Mastectomy Following Preoperative Chemotherapy

Strict Operative Criteria Control Operative Morbidity

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The surgical morbidity associated with aggressive preoperative chemotherapy in 106 patients with advanced primary breast cancer who had chemotherapy followed by mastectomy was examined. These patients were compared with a group of 91 consecutive patients who had mastectomy without preoperative chemotherapy. Strict operative criteria were used to determine the timing of mastectomy following chemotherapy. Wound infection rates were no different in the preoperative chemotherapy group compared to the mastectomy-alone groups (7% *versus* 4%; p = 0.62). The incidence of wound necrosis was similar (11% *versus* 6%; p = 0.29). Seroma formation was decreased significantly in the preoperative chemotherapy group compared to the mastectomy-alone group (15% *versus* 28%; p = 0.04). Intensive preoperative chemotherapy did not delay the reinstitution of postoperative treatment (30% *versus* 20%; p = 0.27). However, when delay in instituting postoperative chemotherapy was more than 30 days, there was a significant decrease in overall survival rate (p = 0.04). This study provides evidence that intensive preoperative chemotherapy and mastectomy can be performed without increased morbidity. Furthermore it is important to institute systemic chemotherapy within 30 days of mastectomy to achieve maximum survival.

IN THE PAST three decades progress in the treatment of patients with breast cancer has been marked by an expanding role of aggressive chemotherapy. Currently postoperative chemotherapy or hormonal therapy is the standard treatment for women who have breast cancer metastatic to the axillary lymph nodes.[1] Recent controlled trials indicate that adjuvant treatment also may benefit some subsets of breast cancer patients who have no nodal metastases.[2-4] Preoperative combination chemotherapy has been shown to improve the survival of patients with advanced primary breast cancer and inflammatory breast cancer.[5-7] The recent introduction of trials examining preoperative (neoadjuvant) chemotherapy in patients with less-advanced breast cancer[8] highlights the expanding role of chemotherapy in the treatment of patients with breast cancer. With the increasing use of perioperative chemotherapy, it is important to know that this treatment can be given safely without increasing the morbidity of mastectomy or delaying further therapy.

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In 1974 a strategy of giving preoperative chemotherapy was begun for patients with locally advanced primary breast cancer (stage III) at the University of Texas M.D. Anderson Cancer Center. Overall response rates exceeded 90%, and most of these patients had mastectomy following chemotherapy. We reviewed our experience with preoperative chemotherapy for locally advanced breast cancer, testing the hypothesis that aggressive preoperative chemotherapy and mastectomy would not adversely affect postoperative recovery compared to patients having a mastectomy alone when examining the endpoints of wound infection, wound necrosis, seroma, and delay in resuming postoperative therapy. In addition we examined whether a delay in resuming chemotherapy following mastectomy adversely affected survival rate.

Patients and Methods

The hospital records of 106 patients who presented with advanced breast cancer were reviewed. Patients were clinically staged to have either T3, T4, and/or N2, N3 breast cancer using the 1983 American Joint Committee on Cancer criteria.[9] All patients initially were evaluated in a multidisciplinary breast clinic where surgical oncologists, medical oncologists, and radiotherapists were present. All patients were enrolled in a protocol between 1974 and 1985 and received preoperative chemotherapy followed by total mastectomy with axillary dissection.

The preoperative chemotherapy has been described[5] and consisted of 500 mg/m^2 5-fluorouracil administered intravenously on days 1 and 8, 500 mg/m^2 doxorubicin administered intravenously on day 1, and 50 mg/m^2 cyclophosphamide given intravenously on day 1. Following three to six 21-day cycles of chemotherapy, a total mastectomy and axillary dissection was performed. After operation patients resumed chemotherapy for 6 to 18 months. External beam radiotherapy was given at the completion of postoperative chemotherapy.

These patients were compared to a group of 91 patients with breast cancer who had mastectomy without preop-

erative chemotherapy (mastectomy-alone group) at our institution in 1985. The two groups were analyzed for the following endpoints: (1) wound infection, (2) wound necrosis, (3) seroma, and (4) delay in resuming postoperative chemotherapy.

Strict operative criteria were used to plan the timing of surgery after preoperative chemotherapy. All patients were examined by the surgeon after the completion of chemotherapy and determined to be resectable. If unresectable radiotherapy was given before surgery, laboratory examination was performed, and patients were required to have a white blood cell count (WBC) of more than than 2500 cells/mm^3 and a platelet count of more than than 50,000 cells/mm^3. These criteria avoided the chemotherapy nadir. The operative surgeons and technique were the same in both groups. Demographic data included age, clinical stage of disease, tumor size, and lymph node status. Additional information obtained in the preoperative chemotherapy patients included number of courses of chemotherapy, complications of chemotherapy, WBC count, platelet count, hematocrit level, length of time after the last chemotherapy dose, surgeon, number of lymph nodes removed, number of lymph nodes involved with tumor, operative procedure, recurrence, and survival. Complications analyzed included wound infection, wound necrosis, seroma, and delay in resuming chemotherapy. Wound infection was defined as clinical signs of infection requiring antimicrobial therapy. Wound necrosis was defined as any skin loss requiring therapeutic intervention (*i.e.*, antibiotic administration, debridement, or dressing changes). Seroma was defined as any fluid collection requiring aspiration from the axilla or chest wall. Delay in resuming chemotherapy was defined as treatment that was begun more than 30 days after mastectomy.

Data was analyzed with the D-Base III-Plus® program (Ashton-Tate, Culver City, CA) using a personal computer. Statistical analysis was performed with AbStat® (Anderson-Bell, Parker, CO). Significant differences between groups were analyzed by chi square, and significance was assumed if $p < 0.05$. Survival curves were calculated and plotted using the Kaplan–Meier method,[10] and the generalized Wilcoxon test was used to test differences in survival.[11]

The following null hypotheses were tested.

(1) There is no significant difference in surgical morbidity (wound infection, wound necrosis, seroma, and delay in resuming chemotherapy) in preoperative chemotherapy patients compared to patients who had mastectomy without preoperative chemotherapy.

(2) There is no significant difference in survival of patients treated with preoperative chemotherapy who have delay in resuming chemotherapy after mastectomy compared to patients who do not have a delay in resuming chemotherapy.

Results

There were 106 patients in the preoperative chemotherapy group and 98 patients in the mastectomy-alone group. The average age was 50.1 years (range, 20 to 76 years) in the preoperative chemotherapy group and 55.2 years (range, 31 to 96 years) in the mastectomy-alone group. Tumor stage in the preoperative chemotherapy group was I (0%), II (1%), IIIA (29%), IIIB (66%), IV (2%), and bilateral (2%). Patients in the mastectomy-alone group had the following stage: I (53%), II (44%), IIIA (1%), IIIB (0%), IV (1%), and bilateral (1%).

Preoperative Chemotherapy

Patients who had preoperative chemotherapy had a median of three courses of treatment (range, 2 to 21 courses). The overall response rate was 90%. Six patients had a complete response (5.7%), and 90 patients had a partial response (84.9%). Seven patients had no response (6.6%), and two patients progressed while on treatment (1.9%) Response could not be determined for one patient by a review of the chart. Ninety-one patients (85.8%) had no complications related to their chemotherapy before surgery, and only four patients (3.8%) were thought to have had their surgery delayed by a complication of chemotherapy. One patient required preoperative radiation therapy; she had no response to preoperative chemotherapy and was not surgically resectable. She had no postoperative complications.

Patients had mastectomy a median of 27 days after their last chemotherapy course (range, 6 to 108 days). Two patients had a significant delay in surgery after preoperative chemotherapy (381 and 526 days) and were excluded from analysis. The median WBC count was 5.2 cells/mm^3 (range, 1.7–13.6 cells/mm^3), and the median platelet count was 293,000 cells/mm^3 (range, 3.67 to 636,000 cells/mm^3). Six patients had a WBC count of less than 2500 cells/mm^3,and one patient had a platelet count of less than 50,000 cells/mm^3. Our criteria for the timing of mastectomy were followed in 100 patients (94%).

Surgery and Surgical Morbidity

The following procedures were performed in the preoperative chemotherapy group: extended simple mastectomy (mastectomy and level I axillary dissection), 72%; modified radical mastectomy, 12%; simple mastectomy, 9%; bilateral mastectomy, 6%; and segmental mastectomy, 1%. The following procedures were performed in the mastectomy-alone group: extended simple mastectomy, 11%; modified radical mastectomy, 61%; simple mastectomy, 1%; bilateral mastectomy, 8%; and segmental mastectomy, 18%. The average number of lymph nodes re-

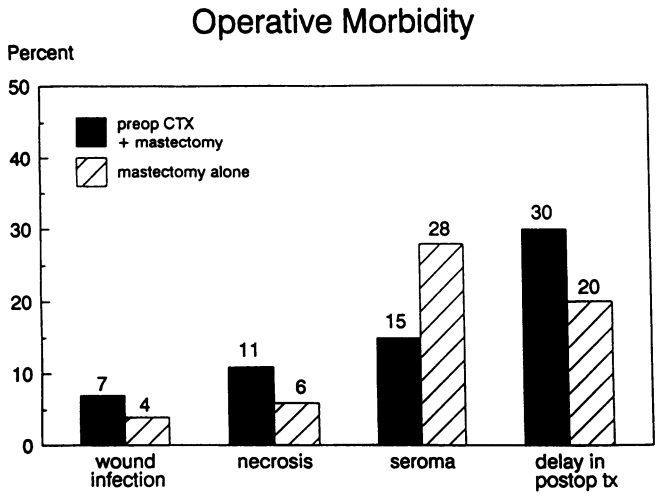

FIG. 1. Surgical morbidity preoperative chemotherapy + mastectomy patients *versus* mastectomy alone patients. No significant differences were noted with respect to wound infection (chi square, p = 0.62), wound necrosis (chi square, p = 0.29), and delay in postoperative treatment (chi square, p = 0.27). There was a significant difference in seroma formation (chi square, p = 0.04).

moved at surgery was similar in the two groups (13 *versus* 16).

Surgical morbidity is compared in Figure 1. There were no significant differences in wound infection, wound necrosis, or delay in resuming chemotherapy rates between the two groups. There was a significant difference in seroma rates between the two groups (15% *versus* 28%; p = 0.04).

In the preoperative chemotherapy group, chemotherapy was resumed a median of 27 days after mastectomy discharge (range, 0 to 1478 days). Two patients did not have chemotherapy after surgery (1.9%), and three patients had chemotherapy reinstituted more than 2 years after surgery (2.8%). They were excluded from the survival analysis. Seven patients had chemotherapy started within 14 days of mastectomy. There was one seroma in this group (14%). Forty-six patients in the mastectomy-alone group had chemotherapy after mastectomy (46.9%).

Effect of Delaying Postoperative Chemotherapy

The survival of preoperative chemotherapy patients who had delay in resuming chemotherapy by more than 30 days following mastectomy was compared to those preoperative chemotherapy patients who had no delay (Fig. 2). Median survival was statistically worse in those patients who had delay compared to those who did not (median survival, 33.2 *versus* 56.1 months; p = 0.04). Overall median survival time was 54.3 months.

Discussion

This study directly examined surgical morbidity in mastectomy patients following aggressive preoperative chemotherapy. Several other studies have examined surgical complications of chemotherapy following mastectomy. Cohn et al.[12] analyzed the surgical complications in the National Surgical Adjuvant Breast Project (NSABP). In this study patients who had 3 days of peri-

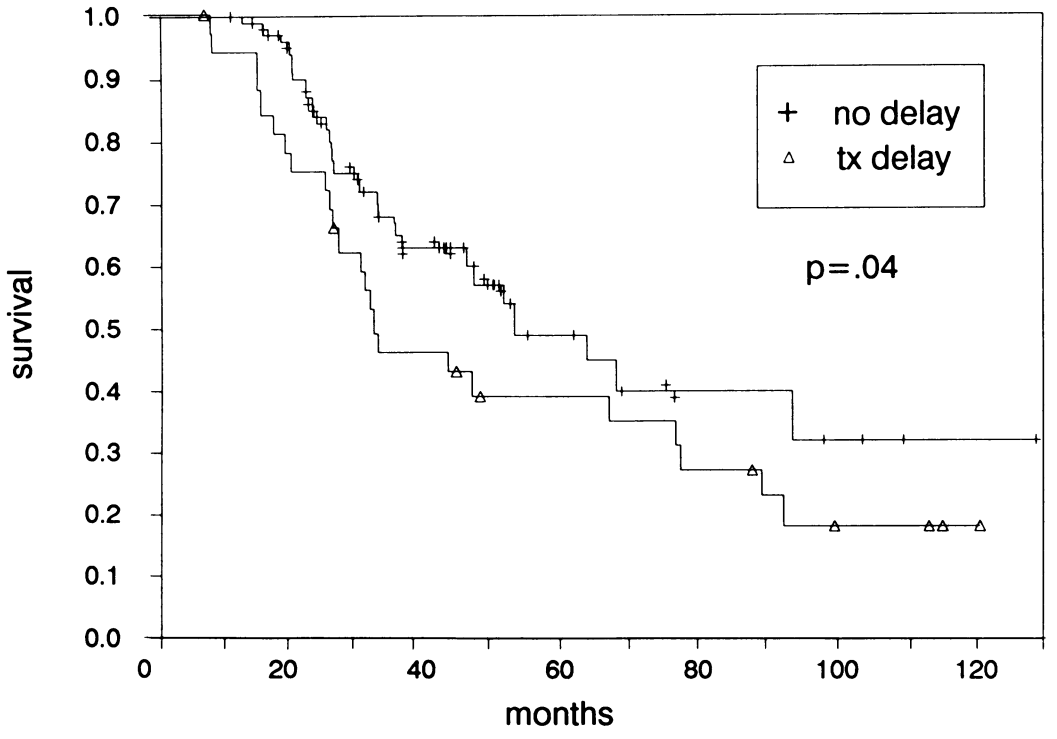

FIG. 2. Survival in advanced primary breast cancer patients grouped by delay *versus* no delay in resuming systemic therapy after mastectomy.

operative thio-tepa and mastectomy were compared to those who had placebo and mastectomy. They found that local complications in both groups were high, but no difference was found in the patients who had perioperative chemotherapy (47% *versus* 43%). Patients had wound infections regardless of whether chemotherapy was given (20% in either group). Knight et al.[13] discussed the surgical results of 18 patients with inflammatory cancer who were treated with preoperative chemotherapy and radiation, followed by mastectomy. They found wound problems in 7 of the 18 patients (39%). Three patients had wound infection (17%), two had seromas (11%), and one patient each had wound necrosis and erythema.

There have been several experimental studies that have examined the effect of chemotherapy on wound healing.[14–17] These studies resulted in conflicting data. Extrapolating the results of chemotherapy on wound healing in rats to humans is important in initial phases of research but has limited clinical value. Our analysis concludes that the rate of complications of mastectomy following preoperative chemotherapy is not significantly different than the morbidity of surgery alone. No significant difference in wound infection, wound ischemia, or delay in instituting chemotherapy between the two groups was found. Interestingly the incidence of seroma formation was significantly decreased in patients who had preoperative chemotherapy. It will be interesting to see whether seroma rates are decreased in patients who receive preoperative chemotherapy in the NSABP B-18 clinical trial.

We developed simple guidelines to determine the timing of mastectomy after preoperative chemotherapy. These require that the patient be resectable without the need for skin grafting or reconstructive surgery and that the WBC and platelet count be adequate to minimize the risk of infection or bleeding. These criteria avoid the patient's chemotherapy nadir.

Our study demonstrated a significant reduction in survival in patients with advanced primary breast cancer who had systemic therapy delayed more than 30 days after mastectomy. While there was no statistical difference in the incidence of delaying postoperative therapy between the preoperative chemotherapy and mastectomy-alone groups, the incidence was high in both groups (30% *versus* 20%). These findings provide an argument for designing strategies that resume systemic treatment early after mastectomy.

The use of preoperative chemotherapy in patients with advanced primary breast cancer has been a major advance. Patient survival has been improved, and the high response rates have allowed for mastectomy without the need for more extensive surgical procedures. This study shows that strict operative criteria that determine the timing of surgery allow mastectomy without increasing surgical complication rates.

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