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Five-Year Results of a Randomized Clinical Trial Comparing Modified Radical Mastectomy and Extended Radical Mastectomy for Stage II Breast Cancer

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Abstract: A controlled cooperative study was carried out to assess the value of modified radical mastectomy for patients with stage II breast cancer. The data was analyzed from 11 institutions in the Shikoku District participating in a prospective clinical trial in which patients were randomly assigned either to a modified radical mastectomy group or an extended radical mastectomy group. These two groups of patients were similar to each other in terms of such background factors as age distribution, menopausal status, TNM classification, tumor size, location of the primary tumor, axillary nodal involvement, histological type, and estrogen receptor status. The median follow-up times in the modified and extended radical mastectomy groups were 4.7 and 4.5 years, respectively. The cumulative curves indicated no difference between the two groups in either disease-free survival or overall survival. The survival rates were classified according to the presence or absence of axillary nodal metastases. However, no significant difference was found between the two groups. These findings thus suggest that the routine removal of the grossly uninvolved major pectoral muscle and parasternal lymph nodes is not necessary in patients with stage II breast cancer.

Key Words: Breast cancer, stage II, randomized study, modified radical mastectomy, extended radical mastectomy

Introduction

With the recent increasing awareness of the potential of minor surgery for breast cancer, modified radical mastectomy and breast-conserving treatment have been employed for early-stage breast cancer in Japan. This trend has been based on the results of randomized clinical trials conducted in both Europe and the United States.[1] In Japan, no prospective randomized study has yet dealt with the surgical procedures for breast cancer, and hence there has previously been no available data. We, therefore, carried out a cooperative prospective study to compare modified radical mastectomy, involving major pectoral muscle conservation, with an extended radical mastectomy, involving parasternal lymph node dissection for stage II breast cancer.

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Patients and Methods

Eleven institutions in the four prefectures of the Shikoku District in Japan participated in this study from 1986 through 1989. Patients were selected from those who met the following criteria: Patients with primary breast cancer of stage II, no more than 75 years of age, expected to receive no postoperative radiation or oophorectomy, no history of treatment for cancer, and who had confirmed laboratory results of red blood cell $\geq 3{,}000/mm^2$, platelet $\geq 70{,}000/mm^2$, serum protein $\geq 6.0\,g/dl$, and urinary protein (−). Patients with bilateral cancer, inflammatory cancer, double cancer, non-invasive cancer, breast cancer during pregnancy or lactation, and male breast cancer were excluded from the study.

Prior to operation, the patients were randomly allocated, by the envelope method, to a modified radical mastectomy group (group A) or an extended radical mastectomy group (group B). Informed consent was obtained from eligible patients before assignment to treatment. The modified radical mastectomy consisted

of a complete removal of the breast, minor pectoral muscle and axillary contents en bloc. The extended radical mastectomy was performed in the same manner at all institutions, using the classic Halsted mastectomy plus parasternal dissection which included the removal of the parasternal lymph nodes, the internal thoracic vessels and adjoining costal cartilages of ribs 2–4. A postoperative adjuvant therapy regimen of mitomycin C (MMC), 5-fluorouracil (5-FU) and tamoxifen (TAM) was administered to all patients in both groups. MMC was given intravenously at a dose of 13 mg/m^2 on the day of operation. Two hundred mg/day of 5-FU and 20 mg/day of TAM were administered orally for 1 year beginning 2 weeks after the operation.

Of the 207 patients enrolled in this study, 103 patients were allocated to group A and 104 to group B. Among them, 4 patients turned out to have no cancer and became ineligible, while 11 dropped out during the study because of treatment failure or patient refusal. Consequently, a total of 192 patients with stage II breast cancer (4T1N1b, 67T2N0, 82T2N1a, 39T2N1b), 96 in each group, were identified as eligible for this study.

The stage classification and histological type of each case were based on The General Rules for Clinical and Pathological Recording of Breast Cancer, established by the Japanese Breast Cancer Society.[2] The postoperative cumulative disease-free survival and overall survival rates were calculated using the Kaplan-Meier method. A statistical analysis of the data was performed using the chi-square test, the analysis of variance, and the generalized Wilcoxon test.

Results

No significant differences were found between the two groups in relation to such background factors as age distribution, menopausal status, tumor size, location of the primary tumor, TNM classification, axillary nodal involvement, histological type, or estrogen receptor status (Table 1). The median follow-up times in groups A and B were 4.7 and 4.5 years, respectively. The number of dissected axillary lymph nodes in groups A and B were 18.2 ± 5.9 and 19.0 ± 5.9, respectively, which showed no significant difference. In the 96 group B patients treated by extended mastectomy, the number of dissected parasternal nodes was 2.9 ± 1.4, and the incidence of histologically proven parasternal node metastases was 9.4%. In this series, 10.6% (5 of 47) of the patients with a primary tumor located in the medial or central quadrants had positive parasternal nodes, whereas the same finding was observed in only 8.2% (4 of 49) of those with primary cancer located in the lateral quadrants (Table 2).

Table 1. Characteristics of 192 patients enrolled in the study

	Group A (n = 96)	Group B (n = 96)	
Age at operation (mean, years)	52.7	52.3	N.S.
Menopausal status			
Premenopausal	46	39	
Postmenopausal	50	57	N.S.
Location of primary tumor			
Medial, Central	39	47	
Lateral	57	49	N.S.
T T1a	0	3	
T1b	0	1	
T2a	92	83	
T2b	4	9	N.S.
N N0	36	31	
N1a	45	37	
N1b	15	28	N.S.
Axillary involvement			
Not involved	54	45	
Involved	42	51	N.S.
Histological type			
Pap. tub. ca.	18	19	
Solid. tub. ca.	36	25	
Scirrhous ca.	38	38	
Other	4	14	N.S.
Estrogen receptor			
Positive	57	52	
Negative	39	43	N.S.

N.S., Not significant; *Pap. tub. ca.*, papillotubular carcinoma; *Solid. tub. ca.*, solid-tubular carcinoma

Table 2. Positive parasternal nodes in patients with extended radical mastectomy

Location of primary tumor	Total		A.N. (+)		A.N. (−)	
	No.	%	No.	%	No.	%
Medial, central	5/47	10.6	5/20	25	0/27	0
Lateral	4/49	8.2	4/31	12.9	0/18	0
Total	9/96	9.4	9/51	17.6	0/45	0

A.N., Axillary nodes

After the first operation, relapse occurred in 15 group A patients and 17 group B patients. No significant difference was observed in the site of recurrence between the two groups. Regarding local regional recurrences, Table 3 show that there was no difference in the percent of relapse in the operative field, the homolateral axilla, or in the supraclavicular region. In addition, no parasternal relapse was observed in either Group.

The 5-year disease-free survival rates for groups A and B were 87.2% and 82.7%, respectively, and the difference was not significant (Fig. 1). Furthermore, the patients were classified for further assessment based on the presence or absence of axillary nodal metastases.

Table 3. First recurrent sites related to the type of treatment. Numbers in parentheses indicate deceased patients

Site of relapse	Group A (n = 96)	Group B (n = 96)
Operative field	2 (1)	2 (1)
Regional lymph node		
Axillary node	1 (1)	0
Supraclavicular node	4	2 (1)
Parasternal node	0	0
Distant metastases		
Lung, pleura	1 (1)	4 (1)
Bone	4 (1)	4
Liver	3 (1)	4 (4)
Other	0	1
Total	15 (5)	17 (7)

Comparison of the 5-year disease-free survival rates in the patients with involved nodes showed no significant difference between the two groups: 75.6% in group A and 73.3% in group B (Fig. 2).

The 5-year overall survival rates for groups A and B were 93.2% and 92.4%, respectively. The two groups were also comparable to each other in overall survival (Fig. 3). Figure 4 shows the classification between the patients based on the presence or absence of axillary nodal involvement. The 5-year overall survival rates for groups A and B for the patients with involved nodes were 84.4% and 87.8%, respectively, with no significant difference.

The adverse effects of the postoperative adjuvant therapy employed in this study were recognized in 65 cases, or 33.9% of all the patients. The major adverse effects included mild and transient alimentary symptoms such as anorexia, nausea, and vomiting. However, these adverse effects did not generally pose a serious problem, and continued therapy was feasible in all cases after suspension of the drugs until the symptoms cleared up.

Discussion

Donegan[1] summarized the results of randomized clinical trials in Europe and the United States as follows. The routine removal of grossly uninvolved pectoral muscles is not necessary in cases of early-stage breast cancer. Prophylactic regional node dissection, such as axillary and parasterenal lymph nodes, is useful for reducing regional tumor recurrence, providing prognostic information, and establishing the need for adjuvant treatment, but does not improve overall survival. Metastasis to regional lymph nodes appears to be a sign, rather than a source, of tumor dissemination. The difference in surgical procedures would not affect the postoperative survival of patients with breast cancer. Therefore, modified radical mastectomy (total mastectomy plus axillary dissection) has replaced radical mastectomy as the standard precedure for cases of TNM clinical stages I and II. In addition, since much importance has been placed on the maintenance of an acceptable quality of life for patients, there is now an ever-increasing tendency to perform minor surgery for breast cancer.

In recent years, modified radical mastectomy has been commonly used in Japan due to the trends in Europe and the United States. Furthermore, breast-conserving surgery has also been recently attempted. It is generally known that there are some differences in breast cancer development between Japan and both Europe and the United States.[3] In Japan, there have been no randomized clinical trials comparing the various kinds of surgical procedures. The present study, which compared modified radical mastectomy and extended radical mastectomy, was thus designed to assess the influence of the different surgical methods on the survival of patients with breast cancer of stage II. The necessity of routine removal of the major pectoral muscle and parasternal node dissection were evaluated.

In this study, a comparison of the number of dissected axillary lymph nodes showed no significant difference between the two groups. Furthermore, there was no difference in the incidence of relapse in the operative field, interpectoral region, or the ipsilateral axilla. These findings suggest that the routine removal of the grossly uninvolved major pectoral muscle is not necessary in patients with stage II breast cancer. the incidence of histologically proven parasternal node metastases was 9.4% in the patients who received parasternal dissection. However, no parasternal relapse was present in the patients treated by modified radical mastectomy. Veronesi et al.[4,5] also reported that parasternal recurrence occurred in only 3.7% of the patients treated by radical mastectomy, whereas the incidence of parasternal nodal metastasis was 20.5% in the patients treated by extended radical mastectomy, and that parasternal node dissection was ineffective. Thus, the incidence of parasternal recurrence after mastectomy was surprisingly low, and the hypothesis that microscopic metastasis in the parasternal nodes may remain silent for a very long time cannot be ruled out.

A similar phenomenon was also observed in axillary lymph node dissection in NSABP protocol No. 4,[6,7] that is, a radical mastectomy versus a total mastectomy with or without postoperative axillary radiation. When a radical mastectomy was performed on patients with clinically negative axillary nodes, 40% of them turned out to be histologically positive. On the other hand, only 15% of the patients undergoing total mastectomy without removal of the histologically positive nodes developed positive nodes requiring axillary dissection. Furthermore, Fisher et al.[7] reported that there was no significant difference in the 10-year survival rates

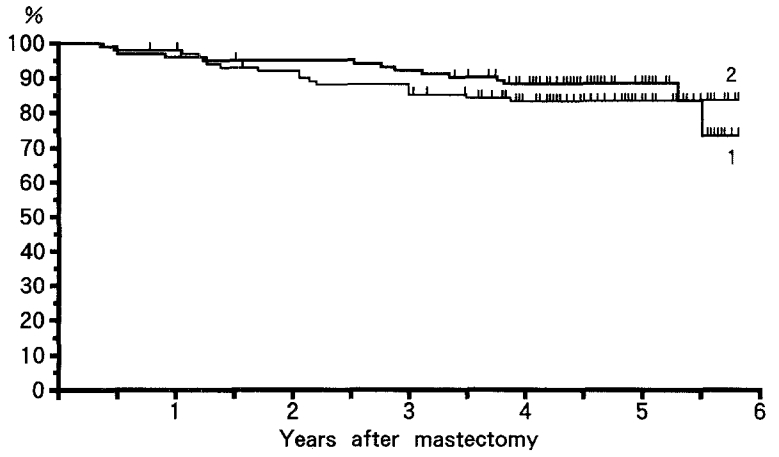

Fig. 1. Disease-free survival curves for all patients. *1*, Group A (modified radical mastectomy, $n = 96$); *2*, group B (extended radical mastectomy, $n = 96$)

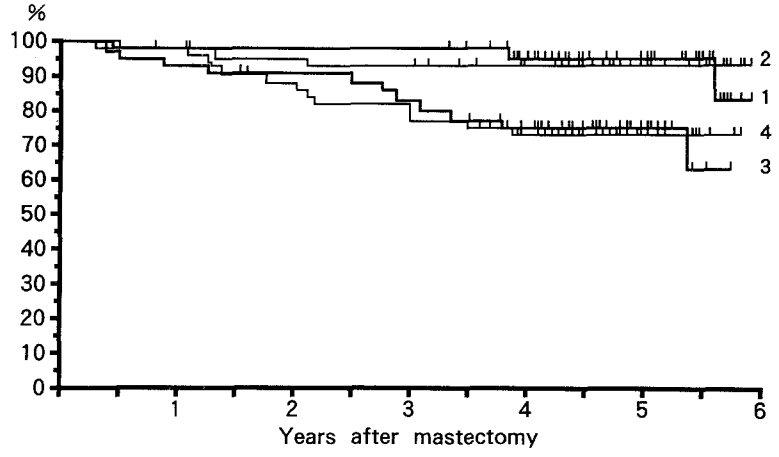

Fig. 2. Disease-free survival curves for patients according to nodal involvement. *1*, Group A patients without node metastases (modified radical mastectomy, $n = 54$); *2*, group B patients without node matastases (extended radical mastectomy, $n = 45$); *3*, group A patients with node metastases (modified radical mastectomy, $n = 42$); *4*, group B patients with node matastases (extended radical mastectomy, $n = 51$)

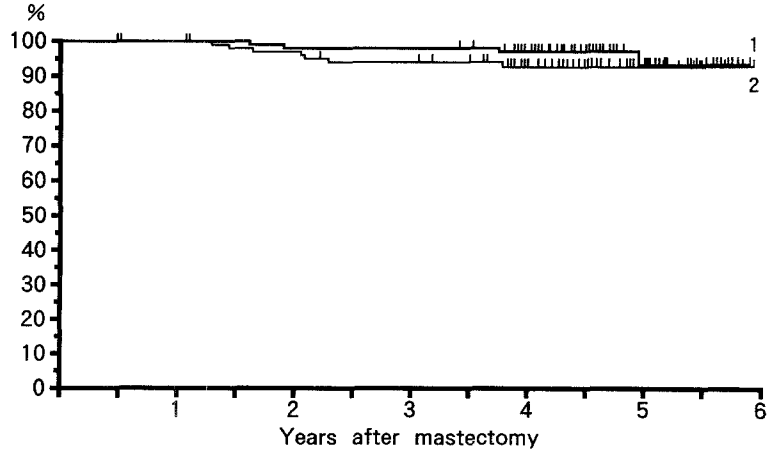

Fig. 3. Survival curves for all patients. *1*, Group A (modified radical mastectomy, $n = 96$); *2*, group B (extended radical mastectomy, $n = 96$)

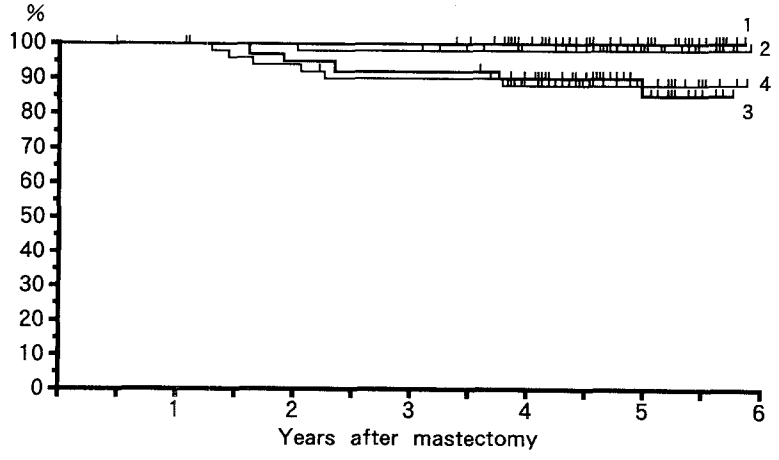

Fig. 4. Survival curves for patients according to nodal involvement. *1*, Group A patients without node matastases (modified radical mastectomy, $n = 54$); *2*, group B patients without node matastases (extended radical mastectomy, $n = 45$); *3*, group A patients with node metastases (modified radical mastectomy, $n = 42$); *4*, group B patients with node matastases (extended radical mastectomy, $n = 51$)

among these three therapeutic groups, and concluded that axillary dissection does not alter the incidence of systemic recurrence or patient survival. They further contended that the positive axillary lymph nodes are not a source of distant tumor metastasis, but rather are a manifestation of disseminated disease. Therefore, a variation in the local and regional treatments does not alter the survival of patients with breast cancer.

In this study, no significant difference was observed in the disease-free survival or overall survival rates between the modified radical mastectomy and extended radical mastectomy groups. These findings are in agreement with the results of the randomized clinical trials conducted in Europe and the United States. We thus conclude that the routine removal of the grossly uninvolved major pectoral muscle and prophylactic parasternal node dissection are unnecessary in mastectomy for patients with stage II breast cancer.

The efficacy of parasternal dissection in patients with medial or central breast cancers is still controversial in the literature. Lacour et al.[8,9] observed that an extended radical mastectomy significantly decreased the risk of death in patients with sternal or medial tumors and positive axillary nodes. On the other hand, Veronesi et al.[4,5] concluded that parasternal node dissection was ineffective, and that information on the presence or absence of parasternal nodal metastasis would be of great importance in formulating the prognosis of breast cancer patients. Therefore, to draw a conclusion about the usefulness of parasternal dissection for patients with medial or central tumors in Japan, it is necessary to more fully investigate the outcome of clinical trials involving cases of medial or central tumors.

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