

Utility of regional nodal irradiation in Japanese patients with breast cancer with 1-3 positive nodes after breast-conserving surgery and axillary lymph-node dissection

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Abstract. The utility of regional nodal irradiation (RNI) is being considered in cases of 1-3 axillary node metastases after breast-conserving surgery (BCS) with axillary lymph-node dissection (ALND). Therefore, we examined the necessity of RNI by examining the sites of recurrences in cases at our institution. We retrospectively analyzed 5,164 cases of primary breast cancer between January 2000 and December 2014 at the Aichi Cancer Centre, identifying local and distant recurrences in 152 patients with primary breast cancer treated with BCS and ALND and who had 1-3 positive axillary nodes. All patients received whole-breast irradiation (WBI) and adjuvant systemic therapy with either chemotherapy or anti-endocrine therapy with or without anti-human epidermal growth factor receptor 2 therapy. The present study excluded patients with ipsilateral breast tumor recurrence, contralateral breast cancer, neoadjuvant chemotherapy, T4 tumors or N2-3 nodes and distant metastasis. From the database of our institution, we identified 152 cases that met the defined criteria. The median follow-up period was 71 months (1-176). Isolated locoregional recurrences were found in three patients (2.0%) and were recurrent only in the breast. Only one patient had local lymph node recurrence with distant recurrence. The 10-year rates of isolated regional disease-free survival (DFS), DFS, and overall survival were 95.41, 89.50 and 96.75%, respectively, which was better compared with previous studies. We conclude that the addition of RNI to WBI is not necessary for Japanese patients who have 1-3 positive axillary nodes and ALND.

Introduction

Three randomized controlled trials for high-risk breast-cancer patients with axial lymph node metastasis and a maximum primary-tumor diameter of 5 cm or more have shown that radiotherapy combined with systemic therapy after mastectomy not only reduces locoregional recurrence to one-third to one-quarter, but also improves survival rates (1-4). These meta-analyses have also shown decreased rates of locoregional lymph node recurrence and increased survival rates (5).

After breast-conserving surgery (BCS), locoregional recurrence tends to increase as axial lymph node metastases increase (6,7). When there are more than four lymph node metastases after BCS, improvement of local control by regional nodal irradiation (RNI) has been reported in several retrospective studies, but high-quality evidence is sparse (6,7). Considering the suppressive effect of four or more lymph node metastases at the time of mastectomy, RNI after BCS with four or more lymph node metastases is recommended by the guidelines of both the U.S. National Comprehensive Cancer Network (NCCN) and the Japanese Breast Cancer Society (8,9). Few randomized controlled trials have examined the significance of RNI in cases with 1-3 axillary lymph node metastases after BCS with axillary lymph-node dissection (ALND). In the MA 20 study, which showed a beneficial effect of RNI, the proportion of lymph nodes having from 1-3 and 0 metastases was 85 and 10%, respectively (10). In the MA 20 study, 1,832 high-risk breast cancer patients who were either lymph node metastasis-negative or lymph node metastasis-positive after BCS were randomly assigned to either the group receiving WBI alone or a group receiving WBI plus RNI. In the median follow-up (9.5 years), the 10-year disease-free survival rates were 82.0% in the nodal-irradiation group and 77.0% in the control group (hazard ratio, 0.76; $P=0.01$), and the overall survival rate increased from 81.8 to 82.0% (hazard ratio, 0.91; $P=0.38$) (10). According to the NCCN guideline, RNI should be strongly considered when the number of metastasis-positive lymph nodes is between 1-3 after BCS. However, the recurrence rate in the regional lymph nodes, including the supraclavicular region, in patients with 1-3 metastasis-positive lymph nodes is not high when ALND is

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performed (11,12). Due to recent advances in systemic therapy, local and regional lymph node recurrence has been decreasing with age (13). According to a retrospective study by the M.D. Anderson Cancer Centre, for patients with 1-3 metastatic lymph nodes, post-mastectomy radiation therapy (PMRT) has not been effective for 5-year local and regional lymph node recurrence since the year 2000 (14). If adequate ALND and systemic therapy is properly conducted after BCS, locoregional recurrence seems to be lessened.

Recently, a study by the American Surgical Oncology Group (ACOSOG) Z0011 showed that patients with micro-metastatic and macrometastatic nodular disease after BSC do not require ALND (15). Besides, a study by the European Cancer Research and Treatment Organization (EORTC) 10981-22023 (AMAROS) has shown that the efficacy and prevalence of ALND and axillary RT are comparable (16). Based on these results, the number of patients undergoing BSC and ALND is expected to continue to decline, and it is difficult to show substantial evidence of additional effects of adding RNI to patients with 1-3 metastases after BCS and ALND. Therefore, we retrospectively examined the recurrence pattern in the Aichi Cancer Centre (ACC) of patients who had between 1-3 axillary node metastases after BCS with ALND and whether the addition of RNI to WBI was necessary for Japanese patients.

Patients and methods

Patient selection. The present study retrospectively analyzed local and distant recurrences in 152 primary breast cancer patients who were treated with BCS and ALND and who had 1-3 positive axillary nodes. These patients were identified from among 5,164 primary breast cancer cases seen between January 2000 and December 2014 at the ACC. All patients received WBI and adjuvant systemic therapy with either chemotherapy or endocrine therapy and with or without HER2 therapy. The study excluded patients with ipsilateral breast tumor recurrence, contralateral breast cancer, neoadjuvant chemotherapy, T4 tumors, or N2-3 nodes and distant metastasis. The study protocol was approved by The Certified Review Board of Aichi Cancer Center and written informed consent was obtained from all the patients.

Adjuvant therapy. Adjuvant chemotherapy was delivered before the radiation. Endocrine therapy with tamoxifen or an aromatase inhibitor was administered concurrently with radiotherapy based on several guidelines. After May 2005, trastuzumab was recommended for patients who had HER2-positive disease. All patients were treated with external beam radiotherapy. The dose to the breast was either 50 Gy in 25 fractions or 42.56 Gy in 16 fractions. In cases requiring boost irradiation to the breast, irradiation was delivered at either 60 Gy in 30 fractions or 53.2 Gy in 21 fractions.

Histopathological evaluation. The statuses of the estrogen receptor (ER), progesterone receptor (PR) and HER2 were evaluated using immunohistochemical (IHC) analysis. The ER and PR status are obtained by summing the score of the percentage abundance and the staining intensity of ER or PR-stained nuclei of tumor cells (the so-called Allred score,

ranging from 0 to 8). ER and PR positivity were defined as >3 points using the Allred score. Positive HER2 status was defined as either 3+ or else 2+ and c-erbB2 gene amplification that used fluorescent *in situ* by hybridization (FISH), and both were confirmed using IHC. The margins positive are defined as cancer detected <5 mm from the stamp.

Statistical analysis. The survival endpoints evaluated were isolated locoregional disease-free survival (ILDDFS), DFS and overall survival (OS). ILDFS was defined as the time from surgery to the time of the first recurrence in the ipsilateral breast or in axial, supraclavicular or internal mammary nodes without evidence of distant disease. DFS was defined as the time from surgery to the time of the first recurrence, such as relapse including ipsilateral breast cancer recurrence; the appearance of second primary cancer, including contralateral breast cancer; or death, whichever occurred first. OS was defined as the time from surgery until the date of death from any cause. ILDFS, DFS and OS functions were estimated using the Kaplan-Meier method. All statistical analyses were conducted using Stata[®] V12 software (StataCorp LP).

Results

Patient characteristics. The total number of eligible patients who had ALND, between 1-3 lymph node metastases and breast radiation after BSC was 152. The median follow-up at the time of the analysis was 71 months (range: 1-176). Table I shows the patients' characteristics. The median age was 54 (range: 29-82). The median number of axillary nodes removed was 17. The proportions of ≤9, from 10 to <20 and from ≥20 were 7.2, 52.0 and 40.8%, respectively. In 120 patients (78.9%), the tumor diameter was ≤2 cm and in 32 patients (21.1%), it was >2 cm. Ninety-one patients (59.9%) had 1 metastasis to the lymph nodes, 49 (32.2%) had 2 metastases, and 12 (7.9%) had 3 metastases. The surgical margin was positive in 22 patients (14.5%).

Treatment characteristics. Table II shows the treatment characteristics. Nearly 40% of the cases in the ACC received anthracycline with taxane. Thirty-one patients (20.4%) did not receive chemotherapy. One hundred twenty-six patients (82.9%) received hormone treatment with either aromatase inhibitors or tamoxifen. Boost radiation was administered to 17 (11.1%) due to positive margins.

Recurrence and deaths. Table III shows statistics regarding the sites of recurrence and the deaths. The most common site of isolated locoregional recurrence was the breast. There were no isolated regional-only recurrences, including axillary, supraclavicular nodal, or subclavian lymph nodal. Only one patient had a distant recurrence at the same time as the supraclavicular lymph node recurrence. Seven patients (4.6%) had distant metastases, including in the lung, bone, and liver, without local recurrence. Of the four deaths, three were caused by breast cancer. Table IV and Fig. 1 show the 5- and 10-year Kaplan-Meier ILDFS, DFS, and OS. The recurrence rates at 5 and 10 years, respectively, were 99.2 and 95.4% for ILDFS, 95.0 and 89.5% for DFS, and 99.2 and 96.8% for OS.

Table I. Patient characteristics.

Patient characteristic	n (%)
Median age (range), year	54 (29-82)
Patients who underwent initial sentinel-lymph-node biopsy	101 (66.4)
Axillary nodes removed, median (interquartile range)	17 (15-23)
1-9	11 (7.2)
10-19	79 (52.0)
≥20	62 (40.8)
Tumor size, cm	
≤2	120 (78.9)
>2	32 (21.1)
Number of positive axillary lymph nodes	
1	91 (59.9)
2	49 (32.2)
3	12 (7.9)
Histological grade	
1	27 (17.8)
2	71 (46.7)
3	36 (23.7)
Unknown	18 (11.8)
ER status	
Positive	122 (80.3)
Negative	26 (17.1)
Unknown	4 (2.6)
Progesterone receptor status	
Positive	105 (69.0)
Negative	43 (28.2)
Unknown	4 (2.6)
HER2 status -no. (%)	
Positive	14 (9.2)
Negative	120 (78.9)
Unknown	18 (11.8)
Body mass index	
<18.5 kg/m ²	7 (4.6)
18.5≤x<25.0 kg/m ²	109 (71.7)
25.0≤x<30.0 kg/m ²	25 (16.4)
≥30 kg/m ²	11 (7.2)
Margin positive	22 (14.5)

n=152. Status of ER and PR were evaluated using immunohistochemical analysis. The ER and PR status are obtained by summing the score of the percentage abundance and the staining intensity of ER or PR-stained nuclei of tumor cells (the so-called Allred score, ranging from 0 to 8). ER and PR positivity were defined as more than 3 points using the Allred score. ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2.

Discussion

The utility of RNI is in question in patients with 1-3 axillary node

Table II. Treatment characteristics.

A, Adjuvant chemotherapy, n=121 (79.6%)	
Treatment characteristic	n (%)
Anthracycline with taxane	66 (43.4)
Anthracycline without taxane	12 (7.9)
Other ^a	43 (28.2)
No chemotherapy	31 (20.4)
B, Adjuvant endocrine therapy, n=126 (82.9%)	
Treatment characteristic	n (%)
Aromatase inhibitors	66 (43.4)
Tamoxifen	60 (39.5)
No endotherapy	26 (17.1)
Boost irradiation-number and (%)	17 (11.1)

^aOther types of chemotherapy included 22 patients treated with cyclophosphamide, methotrexate and fluorouracil and 16 patients treated with taxotere and cyclophosphamide.

Table III. Disease recurrence or death.

Event	n (%)
Isolated locoregional recurrence	3 (2.0)
Local (in breast) only	3 (2.0)
Regional only	0 (0.0)
Local+regional	0 (0.0)
Distant recurrence	1 (0.01)
First or concurrent with locoregional recurrence	1 (0.01)
After locoregional recurrence	0 (0.0)
Any recurrence or contralateral breast cancer	7 (4.6)
Any recurrence	7 (4.6)
Contralateral breast cancer	0 (0.0)
Death	4 (2.6)
Breast cancer	3 (2.0)
Other cause	0 (0.0)
Unknown	1 (0.01)

n=152.

Table IV. Recurrence-free survival rates at 5- and 10-years.

Rate	5 years, %	10 years, %
Isolated locoregional DFS	99.20	95.41
DFS	95.00	89.50
OS	99.22	96.75

DFS, disease-free survival; OS, overall survival.

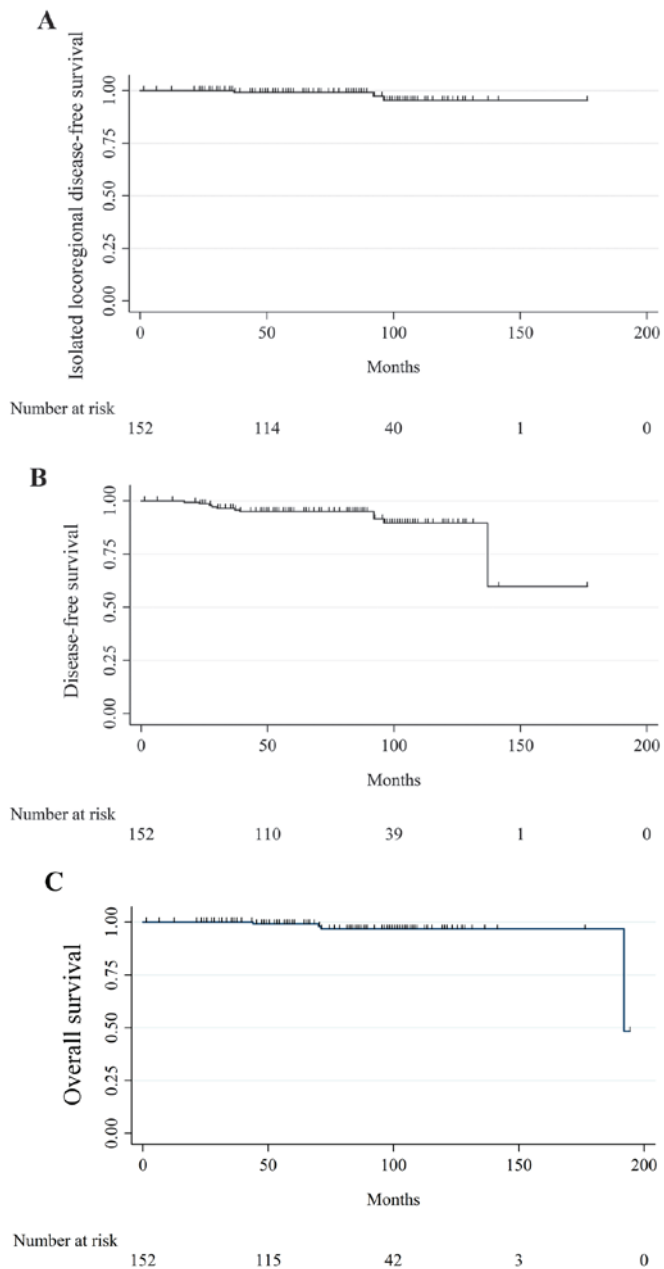


Figure 1. Kaplan-Meier estimates of survival. (A) Kaplan-Meier locoregional disease-free survival in months. A total of three patients had isolated locoregional recurrences, all of which were in the breast. (B) Kaplan-Meier disease-free survival in months. A total of 11 patients had local or distant recurrences. A total of seven patients (4.6%) had only distant metastases of the lung, bone and liver, and had no local recurrence. (C) Kaplan-Meier overall survival in months. A total of four people died, of which three were diagnosed with breast cancer.

metastases after BCS with ALND. Therefore, the present study examined the utility of RNI by examining the site of recurrence in our institution, the ACC. Surprisingly, the isolated local recurrence rate was very low (2.0%). In the MA 20 study, isolated locoregional recurrence was observed in 62 patients (6.8%) in the WBI group, and 39 (4.3%) in the WBI + RNI group. There were 23 (2.5%) regional-only recurrences in the WBI group and 5 (0.5%) each in the WBI and RNI groups, indicating that RNI reduced regional-only recurrence by 18 patients, which was 2.0% (10). Regarding the locations of regional-only recurrences, the WBI group had axillary recurrences in 14 patients (60.9%), and the

WBI + RNI group had axillary recurrences in 5 patients (100%). This suggests that the effect of RNI is to suppress axillary lymph node recurrence. An analysis of 5688 women using the British Columbia Cancer Agency (BCCA) Breast Cancer Outcomes Unit Database showed that 40 of the 68 (58.8%) who experienced local recurrences after BCS and ALND had an axillary node recurrence (17). In contrast, at the ACC, local recurrence was very low and no axillary recurrences were found. In addition, at the ACC, the 10-year recurrence rate was 89%, which tended to be higher than those in the MA 20 study (77.0% for WBI and 82% for WBI + RNI, respectively). In the ACC, the 10-year isolated locoregional recurrence rate was 95.4%, which was nearly identical to the 95.2% for the WBI + RNI group in the MA 20 study.

Three hypotheses were formed on why the recurrence rate was so low in the ACC. First, we considered the early clinical stages of eligible patients. In the ACC study, the percentage of patients who had tumors with diameters of ≤ 2 cm was 78.9% (120 patients), which was about half the percentage in the MA 20 study, indicating that the ACC patients tended to have smaller tumors diameters than those in the MA 20 study. Additionally, in the MA 20 study, about half the patients had one axillary metastasis, but in the present study, $\sim 60\%$ had them. The number of axillary lymph node metastases also tended to be smaller in the ACC than in the MA 20 study. The second hypothesis regarding the lower recurrence rates at the ACC involved the difference in the number of lymph nodes removed. In the ACC, $\sim 7\%$ of patients had < 9 lymph nodes removed, and about 40% had > 20 removed. In contrast, in the MA 20 study, about 30% of patients had ≤ 9 lymph nodes removed, and about half of patients had 10 or fewer lymph nodes removed, according to an analysis that used BCCA (10,17). Generally, to accurately stage the axilla, it is recommended that the number of resected axillary lymph nodes to be ≥ 10 . Besides, with the progress in systemic therapy and radiation therapy, there is concern regarding the decreased quality of life (QOL) due to axillary dissection, and the range of ALND tends to be minimized, resulting in a decrease in the absolute number of resected lymph nodes. However, the absolute number and ratio of positive lymph nodes have been reported as a prognostic factor for other carcinomas, and similar results have been reported for breast cancer (18-21). In the ACC, the large number of resected lymph nodes may have resulted in a low lymph node ratio and lower local recurrence rates and prognoses. Finally, it was hypothesized that the low body mass index (BMI) of eligible patients had an effect. High BMI has been reported as resulting in higher local recurrence rates and recurrence rates (22-24). In the ACC, the median BMI was 22.8 kg/m², and only 11 patients (7.2%) had a BMI > 30 kg/m², which differs significantly from the BMI distribution of Westerners, of whom 30% are obese (25). The recurrence rate for the ACC patients appeared to be lower because that study targeted patients who had lower BMIs.

Considering that the addition of RNI increases adverse events including lymphedema, dermatitis, and pneumonia, RNI is less useful for Japanese patients because they have a very low risk of local recurrence. Patients with young, grade III or ER-negative tumors have been reported to have a $\sim 15\text{-}20\%$ risk of locoregional recurrence despite WBI and systemic therapy (17). RNI should be considered only for these patients.

The present study had some limitations, notably the small number of patients and the fact that it was a single-center retrospective analysis. In addition, the observation period was short, with the median observation period being 71 months.

Despite these limitations, the present study's results suggest that the addition of RNI is not effective in patients in Japan who have 1-3 metastases after BCS and ALND. In the future, it is expected that patients with 1-3 lymph node metastases will undergo no ALND due to the ACOSOG Z0011 trial and AMOROS trial. For these patients, RNI may be even more important.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

NG conceived the present study and wrote the manuscript. MS, MH, AY, HK, YA and HI made substantial contributions to the interpretation of data and the research concept and design. AK, KS, NH, YO and YE helped with data acquisition, analysis and interpretation. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The study protocol was approved by The Certified Review Board of Aichi Cancer Center and written informed consent was obtained from all the patients. All procedures involving human participants were conducted in accordance with the ethical standards of the Institutional Review Board of Aichi Cancer Centre and with the 1964 Helsinki Declaration and its later amendments.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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