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Effectiveness of Mastectomy by Response to Induction Chemotherapy for Control in Inflammatory Breast Carcinoma

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Background: Controversy exists as to the treatment regimen necessary to best provide optimal local control for inflammatory breast carcinoma (IBC). This study was conducted to determine if mastectomy combined with radiotherapy offered any advantages over radiotherapy alone in patients with IBC who had been treated with doxorubicin-based combination chemotherapy.

Methods: A retrospective review of 178 women treated for IBC on doxorubicin-based multimodality therapy protocols between January 1974 and September 1993 was performed. Clinical and histologic response to treatment, time to local recurrence, survival, and ultimate control of local disease were analyzed. Kaplan-Meier analysis was used to examine survival and relapse times, and Fisher's exact test was used to test differences in treatment outcomes. Significance was determined at $p \leq 0.05$.

Results: Median follow-up was 89 months (range 22 to 223 months). Locoregional disease persisted in seven patients and recurred in 44 patients who had been rendered disease free at a median time of 10 months. The mortality rate after a local recurrence (LR) was 98%, and all patients but one with LR developed systemic metastases. Response to induction chemotherapy influenced the incidence of LR, and the amount of residual disease found on histologic examination of mastectomy specimens was highly prognostic for local failure. Patients who underwent mastectomy in addition to radiotherapy had a lower incidence of LR than did patients who received radiotherapy alone (16.3% vs. 35.7%, $p = 0.015$).

Conclusions: The addition of mastectomy to combination chemotherapy plus radiotherapy improved local control in patients with IBC. The addition of mastectomy to chemotherapy plus radiotherapy improved distant disease-free and overall survival in patients with a clinical complete or partial response to induction chemotherapy. Patients who had no significant response to induction chemotherapy received no survival or local disease-control benefit from the addition of mastectomy to their treatment regimen. These patients should be considered for entry into clinical trials of new treatment regimens.

Key Words: Inflammatory breast carcinoma—Local recurrence—Chemotherapy—Mastectomy—Radiotherapy.

Inflammatory breast cancer (IBC) is the most aggressive form of locally advanced breast cancer. The first description of the disease is attributed to Sir Charles Bell in the early 19th century (1). However, it was not until 1924 that Lee and Tannenbaum provided a clear clinical definition and introduced the term "inflammatory breast carcinoma" (2). Early attempts to control IBC with either surgery alone (2–9) or surgery combined with radiotherapy (2,7,10–16) resulted in a median survival of ≤24 months and palliative local control rates of <50%. As potentially effective chemotherapeutic agents became available in the 1970s, the approach to IBC became systemic chemotherapy followed by irradiation (17–20). Survival rates were improved to 25% to 40% by this approach. Radiotherapy in these protocols interrupted the systemic therapy for as long as 9 to 10 weeks, and locoregional failure rates remained as high as 25%, so the use of mastectomy was introduced for patients in whom

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induction chemotherapy rendered the tumor resectable (21).

Whether the addition of mastectomy significantly improves local control in patients with IBC remains controversial (22–28). Patients who have achieved a clinical complete response (CR) to induction chemotherapy frequently inquire whether a mastectomy is necessary. Similarly, the question exists whether "debulking" mastectomy produces any long-term benefit in patients with minimal or no response to induction chemotherapy because their life expectancy is very short. Because IBC still accounts for 1% to 6% of all breast cancers in the United States (29,30), we conducted a retrospective review to determine if mastectomy combined with radiotherapy offered any advantages over radiotherapy alone in patients with IBC who had been treated with doxorubicin-based combination chemotherapy.

PATIENTS AND METHODS

Between 1974 and 1993, 178 consecutive patients with IBC who had no prior therapy and no known evidence of distant metastases were treated on protocol at the University of Texas M.D. Anderson Cancer Center. IBC was defined as biopsy-proven adenocarcinoma of the breast with clinical onset of erythema, peau d'orange, and ridging of the breast mound within ~3 months before presentation. Each patient was examined by a group of physicians in a multidisciplinary setting to confirm the diagnosis of IBC and to assess the clinical stage of disease at presentation. Patients with locally advanced breast cancer with secondary skin involvement were excluded from the study. The staging workup included a complete history and physical examination, complete blood count with differential and platelet counts, blood chemistry analysis, electrocardiogram, chest roentgenogram, abdominal computerized tomography or ultrasonography (when available), bone scan, and bilateral mammography. Bone marrow biopsy, brain scan, and skeletal radiographic survey were performed if clinically indicated. Each patient was entered prospectively into a database and followed longitudinally. The medical records of all the patients were available at the time of this study for retrospective analysis. Six patients were excluded because mastectomy had been performed before presentation at our institution and initiation of induction chemotherapy.

The patients were entered into one of four different treatment protocols. Protocol A was active from 1974 until 1977, protocol B was active from 1977 until 1982, protocol C was active from 1982 until 1986, and protocol D was active from 1986 until 1993. Treatment in protocol A consisted of chemotherapy ± immunotherapy and definitive irradiation; protocols B through D included both mastectomy and radiotherapy in addition to the chemotherapy. Details of these treatment regimens are described briefly below and have been reported previously (17,21,22,31–33).

All patients (n = 172) received induction doxorubicin-based combination chemotherapy before local therapy. Initially, the chemotherapy regimen was 5-fluorouracil, doxorubicin, and cyclophosphamide (FAC). In 1982, vincristine and prednisone were added (FACVP). A median of three courses (range two to nine) of 21- to 28-day cycles were given before assessing clinical response and planning local therapy. In a few patients before 1980, immunotherapy was administered with the chemotherapy as previously reported (31,32).

Maintenance chemotherapy after locoregional treatment consisted of FAC to a cumulative doxorubicin dose of 450 mg/m^2 and then cyclophosphamide, methotrexate, and 5-fluorouracil for a total duration of 24 months. In 1982, the maintenance program was shortened to eight cycles of FACVP postoperatively. A strategy of alternative chemotherapy using methotrexate and vinblastine (MV) on the basis of response to FACVP was initiated in 1987. In patients with a CR, only FACVP for eight cycles was given after surgery. In patients who had only a PR, six cycles of MV were added to the eight cycles of FACVP. If less than a PR was observed, the patient received two cycles of MV preoperatively. If this produced an additional tumor response, four cycles of MV were given after surgery. If no response to MV was observed, the patient was treated with preoperative irradiation and then mastectomy without further chemotherapy. Details of these chemotherapy regimens during the period of this study, including drug doses, have been published previously (21,22).

Locoregional therapy evolved from definitive radiotherapy alone to interval mastectomy with consolidation radiotherapy to the chest wall and nodal basins after completion of chemotherapy in patients with tumor response. Details of the radiotherapy have been described elsewhere (17,22,33). Initially, a twice-daily fractionation with cobalt 60 and electrons was used; a total dose of 71 Gy was delivered if irradiation was the only local modality. In patients who underwent mastectomy, consolidation irradiation consisted of either 45 Gy given over 3 weeks in 30 fractions to the chest wall and an additional 15 Gy to the surgical scar or daily irradiation using standard fractionation to 50 Gy followed by a 10-Gy boost.

TABLE 1. *Characteristics of patients by treatment received*

Treatment received	C + M + RT (n = 98)	C + RT (n = 42)	C + M (n = 27)	Chemo (n = 5)	Total (n = 172)
Age (median yr)	50	52	51	51	51
Menopause					
Pre	44	13	11	1	69
Post	54	29	16	4	103
Estrogen receptor					
Positive	20	11	5	3	39
Negative	30	15	11	0	56
Unknown	48	16	11	2	77
Nodes					
0	17	—	1	—	18
1–3	27	—	7	—	34
⩾4	50	—	19	—	69
Missing	4	42	—	5	51
Nuclear grade					
NG1	28	16	10	2	56
NG2	25	11	8	1	45
Unknown	45	15	9	2	71
Chemotherapy response					
Complete response	14	5	2	0	21
Partial response	57	27	21	1	106
No significant response	27	10	4	4	45
Distant recurrence					
Yes	55	30	24	5	114
No	43	12	3	0	57
Local recurrence					
Yes	15	12	16	1	44
Persistent disease	1	3	0	3	7
No	83	27	11	4	121
Status					
Alive	42	3	4	0	49
Dead of disease	53	31	23	5	112
Dead other	3	8	0	0	11

Criteria for Response

Clinical response to induction chemotherapy was defined according to the following criteria: CR, total resolution by physical and radiographic examination of the inflammatory skin changes, any mass in the breast, or axillary adenopathy; partial response (PR), ⩾50% reduction in the surface area of the inflammatory skin changes or the product of the two largest perpendicular dimensions of the breast mass described; and no significant response (NSR), less than a PR, no change in clinical status, or disease progression. Histologic response to induction chemotherapy was characterized as no residual tumor, ⩽1 cm^3 of residual tumor, or >1 cm^3 of residual tumor. Patients with microscopic or no breast disease and who had negative or only one to three positive axillary nodes on histologic examination were considered to have ⩽1 cm^3 of residual disease.

Statistical Method

Statistical analyses were conducted using Statistica software (Statsoft, Inc., Tulsa, OK, USA). Data analyzed included clinical and histologic response to treatment, time to recurrence, survival after local recurrence, and ultimate control of local disease. Relapse-free interval and survival rates were calculated from the date of initiation of treatment by the method of Kaplan and Meier (34), and differences among the distributions were tested using the log-rank test (35). Comparability of group outcomes was assessed using either the χ^2 or Fisher's exact test. Univariate and multivariate analyses were performed using the Cox proportional hazards model. The statistical significance level (p) was taken as a measure of the strength of evidence against the null hypothesis, and the level of $p = 0.05$ was considered statistically significant.

RESULTS

All 172 patients were female. Table 1 summarizes the patient characteristics by treatment received. The median age was 51 years (range 27 to 78 years). Only 40.1% of the women were premenopausal. The ethnic distribution was as follows: 79.7% white, 8.1% African-American,

and 12.2% Hispanic. Palpable axillary nodes were present in 72% of patients. Clinically positive supraclavicular disease was described in 2.9%. Of 95 patients whose estrogen receptor status was known, 41.1% were considered estrogen receptor positive (>10 fmol). Median follow-up was 89 months (range 22 to 223 years) in patients who were alive at the time of the review.

Clinical rates of response to the induction chemotherapy were as follows: CR, 12.2%; PR, 61.6%; and NSR, 26.2%. Rates for CRs and PRs were not different between the two induction chemotherapy regimens, (71.4% and 75.2%, respectively, for FAC and FACVP) or between the three treatment modalities (76.6% for chemotherapy plus radiotherapy, 85.2% for chemotherapy plus mastectomy, and 72.5% for all three treatment modalities).

After induction chemotherapy, treatment of the breast consisted of radiotherapy alone in 42 patients, mastectomy alone in 27 patients, and mastectomy plus radiotherapy in 98 patients. Five patients received chemotherapy as their only treatment modality because of early onset of progressive disease.

Of the 125 patients who underwent mastectomy after induction chemotherapy (10 having received preoperative radiotherapy), 19 (15.2%) had no tumor detected in the specimen, and 19 (15.2%) had minimal residual tumor (estimated to be ≤ 1 cm^3). Of the 16 patients who had a clinical CR and underwent mastectomy, 37.5% had >1 cm^3 of tumor within the mastectomy specimen. Nine of these patients underwent axillary dissection in addition to mastectomy. Three of these nine patients (33.3%) had one to three positive axillary nodes, and five (55.6%) had four or more positive axillary nodes. Similarly, of the 78 patients who had a clinical PR and underwent mastectomy, the majority (73.1%) had >1 cm^3 of disease present in the mastectomy specimen. Fifty-four of these patients with a PR underwent axillary dissection. Twelve of these patients (22.2%) had one to three positive axillary nodes, whereas 35 (64.8%) had four or more positive nodes.

Locoregional disease persisted in seven patients and recurred in 44 patients who had been rendered disease free. For the latter group, the median time to locoregional recurrence was 12 months (range 3 to 65 months). Sites of recurrence were chest wall in 83.3% of patients, regional nodal basins in 11.9%, and both in 4.8%. Locoregional recurrence was the first relapse event in 16.3% of all patients. All but one of the patients with locoregional relapse subsequently developed distant metastases, and in all cases these metastases developed within 6 months. Sixty percent of patients who experienced local failure died with persistent locoregional disease.

TABLE 2. *Incidence of local recurrence (LR) by treatment modality and response to induction chemotherapy*

Response to induction chemotherapy	Treatment modality		
	C + RT (n = 42)	C + M (n = 27)	C + M + RT (n = 98)
Clinical response			
Complete	1/5 (20)	1/2 (50)	0/14 (0)
Partial	8/27 (30)	13/21 (62)	7/57 (12)[a]
No significant response	3/10 (30)	2/4 (50)	8/27 (30)[b]
Histologic response (residual disease)			
None[c]	NA	0/0 (0)	0/19 (0)
≤ 1 cm^3	NA	0/2 (0)	0/17 (0)
>1 cm^3	NA	16/25 (64)	15/62 (24)[d,e]

Data are patients with LR/total patients by response (%).
C, chemotherapy; M, mastectomy; RT, radiotherapy.
[a] $p < 0.05$, C + M + RT vs. C + M and vs. C + RT by Fisher's exact test.
[b] $p < 0.05$, no significant response vs. complete and vs. partial by Fisher's exact test.
[c] Four patients received preoperative radiotherapy.
[d] $p < 0.05$, >1 cm^3 vs. none and vs. ≤ 1 cm^3 by Fisher's exact test.
[e] $p < 0.05$, C + M + RT vs. C + M by Fisher's exact test.

The rate of locoregional relapse was similar for premenopausal and postmenopausal patients (30.4% and 29.1%, respectively), and estrogen receptor status was not predictive of locoregional recurrence: 30.8% of patients with estrogen receptor–positive tumors had local relapse compared with 37.5% of patients with estrogen receptor–negative tumors. Furthermore, the type of induction chemotherapy used did not alter locoregional relapse rates (28.6% and 30.2%, respectively, for FAC and FACVP).

The percentage of patients with locoregional recurrence by local treatment modality and by response to induction chemotherapy is shown in Table 2. The addition of mastectomy led to significant improvement in locoregional disease control for the patients as a whole. Locoregional relapse rates were 16.3% (16 of 98 patients) for patients who underwent chemotherapy, mastectomy, and radiotherapy and 35.7% (15 of 42 patients) for patients who underwent only chemotherapy plus radiotherapy ($p = 0.016$). However, within response groups, only patients in the PR group demonstrated significant improvement in local control with the addition of mastectomy (see Table 2). Although there was a noticeable decrease in the rate of locoregional recurrence between the patients with a clinical CR who received all three treatment modalities as compared with those who received only chemotherapy and radiotherapy (0% and 20%, respectively), the small number of patients in this subset did not allow demonstration of a statistically significant difference. The amount of residual disease found on histologic examination of the mastectomy specimen

TABLE 3. *Incidence of development of distant metastasis by treatment modality and response to induction chemotherapy*

Response to induction chemotherapy	Treatment modality		
	C + RT (n = 42)	C + M (n = 27)	C + M + RT (n = 98)
Clinical response			
Complete	3/5 (60)	2/2 (100)	4/14 (27)
Partial	19/27 (69)	18/21 (86)	27/57 (47)[a]
No significant response	9/10 (90)	4/4 (100)	24/27 (89)[b]
Histologic response (residual disease)			
None[d]	N/A	0/0 (0.0)	8/19 (42)
≤ 1 cm^3	N/A	1/2 (50)	5/17 (29)
>1 cm^3	N/A	23/25 (92)[c]	42/62 (67)[c]

Data are patients with metastasis/total patients by response (%).
[a] $p < 0.05$, C + M + RT vs. C + M by Fisher's exact test.
[b] $p < 0.05$, no significant response vs. complete and vs. partial by Fisher's exact test.
[c] $p < 0.05$ >1 cm^3 vs. none and vs. ≤ 1 cm^3 by Fisher's exact test.
[d] Four patients received preoperative radiotherapy.

was highly predictive of local failure. No patient with histologic residual disease ≤ 1 cm^3 (n = 38) developed locoregional recurrence (see Table 2).

Distant metastases occurred in 115 of 172 patients (66.9%). The most common locations of distant disease were bone (19%), liver (13%), brain (11%), and lungs (8%). The median time to distant failure was 16 months (range 2 to 121 months). The incidence of distant metastases was not significantly affected by menopausal status (72.5% and 63.1%, respectively, for premenopausal and postmenopausal patients), estrogen receptor status (69.2% and 66.1%, respectively, for positive and negative status), or type of induction chemotherapy (65.1% and 67.9%, respectively, for FAC and FACVP). The incidence of distant disease recurrence by treatment modality and response to induction chemotherapy is shown in Table 3. Similar to the trend seen for local recurrence, the incidence of distant metastatic disease was lower in patients who had ≤ 1 cm^3 of residual disease than in those who had >1 cm^3 of residual disease (36.8% and 74.7%, $p < 0.001$).

At the time of this review, 49 of the 172 patients remained alive. Overall survival rates for the entire group were $36.2 \pm 3.8\%$ at 5 years and $24.4 \pm 3.8\%$ at 10 years. Overall survival rates at 5 years were not significantly affected by menopausal status (28.5% and 41.6%, respectively, for premenopausal and postmenopausal patients; $p = 0.210$), estrogen receptor status (43.6% and 33.7%, respectively, for positive and negative status; $p = 0.915$), or type of induction chemotherapy (34.0% and 37.6%, respectively, for FAC and FACVP; $p = 0.823$). Only 11 of the patients died of causes other than their breast carcinoma. A total of 18 patients survived 10 years or longer, 13 of whom remain alive with no evidence of recurrence at the time of this review.

The clinical response to induction chemotherapy was highly predictive of both disease-specific and disease-free survival (Fig. 1). In patients with a clinical CR, the 5-year disease-specific and disease-free survival rates were 69.7% and 62.8%, respectively, compared with only 43.9% and 37.4% in patients with a clinical PR and 12.0% and 7.3% in patients with a clinical NSR ($p < 0.001$). The amount of residual tumor found on histologic examination of the mastectomy specimen was also highly predictive of disease-specific and disease-free survival ($p < 0.001$ for both) (Fig. 2). For the 38 patients with ≤ 1 cm^3 of residual tumor in the mastectomy specimen after induction chemotherapy, the 5-year disease-specific and disease-free survival rates were 71.4% and 59.2%, respectively, compared with 31.2% and 25.6% in patients with >1 cm^3 of remaining tumor.

The effect of the addition of mastectomy to chemotherapy plus radiotherapy on disease-specific and disease-free survival in patients with IBC was dependent on the patient's response to induction chemotherapy (Fig. 3). Patients who had a clinical CR or PR to induction chemotherapy and were treated with mastectomy in addition to chemotherapy and irradiation had improved disease-specific and disease-free survival compared with those patients with a CR or PR who underwent only chemotherapy plus irradiation. Five-year disease-specific and disease-free survival rates were 62.0% and 52.6%, respectively, for patients treated with mastectomy compared with 43.0% and 31.2% for patients who were treated with only chemotherapy and irradiation ($p = 0.018$ and $p < 0.023$ for disease-specific survival and disease-free survival, respectively). Patients who had NSR to induction chemotherapy demonstrated no improvement in disease-specific ($p = 0.676$) or disease-free survival ($p = 0.637$) with the addition of mastectomy to chemotherapy plus irradiation.

Results of a multiple regression analysis examining the effects of age, protocol into which each patient was entered, response to induction chemotherapy, use of surgery, and use of radiotherapy on disease-specific survival are shown in Table 4. A CR or PR to induction chemotherapy, the use of radiotherapy, and the addition of mastectomy to the therapeutic regimen all were found to significantly ($p < 0.05$) improve disease-specific survival.

DISCUSSION

Determining the optimal therapy for IBC remains a challenge. The aggressive nature of the disease, the

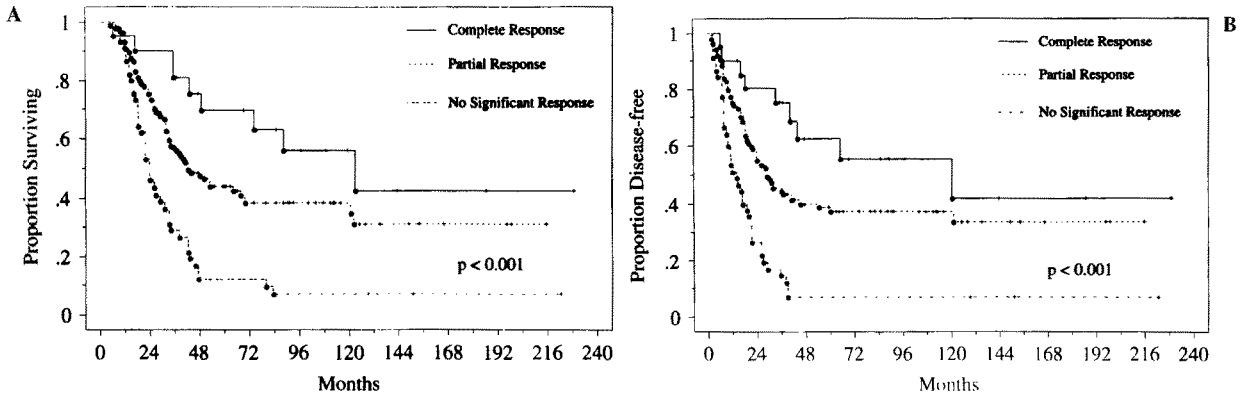

FIG. 1. Kaplan-Meier actuarial survival curves for disease-specific (**A**) and disease-free (**B**) survival stratified by response to induction chemotherapy.

variation in the criteria used to reach the diagnosis of IBC in several previous studies, the relatively small number of patients with the disease, and the broad variety of treatment regimens have made the evaluation of this disease in a standardized and effective fashion difficult. The dismal results of mastectomy alone in the treatment of IBC (median survival times of only 24 months and local recurrence rates of ≥50%) led many to consider IBC an inoperable condition (36). Radical radiotherapy became the primary treatment regimen, and although it did reduce the incidence of skin ulceration, it did not improve the survival rate. However, the use of combination chemotherapy regimens ushered in a new era of treatment for IBC, improving long-term survival and often rendering the disease resectable. Mastectomy has again emerged with a role in combined modality therapy. Most series that attempt to define the benefit of mastectomy in IBC are limited by an inherent patient selection bias—patients with the best response to induction chemotherapy have their disease rendered technically resectable and are the only ones offered surgical treatment (23–28). The effect of any selection bias for type of local therapy was minimized in this study by examining the local treatment modality by clinical response to induction chemotherapy.

In this review, the median follow-up of 89 months for those 49 patients remaining alive was long enough that the majority of patients at risk for relapse should have experienced their local recurrence. Only five of these patients had follow-up of <36 months, and only 15 of these patients had follow-up of <60 months. The median time to the development of a local recurrence was 10 months, and 94% of these relapses occurred within 36 months. Patients with a PR to induction chemotherapy had a significant reduction ($p = 0.015$) in the locoregional recurrence rate with the addition of mastectomy to irradiation. Similarly, no local recurrence was observed in patients with a clinical CR to induction chemotherapy who underwent mastectomy and irradiation, whereas one of five patients (20%) with a clinical CR who were treated with irradiation alone had a local recurrence. Patients with no significant tumor response to induction

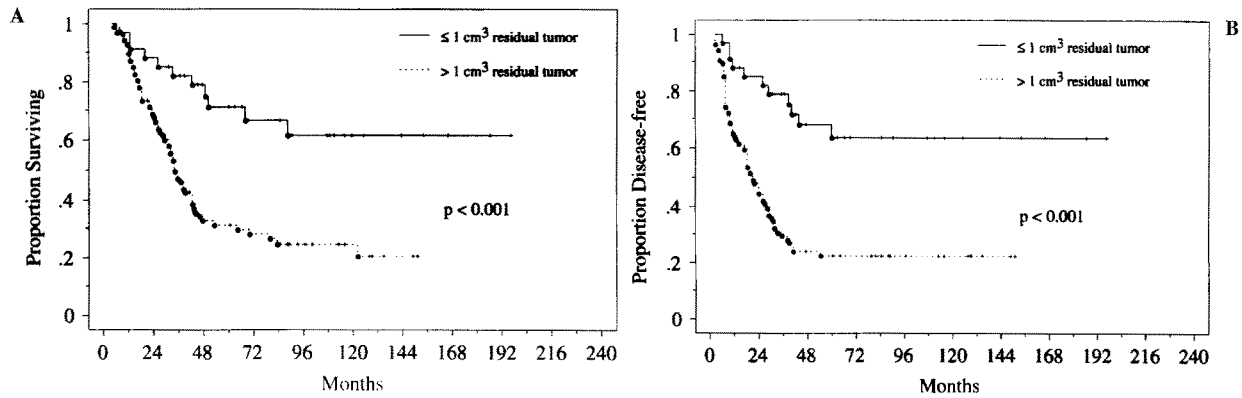

FIG. 2. Kaplan-Meier actuarial survival curves for disease-specific (**A**) and disease-free (**B**) survival stratified by amount of residual tumor found on histologic examination of mastectomy specimens.

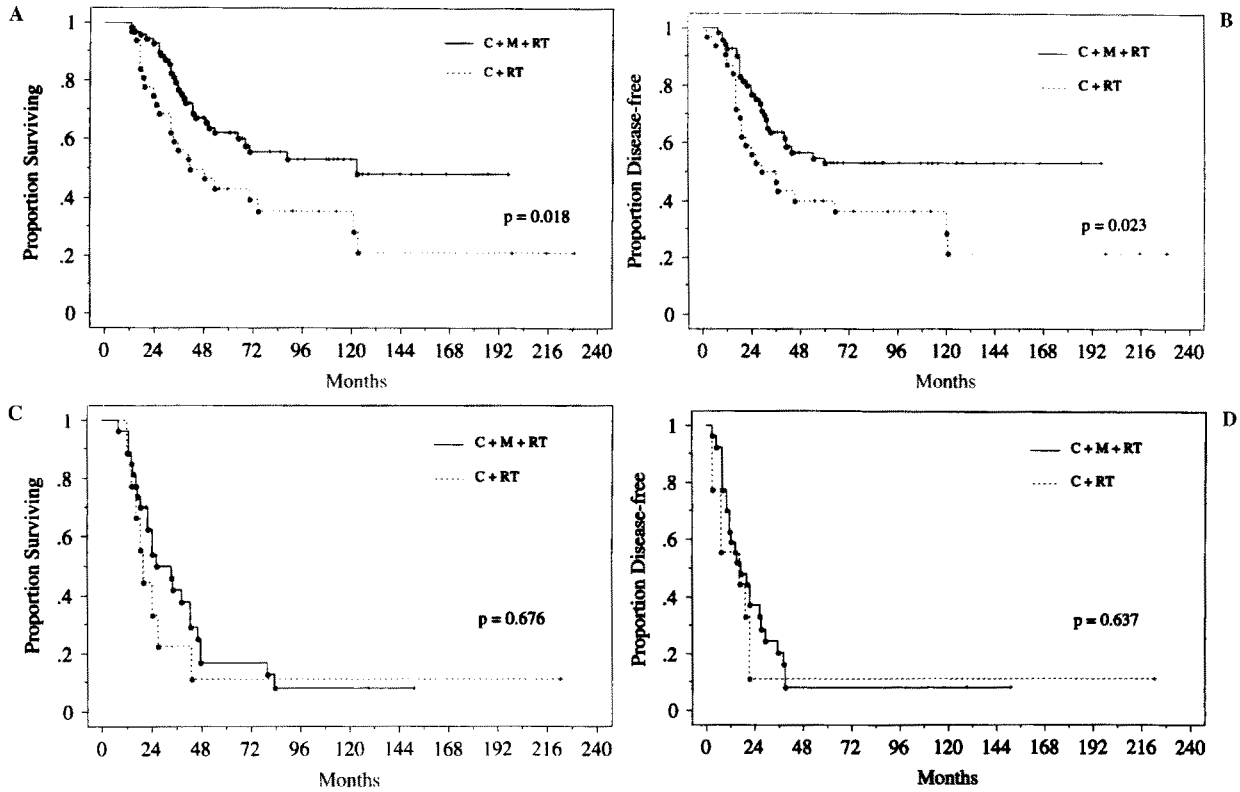

FIG. 3. Kaplan-Meier actuarial survival curves for disease-specific **(A)** and disease-free **(B)** survival in patients with a complete or partial clinical response to induction chemotherapy and for disease-specific **(C)** and disease-free **(D)** survival in patients with no significant response to induction chemotherapy, stratified by type of treatment received. C, chemotherapy; M, mastectomy; RT, radiotherapy.

chemotherapy had almost equivalent local recurrence rates regardless of the use of mastectomy.

Attempts to conserve the breast by substituting interstitial irradiation for mastectomy in patients who experience substantial tumor reduction with chemotherapy has met with limited success. Brun et al. found local recurrences in seven of 13 patients treated with breast conservation and interstitial irradiation but found only two relapses in 10 patients who underwent mastectomy (28). However, definitive primary irradiation may be a reasonable option for local control in patients whose tumors fail to respond to induction chemotherapy because mastectomy serves primarily as a palliative tumor-debulking procedure and does not reduce the rate of local recurrence. Furthermore, survival of patients in this subgroup is very poor (9.6% at 5 years); therefore, the late effects of high-dose irradiation are of less concern.

TABLE 4. *Multiple regression analysis (Cox's proportional hazard model) of factors affecting survival in patients undergoing treament for IBC*

	Univariate p	Multivariate p
Age ≥50 years	0.307	
Complete or partial response to induction chemotherapy	0.024	<0.001
Radiotherapy added to treatment protocol	<0.001	<0.001
Mastectomy added to treatment protocol	0.022	0.015
Protocol group	0.312	

Clinical and histologic response to induction therapy predicted survival outcome. The addition of mastectomy improved survival in our study. However, this survival benefit was apparent only in patients who had a CR or PR to induction chemotherapy. Other factors such as menopausal status, estrogen receptor status, and the specific chemotherapy protocol did not significantly alter survival rates. Similar to what we found in our study, Fields et al. reported an improvement in the relapse-free survival rate in 53 patients who underwent mastectomy as part of their treatment as compared with 52 patients who did not have surgery (23). In a multivariate analysis, the prognostic factors for improved disease-free survival were use of mastectomy, discrete tumor mass versus diffuse tumor, and to a lesser extent, white race. The most significant factors for overall survival were mastectomy

and the use of chemotherapy (23). Analysis of our data indicates that a CR or PR to induction chemotherapy is most strongly associated with improved disease-free and overall survival, but that the use of either radiotherapy or mastectomy as part of the treatment protocol significantly improved disease-specific and disease-free survival. Others have also suggested that mastectomy may have a marginal effect on survival, but it is unclear whether this survival effect is related to patient selection criteria for surgery (25). Clearly, if definitive radiation without mastectomy were reserved only for those patients whose tumor was too advanced to resect or for those patients who had no significant response to induction chemotherapy, a bias favorable to mastectomy would be introduced into the study. However, the vast majority of the patients who received only chemotherapy plus radiotherapy—40 of 42 (95.2%)—fulfilled the intention to treat. These patients were treated during the time that protocol A was active (1974 to 1977) and their original treatment plan called for only chemotherapy and radiotherapy. No bias was introduced because none of these 40 patients were ever intended to receive a mastectomy. Group A, in fact, may serve as a control for the other patient groups. Furthermore, substratification of patients into responders and nonresponders allows for a reduction in potential bias when comparisons are made between the various treatment groups.

Clinical response to induction chemotherapy correlated inconsistently with histologic residual disease found on examination of mastectomy specimens. Similar to findings in other reports (27,37), extensive amounts of viable tumor were often encountered within the mastectomy specimen despite reports of a CR by clinical and radiographic criteria. Regardless of whether mastectomy itself plays a dominant role in overall survival, the surgical staging of the true tumor response to induction chemotherapy may provide valuable information to guide further therapy. Residual disease, not clinical response, most accurately predicted long-term local control as well as overall and disease-free survival. This finding is similar to our experience with tumor downstaging in patients with non-IBC locally advanced breast cancer (38). Although patients with persistent skin edema were more likely to have extensive multicentric involvement of the mammary parenchyma, the histologic residual disease determined outcome. Histologic assessment of residual disease should be considered the standard for evaluation until imaging methods are developed that can more accurately identify viable residual tumor.

Local recurrence after treatment for IBC is generally an indicator of the presence of advanced distant disease and may be a marker of a biologically more aggressive tumor. In this review, patients most often manifested a local recurrence as the first site of failure. Nearly all of these patients subsequently developed distant metastatic disease. Supporting evidence for the theory that local recurrence is a marker of more aggressive tumor biology may be found in the trend for a relatively early (median 12 months) development of failure, the low incidence of long-term survivors (2%), and the observation that local recurrence occurred much more frequently in tumors that demonstrated a poor response to induction chemotherapy. These findings are similar to those reported for locally advanced, noninflammatory breast carcinoma, where patients who had tumors that demonstrated minimal response to induction chemotherapy generally had shorter disease-free and overall survival times (37).

The disappointingly small fraction of patients who indeed had a histologic CR as documented by examination of the mastectomy specimen (15.2%) underscores the need to develop more effective strategies to improve tumor downstaging. In a review of five trials of either single or multiple chemotherapeutic drugs followed by autologous bone marrow transplantation (ABMT) for IBC and other stage III breast cancers, Antman et al. (39) reported that 44 of 56 patients included in the review (79%) had a clinical CR after induction chemotherapy but before ABMT and that 89% of patients had a CR after ABMT. Disease-free status was maintained in 54% patients with follow-up ranging from 1 to 37 months. The mortality rate associated with the treatment was 4%. A randomized trial is currently underway at the M.D. Anderson Cancer Center for IBC patients who have four or more positive axillary nodes after induction chemotherapy but are rendered disease free by surgery. This study involves the use of standard-dose FAC or FAC followed by two cycles of high-dose chemotherapy (cyclophosphamide, etoposide, and cisplatin) and either ABMT or peripheral blood stem-cell support. This strategy has become more feasible with the recent addition of granulocyte-macrophage colony-stimulating factor to augment hematopoietic recovery and to reduce treatment-related toxicity.

Another approach to the treatment of individuals with IBC that is not responsive to standard induction chemotherapy is the use of a different crossover chemotherapy regimen before surgical intervention. Nonanthracycline-resistant drugs such as paclitaxel may hold some promise in further enhancing response rates (40). Our current trial involves the use of paclitaxel if less than a PR is obtained with four cycles of induction FAC. If a CR or PR is achieved with paclitaxel, the patient undergoes mastectomy followed by four cycles of paclitaxel and irradiation. In patients who have a CR or PR with the initial

four cycles of FAC, mastectomy is performed, and an additional four cycles of FAC are given followed by four cycles of paclitaxel and irradiation. In patients with NSR to either FAC or paclitaxel induction chemotherapy, the radiation oncologist and surgeon plan whether to treat the breast with preoperative irradiation and then perform mastectomy or to proceed with definitive irradiation as the only local modality with the intent of palliation.

These retrospective data suggest that surgical removal of the affected breast may further reduce the risk of recurrence in patients with inflammatory carcinoma, but prospective studies are needed to confirm these data. The possibility exists that patients with larger amounts of residual disease were felt to be unable to undergo surgery, which may have resulted in the surgical patients having less disease and thus a more favorable prognosis. Nevertheless, at this time, optimal local control for the majority of patients with IBC may be attained by the addition of mastectomy to radiotherapy as local treatment after induction chemotherapy. The improvement in local control translates to an improvement in both overall and disease-free survival, but this benefit is only manifest in those patients who have a significant response to their induction chemotherapy regimen. An additional benefit of mastectomy may be found in the accurate assessment of the amount of residual disease after induction therapy. Patients who have no significant response to induction chemotherapy are at great risk for both local and distant failure. This group of patients receives no additional benefit from mastectomy as compared with radiotherapy alone, and these patients should be considered as candidates for clinical trials of new treatment regimens.

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