shorter follow-up than 5 years. Consequently, 505 cases of IBTR and 1258 cases of no IBTR were subjected to further analyses. Of note, 173 of the former and 70 of the latter had distant metastasis in their disease course. Patient characteristics are shown in Table I.

*Statistical analyses*. Univariate and multivariate Cox regression analyses were used to evaluate the impact of patient and treatment factors on the endpoint. Pearson's Chi-square test was used to evaluate the distribution of the patients' background. A p-value of $<0.05$ was regarded as significant.

## Results

Details of IBTR were available for 245 of 505 patients with IBTR (Table II), the location of IBTR was within or adjacent to original tumor bed in 168 patients (68.6%), in another location in 65 patients (26.5%) and unknown in 12 patients (4.9%). The type of IBTR was nodular in 209

Univariate analyses.

| | No. of available patients | RR | 95% C.I. | P-value |
|---|---|---|---|---|
| Age | 1748 | 1.011 | 1.003-1.020 | P=0.006 |
| Radiation therapy | 1722 | 0.276 | 0.229-0.333 | P=0.000 |
| T stage | 986 | 1.391 | 1.121-1.725 | P=0.003 |
| N stage | 1085 | 1.808 | 1.503-2.174 | P=0.000 |
| Stage | 1032 | 1.328 | 1.178-1.498 | P=0.000 |
| Margin status | 1390 | 1.471 | 1.194-1.812 | P=0.000 |
| Hormone receptor status | 1424 | 0.593 | 0.487-0.721 | P=0.000 |
| Method of surgery | 1309 | | | |
| Method (1) quadrantectomy | | 90.410[a] | 0.000-5.95x10$^{17}$ | P=0.808 |
| Method (2) wide excision | | 205.605[a] | 0.000-1.35x10$^{18}$ | P=0.774 |
| Method (3) lumpectomy | | 612.053[a] | 0.000-4.04x10$^{18}$ | P=0.730 |

[a]Relative risk against method (4) 'other method'.

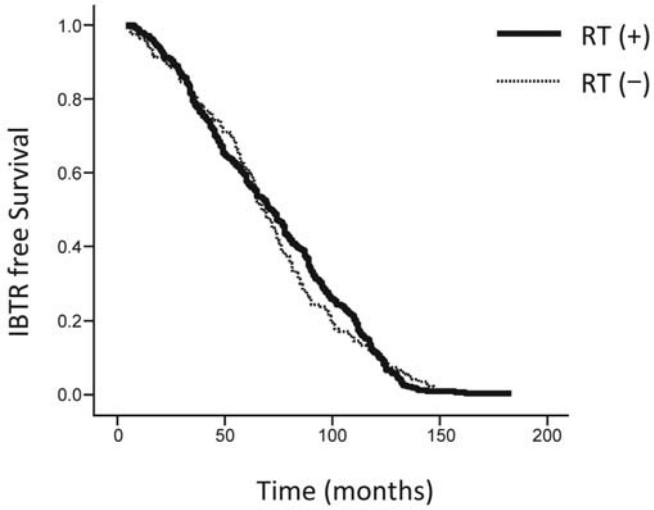


Figure 1. Kaplan-Meier estimate of ipsilateral breast tumor recurrence (IBTR)-free survival of the patients who eventually had IBTR. Note that the rate of IBTR is fairly consistent through 10 years.

patients (85.3%), diffuse/inflammatory in 32 patients (13.1%) and a combination of these in 3 patients (1.2%). IBTR was salvaged with partial mastectomy in 119 patients (48.6%), total mastectomy in 102 patients (41.6%), unknown surgery in 6 patients (2.4%) and no surgery in 18 patients (7.3%), of whom radiation therapy was used as a component of salvage therapy in 36 (14.7%), 3 (1.2%), 2 (0.8%) and 2 (0.8%). Second IBTR was observed in 27 patients (11.0%). Univariate analyses demonstrated that the administration of RT, resection margin status, hormone responsiveness, T stage, N stage and stage were significantly related to IBTR. Univariate analyses demonstrated that the administration of RT, resection margin status, hormone responsiveness, T stage, N stage and stage were significantly related to IBTR (Table III). The test for correlation among these variables demonstrated that several variables are dependent on each other (Table IV). Among them, stage was strongly correlated to T stage and N stage; therefore, RT, resection margin status, hormone responsive-ness, T stage and N stage were employed as variables for multivariate analysis using the Cox regression model. This demonstrated that RT, T stage and N stage were significantly correlated to IBTR. Among them, administration of RT had the largest impact on RT and decreased the risk of IBTR by 77.3% (Table V).

The IBTR-free survival curve was plotted for patients who eventually developed IBTR (Fig. 1). It revealed that the risk of IBTR is fairly constant over time both for patients who received RT and patients who did not.

## Discussion

Several factors may influence the risk of local recurrence after BCT. Among them, administration of RT has been shown to have a large impact on local control, as shown in this study. According to a meta-analysis by EBCTCG, the effect of RT after BCS is highly consistent and reduces the risk of isolated IBTR by ~70% compared to those allocated to no RT (5). Other factors which are known to increase the risk of IBTR include young age, positive resection margin and existence of EIC.

There have been continuous efforts to identify a subgroup of patients for whom RT after BCS can be safely omitted. In the Joint Center for Radiation Therapy at Harvard Medical School, women considered to be at low risk for IBTR were prospectively observed without RT after BCS. The patients in this study had pT1N0 tumor, absence of both lympho-vascular invasion and extensive intraductal component and no cancer cells within 1 cm of resection margins. This study was terminated before it reached accrual goal because of an excessive number of IBTR. Of note, there were no eligibility limitations on patient age for this study and these patients did not receive any adjuvant chemo-endocrine therapy regardless of the status of hormone receptors (12). Considering that young age is a known risk factor for IBTR (13-19) and that systemic adjuvant therapy provides a benefit for local control (20,21), some patients in this study may not have been at low risk for IBTR. Previously, the CALGB C9343 trial demonstrated that it is a realistic choice for the treatment of

Table IV. Correlation coefficient among factors analyzed.

| | Margin status | RT | HR[a] | T stage[b] | N stage[b] | Stage[b] |
|---|---|---|---|---|---|---|
| Margin status | | | | | | |
| CC[c] | 1 | 0.009 | 0.038 | 0.274 | 0.094 | 0.229 |
| P-value | | 0.748 | 0.192 | 0 | 0.003 | 0 |
| N[d] | 1390 | 1373 | 1185 | 952 | 963 | 953 |
| RT | | | | | | |
| CC | 0.009 | 1 | 0.051 | 0.037 | 0.066 | 0.093 |
| P-value | 0.748 | | 58.058 | 0.245 | 29.029 | 3.003 |
| N | 1373 | 1722 | 1397 | 987 | 1086 | 1033 |
| HR | | | | | | |
| CC | 0.038 | 0.051 | 1 | 0 | 0.025 | 0.042 |
| P-value | 0.192 | 0.058 | | 0.991 | 0.447 | 0.204 |
| N | 1185 | 1397 | 1424 | 876 | 947 | 914 |
| T stage[b] | | | | | | |
| CC | 0.274 | 0.037 | 0 | 1 | 0.201 | 0.733 |
| P-value | 0 | 0.245 | 0.991 | | 0 | 0 |
| N | 952 | 987 | 876 | 987 | 986 | 987 |
| N stage[b] | | | | | | |
| CC | 0.094 | 0.066 | 0.025 | 0.201 | 1 | 0.785 |
| P-value | 0.003 | 0.029 | 0.447 | 0 | _ | 0 |
| N | 963 | 1086 | 947 | 986 | 1086 | 987 |
| Stage[b] | | | | | | |
| CC | 0.229 | 0.093 | 0.042 | 0.733 | 0.785 | 1 |
| P-value | 0 | 0.003 | 0.204 | 0 | 0 | |
| N | 953 | 1033 | 914 | 987 | 987 | 1033 |

[a]Hormone responsiveness. [b]General Rules for Clinical and Pathological Recording of Breast Cancer (13th edition). [c]Pearson's correlation coefficient. [d]Number of available data.

Table V. Multivariate analyses.

| | RR | 95% C.I. | P-value |
|---|---|---|---|
| Margin status | 1.183 | 0.898-1.557 | P=0.231 |
| Radiation therapy | 0.227 | 0.168-0.307 | P=0.000 |
| T stage | 1.293 | 1.009-1.655 | P=0.042 |
| N stage | 1.867 | 1.508-2.312 | P=0.000 |
| Hormone receptor status | 0.796 | 0.615-1.029 | P=0.082 |

Number of available data: 848.

women >70 years of age who have early, estrogen-receptor-positive breast cancer with tamoxifen alone, rather than RT and tamoxifen, because the benefit of RT is still significant but very small (22). Thus, a subgroup of patients who have little or no benefit from RT has not been well defined yet. In Japan, however, whether to give RT after BCS remains controversial. Unfortunately, information regarding why RT was not given was not collected in this study; therefore, it cannot be rejected that a fear of radiation, which is characteristic of Japanese patients, caused them to decline RT, but it is more likely that the presiding surgeons did not offer RT because they believed that the patient's risk of IBTR was low enough to omit RT or that the benefit of RT did not exceed its harm. Consequently, the subjects in this study might have a bias that patients who did not receive RT had an apparently lower risk of IBTR than patients who actually received RT. Therefore, the observed result that the ratio of patients who received RT was significantly lower in patients who eventually had IBTR duplicated existing clinical evidence. In addition, previous meta-analyses suggested that the addition of RT after BCS significantly improved overall survival (5,23). Although the rationale for this observation was not fully explained, it is speculated that reduction of loco-regional recurrence leads to reduction of secondary dissemination to distant sites (23). Thus, omission of RT especially in young patients or patients with a high risk of IBTR, may deteriorate survival. Another interesting finding in this study is that the risk of IBTR is fairly constant over

1 10 years for both patients who received RT and not. Regular check-ups for IBTR may be necessary after 10 years.

Regarding the characteristics of IBTR, 68.6% occurred within or adjacent to the original tumor bed, which is similar to existing observations (16,24,25). Of note, IBTR was salvaged with partial mastectomy in 48.6%. Although data are sparse regarding the method of salvage surgery, partial mastectomy, which is equivalent to breast-conserving salvage surgery, seems higher than in existing studies (26-29). This might be related to the fact that 29% (148/505) of patients had not received RT as initial treatment and RT can be administered safely after salvage surgery.

This study has several limitations. Almost all patients who developed IBTR in participating institutes were registered in this study; however, the completeness of registration for patients who did not develop IBTR is unknown in some institutes. Moreover, information regarding systemic adjuvant therapy and the details of RT were not collected for each patient; therefore, substantial bias may exists regarding systemic therapy and/or the radiation dose to the tumor bed between patients who had IBTR and patients who did not. This might have been why the margin status and young age, both of which are well known risk factors for IBTR, did not have a significant impact in this study. In other words, patients with unfavorable tumor factors who had RT may have had a better outcome than patients without unfavorable tumor factors who did not have RT. In conclusion, the results shown in this study, together with existing evidence, indicate that omission of RT after BCS is the most significant treatment factor related to IBTR. RT should be offered as standard for all patients who undergo BCS. Deterioration of local control and, possibly, overall survival should be discussed with patients before offering to omit RT.

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