

A Retrospective Study of Results of Conservative Therapy for Breast Cancer in Japan

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ABSTRACT. *Purpose:* In Japan, the history of breast conservative breast cancer surgery with radiation therapy is shorter than in Europe and North America, and the number of patients with early breast cancer treated by these therapies has been smaller. Therefore, we consider the accumulation of the results of this conservative therapy to be important. The purpose of this study was to evaluate the results of conservative surgery with radiation therapy in Japan.

Materials and Methods: The subjects of this study were 105 patients (105 breasts) with early breast cancer who received conservative surgery with radiation therapy in our institute between April 1987 and December 1993. Six patients were stage 0 (Tis), 86 patients were stage I and 13 patients were stage II. During the total course of this study, quadrantectomy (84%) was the most commonly performed procedure. A carcinoma-positive resection margin was recognized in seven patients on postoperative histological examination. In axillary lymph node dissection, level I and II lymph nodes were removed except for patients with Tis.

Results: There was no failure in local control in any patients. Distant metastasis without local failure was discovered in three patients (2.9%) during follow-up of 3.0~9.7 years (median: 5.8 years). The 8-year overall survival rate was 94.0% and the 8-year disease-free survival rate was 95.8%. At present, the reason for this low incidence of local recurrence is unclear. Although the follow-up periods have not been enough, the patient selection, the type of surgery and the use of chemohormonal therapy might provide an explanation.

Conclusion: Our analysis supports the continued use of conservative surgery with radiation therapy in the treatment of stage I and II breast cancer.

Key words: Japanese breast cancer — conservative surgery — radiotherapy — retrospective study.

During the past two decades, many retrospective studies have supported the efficacy of conservative surgery followed by radiation therapy in clinical stage I and II breast cancer.¹⁻⁷⁾ Several modern prospective randomized trials with long-term follow-up have demonstrated no adverse effect on the rates of overall survival or local control when the effectiveness of the combination of conservative surgery and radiation therapy has been compared with that of

total mastectomy.⁸⁻¹⁰⁾ This conservative therapy for breast cancer offers the additional advantage of preserving the breast, usually with highly satisfactory cosmetic results. In Europe and North America, conservative therapy has been an accepted alternative to mastectomy in early breast cancer for many years. In Japan, however, the history of conservative therapy is shorter, and the number of patients with early breast cancer treated by this therapy has been smaller.^{11,12)} This therapy is still uncommon in Japan, because physicians, especially surgeons, have several doubts about it. First, there is uncertainty that the local rates after conservative therapy may be lower, because the survival rate after mastectomy in Japan is relatively high compared with those reported in Western countries.¹³⁾ Second, the effect of radiation on intraductal carcinoma is unclear.¹⁴⁾ Lastly, there is concern regarding the possibility of unfavorable radiation effects, including radiation-induced malignancy.

We believe that the accumulation of results of this conservative therapy is important to erase these uncertainties in Japan. The purpose of this retrospective study was to evaluate the results of a combination of conservative surgery and radiation therapy.

MATERIALS AND METHODS

The subjects of this study were 105 patients (105 breasts) with early breast cancer who received conservative surgery at Kawasaki Medical School Hospital or the Center for Adult Disease in Kurashiki and subsequently were irradiated at Kawasaki Medical School Hospital between April 1987 and December 1993. The patients ranged in age from 23 to 83 years old at the time of diagnosis (median: 51.9 years old). The patients and the characteristics of the 105 breast tumors are summarized in Table 1. Clinical staging by the UICC

TABLE 1. Patients and tumor characteristics

	No.	%
Total no. patients	105	
Menopausal status		
Pre-menopausal	57	54
Post-menopausal	48	46
Clinical tumor size (cm)		
≤ 2	92	88
2.1-3.0	13	12
Surgery for primary tumor		
Lumpectomy	17	16
Quadrantectomy	88	84
Final margin assessment		
Negative	98	93
Positive	7	7
Pathologic axillary nodal status		
Negative	87	82
Positive 1-3	9	9
≥ 4	0	0
No dissection	9	9
Estrogen receptor status		
Negative	45	43
Positive	48	46
Unknown	12	11

tumor classification system (1987) indicated that six patients were stage 0 (Tis), 86 patients were stage I and 13 patients were stage II. During the total course of this study, quadrantectomy, which was the most common method of conservative therapy for breast cancer in Japan, was most commonly performed (84%).

A carcinoma-positive resection margin was recognized in seven patients on postoperative histological examination. All of them had a carcinoma-positive resection margin with intraductal spread of the ductal carcinoma at the resection margins. In axillary lymph node dissection, level I and II lymph nodes were removed. When intraoperative examination detected metastasis to these lymph nodes, dissection of level III nodes was performed. The numbers of pathologically positive axillary lymph nodes were 0 in 87 patients, and 1-3 in 9 patients. There were no patients with more than four positive nodes. Nine patients did not undergo axillary node dissection because of noninvasive ductal carcinoma, poor control of diabetes or advanced age.

Systemic adjuvant therapy was given to the majority of patients starting one to two weeks after surgery. Chemohormonal therapy with tamoxifen (TAM) alone or combined with 5-FU derivatives was given to all estrogen receptor (ER)-positive patients. Most of the ER-negative patients (39/45) were treated with 5-FU derivatives combined with cyclophosphamide or CAF (cyclophosphamide, adriamycin, 5-FU). Patients with an unknown ER status received 5-FU derivatives. Drugs were given orally for two years after the operation.

Radiation therapy consisted of 50 Gy over five weeks to the ipsilateral breast delivered via opposed tangential fields (half-field technique) using 4 MV X-rays. Boost irradiation was given to one of the seven patients with a carcinoma-positive resection margin. Since April 1993, we have given boost irradiation to all cases with a carcinoma-positive resection margin. Using high-energy electrons, a dose of 10 Gy was administered from the tumor bed to the nipple in five fractions. During the earlier part of this study external irradiation to the axillary and supraclavicular regions was used for three of nine patients in whom metastasis to the axillary nodes was found.

Follow-up examination after treatment consisted of visual examination and palpation every two weeks, the serum tumor marker test (CEA, CA15-3, TPA) every three months, a bone scan, a chest X-ray and liver ultrasonography every six months, and annual mammography for the first two years. Thereafter, patients underwent examination and palpation every two to three months. Ultrasonography was performed when a lump was palpated or when mammography revealed abnormalities.

A retrospective analysis was made in January 1997. No patient has been lost to a follow-up during periods ranging from 3.0 to 9.7 years (median: 5.8 years). The survival rates were calculated from the time of conservative surgery using the Kaplan-Meier methods.

RESULTS

In the seven patients with a carcinoma-positive resection margin, all tumors were less than 2 cm in diameter. The histological findings at the resection margin demonstrated a comedo pattern in situ in two patients and a

non-comedo pattern in situ in five patients. Neither locoregional nor distant metastasis was observed in any of them.

Of the nine patients in whom metastases to the axillary nodes were found, distant metastases to the thoracic and lumbar vertebrae were noted in one patient 11 months after surgery. The histological diagnosis was invasive ductal carcinoma (scirrhous) and no lymph-vascular invasion was demonstrated. This patient died without evidence of local recurrence.

During the follow-up period, no locoregional recurrence was observed, distant metastases developed in three patients (two to the bone and one to the brain), and death occurred in five patients (Table 2). Of the five patients who died, three died of unrelated disease (myocardial infarction, cerebral infarction and fulminant hepatitis). One patient who died of myocardial infarction had a small metastasis to the lumbar vertebrae recognized at autopsy.

TABLE 2. Clinical results

	No.	%
Locoregional recurrence		
Local	0	0
Regional lymph nodes	0	0
Distant metastasis	3*	2.9
Deceased patients		
Death due to disease	2	1.9
Unrelated death	3	2.9

* : Of the three, one patient died of myocardial infarction and bone metastases were recognized at autopsy

Table 3 shows the five-year and eight-year actual outcomes for overall survival and disease-free survival. The eight-year overall survival rate was 94.0% and the eight-year disease-free survival rate was 95.8%.

TABLE 3. Five-year and eight-year survival rates* of 105 patients

	5-year (%)	8-year (%)
Survival		
Overall	95.8	94.0
Disease-free	97.7	95.8

*Kaplan-Meier method

DISCUSSION

High rates of local tumor control with satisfactory cosmetic results following conservative surgery and radiation for early breast cancer have been reported in numerous retrospective studies from centers in Europe and North America. The incidence of local recurrence has been 4~10% at 5 years and 11~20% at 10 years.^{1-4,15-22)}

Gage, *et al*¹⁸⁾ reported on the time course, frequency and pattern of recurrences with a median follow-up of 9.7 years. In their study, the annual incidence rates of local recurrence ranged from 0.5 to 2.4% and were relatively constant after the first year, and the crude rates of distant regional nodal failure

were 16.6% and 23.1% at 5 years and 10 years, respectively. Fowble, *et al*²⁾ reported that the median interval to local recurrence was 34 months from a study of 1030 cases. In the present study, there was no failure of local control in any patients and distant metastasis without local failure was recognized in three patients (2.9%) during follow-up for 2.7~9.4 years (median: 5.5 years).

These rates appear to be lower than those of other clinical reports. Comparison of the results of retrospective studies is difficult, but there seem to be a number of reasons for our low incidence of local recurrence. The most likely explanation is patient selection. In the present study, almost all of the subjects (88%) had stage I breast cancer. Second is the type of surgery performed on the primary lesion. Almost all of our patients (84%) underwent quadrantectomy as conservative surgery, not excisional biopsy or wide excision (lumpectomy). The smaller the excisional area is, the higher is the possibility of residual tumor (especially, intraductal spread). The majority of local recurrences after conservative operative therapy occur at or near the primary tumor site.^{21,23)} Fourquet, *et al*¹⁾ reported that the most important contributors to local breast control in order of importance were age, adequacy of surgery (status of the resection margin), and endolymphatic extension. In their report, they emphasized the importance of adequate initial surgical procedures, whereas in other series there was no difference in local control between positive and negative margins when an appropriate boost dose was given.^{24,25)} In our study, there was no impact of positive margins on the local control. We also assessed the margin of resection in all cases. The status of the resection margin seems to have an influence on its biological behavior. Furthermore, assessment of the resection margin is important in evaluating the effect of irradiation against intraductal carcinoma. The third reason for our low incidence is the use of chemohormonal therapy.²⁶⁾ In the present study, systemic adjuvant chemotherapy alone or combined hormonal therapy was given to the majority of the cases according to the status of the estrogen receptor, whereas Veronesi, *et al*⁶⁾ administered systemic adjuvant chemotherapy only to patients with axillary lymph node metastasis. Fowble, *et al*¹⁷⁾ reported that the addition of adjuvant chemotherapy significantly decreased the risk of breast cancer recurrence at both 5 and 10 years. The EBCTG (Early Breast Cancer Trialists Collaborative Group) demonstrated the effectiveness of systemic adjuvant chemo-or endocrine therapy for node-negative early breast cancer in the results of an analysis of many clinical trial data.²⁷⁾ However, several authors have reported that when patients treated with and without chemotherapy have been compared, no difference in the recurrence rate in the breast has been found.^{28,29)} Recently, Goldhirsch, *et al*³⁰⁾ reported on some areas of ongoing research and treatment strategies in the commentary of the Fifth International Conference on Adjuvant Therapy of Primary Breast Cancer. In this commentary, they displayed the risk categories for patients with lymph node-negative breast cancer, and noted that for patients considered at high risk, the treatment choice followed an algorithm similar to that for patients with lymph node-positive disease. They indicated that chemotherapy had been used for those high-risk, lymph node-negative patients in clinical trials, and that for patients with minimal-risk or low-risk disease, the question of whether or not to use chemohormonal therapy depended on a cost-benefit analysis. In Japan, Hiraoka *et al*¹¹⁾ treated 198 patients with stage I and II breast cancer and reported

that local recurrence (0.5%) was noted in one patients, a 24-year-old woman with stage II breast cancer (median follow-up duration 35 months). Their recurrence rate was similar to ours. They listed the biological characteristics of Japanese breast cancer, the use of combined chemohormonal therapy, and sophisticated radiation treatment planning using a CT simulator as the potential reasons for their low incidence of local recurrence.

In our previous study, we analyzed acute and late complications of this conservative therapy with irradiation for breast cancer and suggested that there were few severe complications, such as skin-soft tissue reaction and radiation pneumonitis-fibrosis.³¹⁾ The risk of contralateral breast cancer is not greater than that observed following primary radical surgery without radiation therapy.³²⁾

The present study demonstrated that excellent locoregional control of breast cancer could be achieved by conservative surgery with radiation therapy. None of our patients developed local recurrence in the follow-up period of 3.0-9.7 years. Although a longer follow-up is necessary before any definite conclusion can be made, we emphasize the importance of the combination of surgery, irradiation and chemohormonal therapy.

Our analysis supports the continued use of breast conservative surgery with radiation therapy in the treatment of stage I and II breast cancer. In addition, we should study ways to detect those who will not require postoperative irradiation or systemic adjuvant chemohormonal therapy in order to prevent the growth of radiation or chemohormonal therapy-induced secondary malignancy.

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