A Randomized Prospective Trial of Radical (Halsted) Mastectomy Versus *Modified Radical Mastectomy in 311 Breast Cancer Patients*

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This study reports the results of a prospectively randomized trial for treatment of carcinoma of the breast comparing standard (Halsted) radical mastectomy to a modified radical mastectomy. Three hundred eleven patients with primary operable carcinoma of the breast were entered in a surgical and adjunctive chemotherapy trial in Alabama between 1975 and 1978. A total of 91 surgeons participated (all Diplomats of the American Board of Surgery and Members of the American College of Surgeons). All operative reports, pathology and therapy were reviewed by referees. Histologically node positive patients were randomized after operation to receive melphalan or C.M.F. (cytoxan, methotrexate, and 5-FU) for 1 year. After a median follow-up of 5.5 years, there was no significant difference in disease-free survival or in overall survival between the two groups. There was a trend toward improved 5-year survival rates in the radical mastectomy group compared to the modified radical mastectomy group (84% *vs.* 76%, p = 0.14). There was also an increased incidence of local wound recurrence in those patients receiving modified radical mastectomy, but the differences were not statistically significant (p = 0.09). Longer follow-up will be necessary to evaluate these results more fully.

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IN THE 1880s, Dr. William S. Halsted was confronted with patients having extremely large breast cancers that were often fixed to the chest wall. Bulky metastases to the axilla and supraclavicular nodes were also common. To provide effective local disease control, Dr. Halsted devised an operation to remove the entire breast and underlying pectoralis muscles and the axillary lymph nodes. His reported results showed that the local recurrence rate was reduced from greater than 50% in most previous series to 6% in Dr. Halsted's series.[1] Only later did he demonstrate improved survival rates as well.

The radical mastectomy became the standard surgical treatment for comparison with all subsequently described operations for carcinoma of the breast. However, the presenting stage of disease has changed considerably during the past 100 years since Dr. Halsted first described this operation. The average size of a breast cancer, when discovered, has decreased steadily to its current level of about 2 cm in diameter, and it is relatively infrequent that patients present with clinically palpable axillary metastases. As a result of this change, surgeons have explored alternatives to the radical mastectomy during recent decades. The modified radical mastectomy was popularized by Auchincloss, Patey, and others in the 1950s and has been employed increasingly. In fact, a patterns-of-care study conducted by the Commission on Cancer of the American College of Surgeons has shown considerable decline in the use of radical mastectomy during the past decade with a commensurate increase in the use of the modified radical mastectomy.[2] The change in the surgical treatment of primary breast cancer was supported by its advocates who showed similar results compared to radical mastectomy in several retrospective studies comparing the use of the two procedures in the same institution.[3–7] In fact, only one previous randomized prospective clinical trial by Turner et al.[8] has been reported to provide a scientific basis for this shift in the treatment philosophy of primary breast cancer.

In the early 1970s, half or more of the surgeons in the state of Alabama were performing a radical mastectomy for patients with primary operable breast cancer.[9] The other surgeons primarily utilized a modified radical mastectomy, while a few recommended simple mastectomy. In the absence of any clear consensus about the appropriate standard for surgical treatment of primary

Supported by grant from the National Institutes of Health (NOI-CN-45129).

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Submitted for publication: January 26, 1983.

0003-4932/83/0800/0207 $01.10

breast cancer, a cancer control network demonstration project was initiated. This proposal was approved and supported by the Alabama Chapter of the American College of Surgeons. The Alabama Breast Cancer Project evolved from these efforts with a primary goal of conducting a prospective randomized trial to compare alternative forms of surgical treatment and adjuvant chemotherapy. Thus, patients with operable breast cancer were pre-randomized to receive either a radical mastectomy or a modified radical mastectomy. Those patients with histologically positive metastatic axillary lymph nodes were randomized further to receive one of two forms of adjuvant chemotherapy (cytoxan, methotrexate and 5-FU *vs.* melphalan). There were 311 patients entered into the surgical aspect of this trial from 1975 to 1978. The preliminary results are the subject of this report. An additional 171 patients were entered into the chemotherapy trial. The results of the chemotherapy trials have been published elsewhere.[10]

Materials and Methods

Study Design

A detailed description of this study has been published.[9,11] Patients who volunteered to participate in the Alabama Breast Cancer Project were randomized to receive either a classic radical mastectomy or a modified radical mastectomy. The randomization was determined by the year of the patient's birth. Patients with an even year of birth underwent a radical mastectomy, while patients who were born in an odd-numbered year were randomized to receive a modified radical mastectomy.

Patients with histologically positive axillary lymph nodes were randomized further to receive postoperative adjuvant chemotherapy. Patients whose birthday fell on an even numbered month received oral melphalan (L-PAM), while those patients born in an odd numbered month received an intravenous chemotherapy combination of cyclophosphamide, methotrexate, and 5-flourouracil (CMF).

Patient Eligibility

Female patients with histologically documented duct or lobular carcinoma of the breast were eligible to participate in this study. The international classification for staging (UICC) was used. All T1, T2, T3a, N1a, N1b patients were eligible for this study. Categories TIS, T0, T1b, T2b, T3b, N2, N3, and M1 were excluded. In addition, Paget's disease of the nipple without a palpable mass and primary breast cancers less than 0.5 cm in diameter were excluded. No patients older than 70 years were included.

Preoperative Assessment

The preoperative workup included a careful history and physical examination, chest x-ray, complete blood count, liver function studies, and x-rays of any bone suspicious for metastatic involvement. Optional parameters included mammography of the opposite breast and bone scans.

Surgical Technique and Quality Control

The operative procedures were detailed in a series of monographs that were published in the Alabama State Medical Journal and distributed to all participating surgeons.[9,11] The radical mastectomy included both the pectoralis muscles and the axillary contents using the techniques described by Hagansen,[12] Zollinger and Cutler,[13] and by others. The modified radical mastectomy preserved both pectoralis muscles using the technique described by Madden[14] and others.

There were 91 surgeons who participated in this study. To be eligible, the surgeon had to be certified by the American Board of Surgery and a member of the Alabama Chapter of the American College of Surgeons. Qualifications of each participating surgeon were examined and approved by a 19-member Quality Control Advisory Committee of the Alabama Breast Cancer Project.

Pathology

The pathologic diagnosis was first established at each hospital where the patient was treated. Representative slides were then reviewed by one pathologist (Dr. Tariq Murad) at the University of Alabama in Birmingham (UAB). If there was any discrepancy in the pathologic interpretation of the slide, it was sent automatically to a pathologic referee (Dr. Paul Peter Rosen at the Memorial Sloan-Kettering Center in New York City). Axillary lymph nodes were examined by each pathologist for the presence or absence of nodal metastases. Hormone receptor assays were not performed.

Chemotherapy

Patients with histologically positive axillary lymph nodes and no evidence of distant metastases were randomized to receive adjuvant chemotherapy for approximately 1 year, as previously described. Chemotherapy was initiated as soon as feasible, usually within 14 to 21 days after surgery. Patients who randomized to receive L-PAM (melphalan) received 7 mg/M^2 orally per day for 5 days (maximum of 70 mg). This was repeated at 6-week cycles for eight courses. Patients randomized to CMF received pulse intravenous doses of cyclophosphamide (300 mg/M^2), methotrexate (30 mg), and 5-

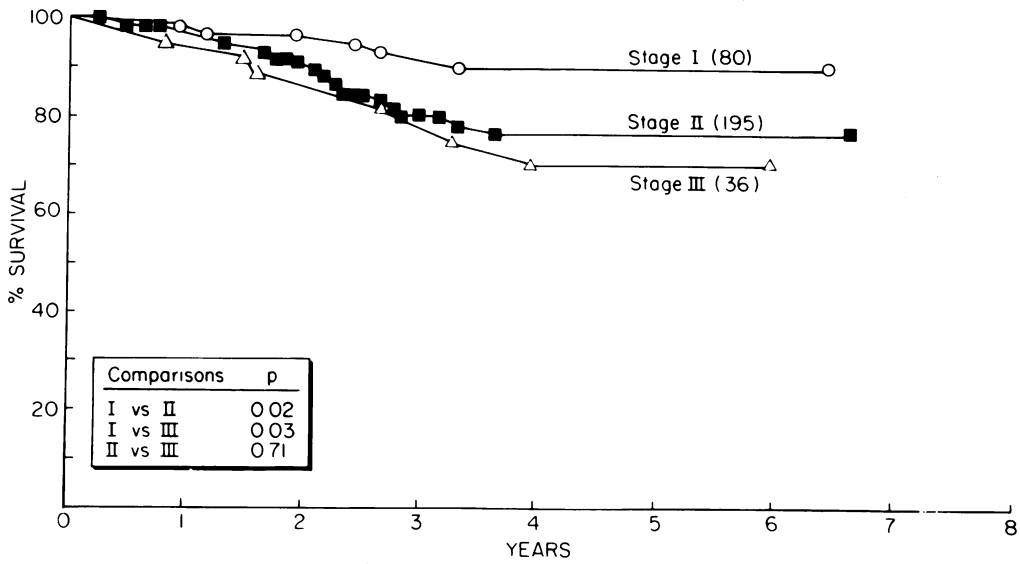

FIG. 1. Overall survival by pathologic stage of disease for all 311 surgical patients expressed in years since mastectomy. The number of patients in each group is shown in parentheses.

flourouracil (300 mg/M^2). These drugs were administered in 2-week cycles for a total of 24 courses. Prior to each drug cycle, the patient's granulocyte count, platelet count, and weight were recorded. Signs or symptoms of gastrointestinal, respiratory, or infectious complications also were recorded if present. If the total white blood cell count was less than 4,000/mm^3 or the platelet count was less than 150,000/mm^3, the treatment was delayed for an additional 2 weeks or longer until the marrow reserves were adequate. The drug dose was then decreased after consultation with the project medical oncologist (J.T.C.).

Statistical Methods

Chi-square tests were used to test the comparability of two surgical treatment groups with respect to race, age, menopausal status, clinical stage, pathologic stage, number of positive nodes, and chemotherapy. Survival curves were calculated based on the method of Kaplan and Meier, and the log rank test was used to determine if significant differences existed between curves. A proportional hazard regression model, proposed by Cox, was utilized to compare two surgical procedures with proper adjustments for patients' characteristics in the two treatment groups.

Results

Patient Characteristics

A total of 311 patients with documented duct or lobular carcinomas of the breast were entered into the surgical arm of the trial between January 1975 and December 1978. All patients received adjuvant chemotherapy if they had histologically positive nodal metastases. The patients were accessioned into the study by 91 participating surgeons from throughout the state of Alabama. Only 15% of the patients were entered from the UAB Medical Center. Twenty-six surgeons (29%) entered one patient each, 39 surgeons (43%) entered two to five patients, ten (11%) entered from six to ten patients, seven (7%) entered from 11 to 20 patients, seven (8%) entered from 21 to 29 patients, one (1%) entered 36 patients, and one (1%) entered 70 patients.

The median age was 54 years; 30.5% of the patients were premenopausal. There was a family history of breast cancer in 18% of the patients. The breast cancer was located most commonly in the upper outer quadrant (45%) and in the lower outer quadrant (11%). The survival curves of patients subgrouped by stage of disease are shown in figure 1.

There were 136 women who received a radical mastectomy and 175 women who received a modified radical mastectomy. A comparison of these two treatment arms, subdivided by major prognostic factors, is shown in Table 1. The two treatment arms are well matched, with no significant differences between the two treatment arms when patients were subdivided by race, age, menopausal status, clinical stage, number of nodes involved, type of chemotherapy employed, or pathologic stage.

There were 501 histologic diagnoses of breast cancer reviewed for this study—311 patients in the surgical study plus 190 patients in a parallel study of breast cancer chemotherapy whose surgical treatment was not randomized. In 93% of patients, the UAB pathologist agreed with the original diagnosis made at the community hospital. In 34 patients, the UAB pathologist disagreed with the original histologic diagnosis, and the slides were sent to the outside pathologic referee. In 18 patients, the ex-

TABLE 1. *Characteristics of Patients*

	Modified Radical Mastectomy	Radical Mastectomy	p Value
Number of patients	175 (56%)	136 (44%)	
Race			
Black	22%	21%	0.66
White	77%	79%	
Other	1%	0%	
Age			
<50	40%	36%	0.42
>50	60%	64%	
Menopausal			
Pre-	35%	30%	0.39
Post-	65%	70%	
Clinical stage			
0	2%	1%	0.90
I	32%	34%	
II	57%	56%	
III	9%	9%	
Pathologic stage			
I	25%	27%	0.87
II	64%	61%	
III	11%	12%	
Nodes involved			
0	55%	57%	0.72
1-3	26%	27%	
>4	18%	16%	
Unknown	1%	0%	
Chemotherapy			
None	57%	57%	0.29
CMF	14%	13%	
MPL	20%	24%	
Switched	1%	2%	
Other	8%	2%	

tramural pathologist agreed with the UAB pathologist, while in 14 patients, he agreed with the original pathologist. In two instances, the extramural pathologist disagreed with both the UAB and the community pathologist. One patient had a diagnosis of cancer made by the original pathologist, but both referees considered the diagnosis to be duct hyperplasia. This patient was not included further in the surgical trial.

Survival Rates

The median duration of follow-up for all patients was 65 months. The disease-free survival curves calculated up to 7 years showed no statistically significant difference between the two surgical treatment arms (Fig. 2). There was a trend for the patients undergoing radical mastectomy to have a better disease-free interval than those who underwent modified radical mastectomy ($p = 0.10$). The number of relapses that have occurred so far was greater for the modified radical mastectomy group (33% *vs.* 24%), but these differences were also not statistically significant.

When comparing overall survival rates, there was again a trend for patients with a radical mastectomy to have a slightly better survival, but these results were also not statistically significant either before or after adjustments for major prognostic factors shown in Table 1 ($p = 0.15$ and $p = 0.20$, respectively). The 5-year survival rate is slightly lower for the modified radical mastectomy group (76% *vs.* 84%) (Fig. 3).

Local Recurrence Rates

Local recurrence was defined as recurrence in the dissected wound of chest wall or axilla. There have been 16 local recurrences in patients undergoing modified radical mastectomy and six patients with local recurrence in the radical mastectomy group. The 3-year recurrence rate was 10% for the modified radical mastectomy group and 3% for the radical mastectomy group

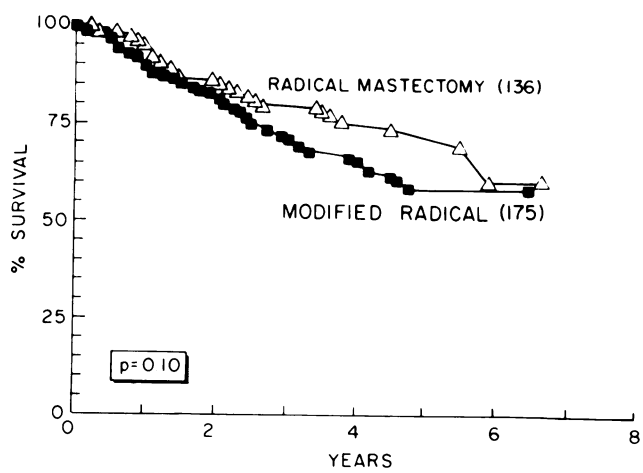

FIG. 2. Disease-free survival comparing radical *vs.* modified radical mastectomy. The differences were not statistically significant. The number of patients is shown in parentheses.

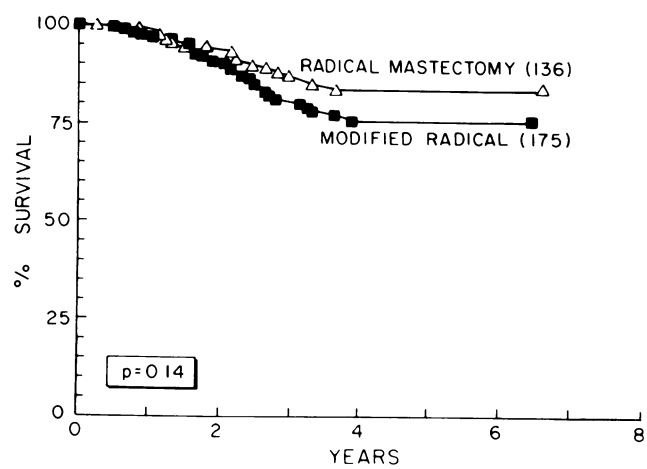

FIG. 3. Overall survival comparing radical *vs.* modified radical mastectomy.

(Fig. 4). Although the local recurrence rate was higher in the modified radical mastectomy group, there was no statistically significant difference in survival between the two treatment groups after adjustments for major prognostic factors (p = 0.09). The recurrence pattern and stage of disease are shown in Table 2. There were a total of 22 patients with local recurrence (with or without other metstases). Sixty-eight per cent of these local recurrences occurred in patients with stage II or stage III disease. Although the sample size for the stage III patients was small (36 patients), the local recurrence rate was the highest for the modified radical group compared to the radical mastectomy group (20% *vs.* 6.3%). The differences were not statistically significant. Almost all local recurrences occurred within the first 3 years after operation.

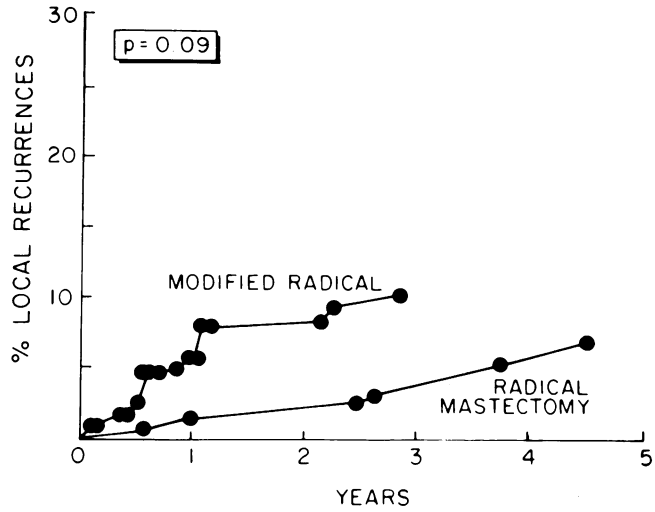

FIG. 4. Local recurrence rates expressed as a percentage of all patients undergoing mastectomy. There was a trend for increased local recurrences in the modified radical mastectomy group (p = 0.09).

Discussion

The results of this prospective randomized trial demonstrated no significant differences in overall survival rates or disease-free survival rates in patients having a Halsted radical mastectomy compared to those having a modified radical mastectomy. There was a trend for increased survival rates for those patients undergoing a radical mastectomy, but it was not statistically significant. In addition, there was a slightly higher local recurrence rate for patients undergoing modified radical mastectomy, especially for stage III disease. The median duration of follow-up in these patients is only 5½ years, and longer follow-up will be necessary to determine whether the present results will hold true. These results are virtually the same as reported by Turner et al.,[8] who reported a randomized prospective trial in England involving 534 patients who underwent a radical or modified radical mastectomy. There was no difference in total survival and disease-free survival. However, there was a trend for improved survival for the radical mastectomy group at 5 years (85% *vs.* 78%).

These two trials are the only prospective and randomized comparison of the standard radical mastectomy *vs.* modified radical mastectomy. An international cooperative group has conducted a randomized trial comparing conventional Halsted mastectomy with the extended radical mastectomy (*i.e.*, with internal mammary node dissection).[15,16] There were 176 evaluable patients who were followed for a median of 10 years after operation. In no subgroups was a statistically significant difference found between these two operative procedures. Fisher et al.,[17] in the National Surgical Adjuvant Breast Project, have also conducted several randomized clinical trials comparing total mastectomy alone *vs.* radical mastectomy. Radiation therapy to the lymphoid tissue was also given in combination with surgery in some treatment arms. No difference in overall survival rate has been demonstrated in these studies so far. Veronesi et al.[18] have reported preliminary results of a randomized prospective study comparing quadrant mastectomy, axillary node dissection, and breast irradiation with radical mastectomy. The study involved 700 women with $T_1N_0M_0$ breast cancers (*i.e.*, <2 cm in

TABLE 2. *Local Recurrence*

	Type of Surgery and Stage						
	Modified Radical Mastectomy			Radical Mastectomy			
	1	2	3	1	2	3	Total
Number of patients	43 (13.8%)	112 (36.0%)	20 (6.4%)	37 (11.9%)	83 (26.7%)	16 (5.1%)	311 (100%)
Number of local recurrences	4 (9.3%)	8 (7.1%)	4 (20.0%)	2 (5.4%)	3 (3.6%)	1 (6.3%)	22 (7.1%)

diameter). Their results have not shown any differences in relapse rate or survival rates calculated up to 7 years after surgery.

The pathology review process in the Alabama Breast Cancer Project demonstrated remarkable concurrence of diagnosis between the community pathologists and referees. Only one patient of the 501 reviewed had a mastectomy for a cancer diagnosis in which both referees interpreted the histology as duct hyperplasia.

The randomized procedure used in this study was a pre-randomization procedure, since the surgeons knew the treatment arm at the time of discussing the protocol with the patient. This method was chosen to maximize patient entry into the protocol. It is unlikely that this clinical trial would have been completed with traditional randomization procedures.

The surgical management of primary breast carcinoma is still in an evolving state. There are three goals of the operation (*i.e.*, cure, local disease control, and staging) and three components of the disease that require treatment (*i.e.*, the primary tumor itself, multifocal carcinoma, and axillary nodal metastases). The design of present and future clinical trials involving primary breast carcinoma must incorporate these goals and components of the disease. For example, axillary nodal metastases might be treated effectively by irradiation therapy, but this treatment approach does not permit staging of nodal metastases so that appropriate decisions can be made regarding adjuvant systemic chemotherapy. A node sampling procedure of the lower axillary nodes (level I) probably underestimates the incidence of nodal metastases by 10% or more.[19,20] A complete axillary lymph node dissection, therefore, is necessary for staging purposes, regardless of the treatment of the breast itself. Whether or not a total mastectomy, primary radiation, or observation is optimal treatment for multifocal breast carcinoma is still the subject of a continuing debate, for which several clinical trials are ongoing.

The results of the present trial so far indicate that there is little, if any, significant difference in the outcome of patients undergoing Halsted radical mastectomy compared to a modified radical mastectomy. These results should be regarded as preliminary. This trial demonstrates that physicians in the community can participate in a clinical research trial with excellent compliance and quality control.

Acknowledgments

The authors thank Ms. Joanie Pigford and Ms. Diane Richards for their valuable assistance.

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