Stage III Carcinoma of the Breast

A Detailed Analysis

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A ten-year study of Stage III breast carcinoma has been reviewed in detail. The single most dominant variable was axillary nodal involvement. Four hundred and thirty patients had nodal metastases, 58 patients did not. Four hundred and thirty patients with axillary nodal involvement had five- and ten-year recurrence rates of 68 and 77%, while the survival rates were 41 and 21%, respectively. Life span was influenced by extent of nodal disease, being best for those with micrometastases only, and worse for those with four or more positive nodes. Skin edema, infiltration, or ulceration in the positive node group were grave signs. Muscle invasion or node matting, however, did not appear to influence length of life. Postoperative prophylactic therapy did not appear to affect survival rates. Radiation therapy alone did not influence either local recurrence or survival rates. Not enough time has elapsed to evaluate the results of postoperative chemotherapy. Patients who underwent oophorectomy and radiation therapy appeared to do better, but the number of patients was small. Of the 58 patients without nodal invasion, 82% were alive at five years and 75% were alive at 10 years. Grave signs did not influence the survival rate in this group. While the majority of patients with Stage III carcinoma had unfavorable variables, there were some patients who demonstrated a low recurrence rate and a long survival time. Aggressive treatment should be designed to save those patients who can be helped and to improve those patients whose life expectancy is limited. There is no place for timid initial treatment whether by operation or by irradiation. It must be given with intent to cure even though palliation is most often attained.

THE EMPHASIS IN the recent medical literature[1-3] on adenocarcinoma of the breast has been on earlier diagnosis and selection of patients for less extensive surgical procedures. This emphasis is not inappropriate, but there remains, and probably will remain, a significant proportion of breast cancer patients whose disease will be diagnosed in a locally advanced stage without demonstrable distant metastases (*i.e.*, Stage III). Despite efforts at education and screening, this unfortunate situation persists and these patients present a greater problem in management than the group with "early" breast cancer.

The traditional role of radical operative procedures in this group of patients has been questioned.[4] Therefore, the results of radical surgical treatment remains an important area of study. Recurrence and survival characteristics of these patients were analyzed over a ten-year period of time. The relevance of these findings to future treatment of patients with Stage III carcinoma and to design of clinical trials is discussed.

Materials and Methods

The case record of all patients with Stage III breast cancer listed in the Tumor Registry of Memorial Hospital presenting from January 1965 through December 1974 were reviewed. Staging criteria used in this study were postsurgical treatment-pathologic parameters identical to those outlined by the Union Internationale Centre le Cancer (UICC) and American Joint Committee for cancer staging and end-results reporting (AJC) in 1972, with the exception that primary inflammatory carcinoma is classified as Stage IV, as recommended in 1978. In contradistinction to the AJC's 1978 recommendation, we have placed breast cancer patients who had chest wall fixation, breast edema, skin ulceration, resectable satellite skin nodules, skin invasion, or pectoral muscle fascia infiltration in Stage III.[5] These "grave signs"[6] were analyzed for their affect on recurrence and survival. Therefore, our criteria for classification as Stage III is as follows:

1) Primary tumor greater than 5 cm in its greatest dimension as measured in the pathology laboratory.
2) Tumor of any size with: a) The presence of breast edema, infiltration of the disease in the skin,

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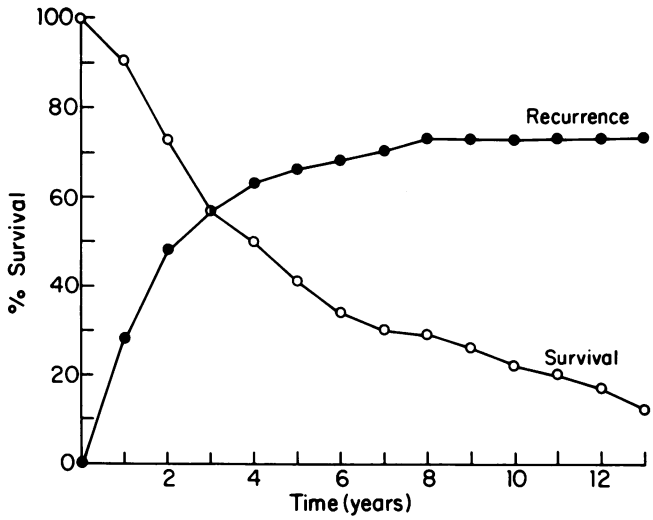

FIG. 1. Stage III breast cancer patients with positive axillary nodes actuarial survival and recurrence curves.

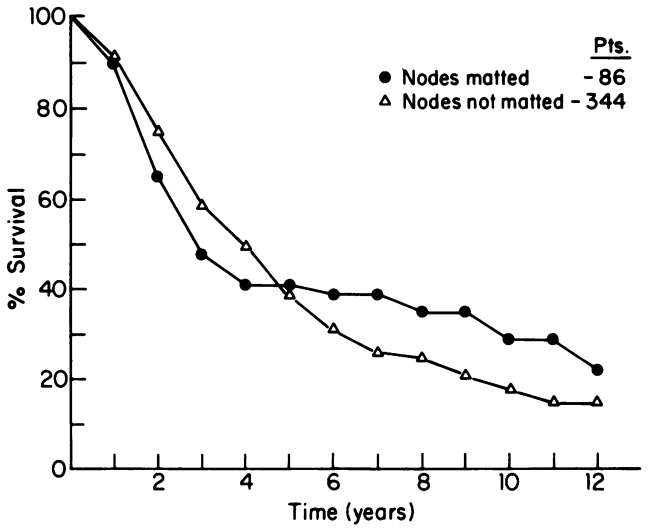

FIG. 3. Effect of node matting on survival in Stage III patients with Positive Nodes.

ulceration, or pectoral muscle/chest wall invasion of the disease. b) And/or the presence of matted or fixed metastatic lymph nodes in the axilla.

The tests for significance levels are based on Breslow's method for testing the equality of tumor recurrence and survival distribution patterns.

Results

In the ten-year period studied, 488 patients with Stage III adenocarcinoma of the breast were studied in detail. Patients with prior, subsequent, or simultaneous malignancies were excluded from this investigation. The first parameter studied was axillary nodal metastases. As would be expected, 430 patients (88.1%) had histologically positive axillary lymph nodes. This group had a high recurrence rate and low survival rate. Overall survival rate at five years was 40.8% and at ten years the survival rate was 21.0% (Fig. 1).

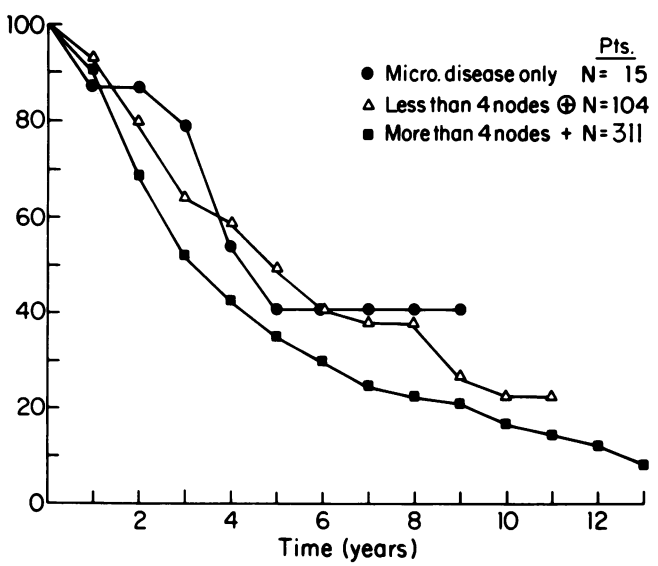

FIG. 2. Survival comparisons for patients with involved axillary nodes actuarial survival curves.

When the nodal status was examined in detail, the number of lymph nodes involved influenced survival. Those patients with less than four involved lymph nodes had a five-year survival rate of 50.0%, compared with a 35.2% survival rate in those patients who had more than four involved lymph nodes. Similarly, the ten-year survival figures were 23.0% and 17.0%, respectively. A small number of patients (15) were identified who had only micrometastases in lymph nodes (less than 2 mm). They appeared to have a better ten-year survival rate (40.8%), but the numbers were too small to make meaningful comparisons (Fig. 2). The bulk of nodal disease alone, however, as manifested by matting or fixation to skin or chest wall, did not appear to influence the recurrence or survival rates. The five-year survival rate in those patients with matted lymph nodes was 41.1%, versus a 38.9% survival rate for those patients whose invaded lymph nodes were not matted. The corresponding ten-year survival rates were 28.7% and 17.6%, and were not considered to be statistically different (Fig. 3). Next, those "grave signs" which classify a patient into Stage III, regardless of the tumor size or lymph node status were studied in those patients with involved axillary lymph nodes. The infiltration of carcinoma in the skin appeared to make an already grim prognosis even poorer. If infiltration was present, the five- and ten-year survival rates were 30.0 and 13.2%, respectively, as compared with 43.7 and 24.1% in the absence of skin infiltration. This difference was

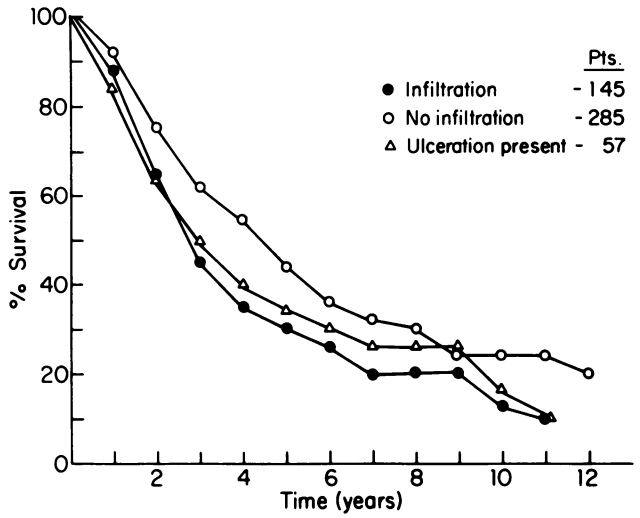

FIG. 4. Effect of skin infiltration or ulceration on survival in Stage III patients with positive nodes.

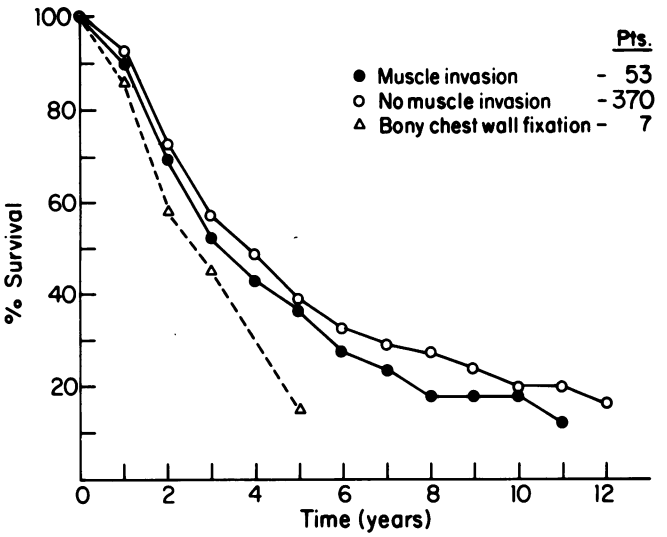

FIG. 6. Effect of muscle invasion or chest wall fixation on survival in Stage III patients with positive nodes.

highly significant ($p < 0.001$, Fig. 4). Similarly, skin edema adversely affected the survival rates of those Stage III patients with involved axillary lymph nodes. The five- and ten-year survival rates in the patients with skin edema were 17.0 and 9.2%, as opposed to 44.1 and 22.3% in those patients without skin edema. This was also significant ($p < 0.001$, Fig. 5). Surprisingly, invasion of the pectoral muscle did not influence survival rates in the patients with involved axillary lymph nodes. Although we assume an adverse effect on chest wall (ribs, intercostals, or serratus) fixation, the number of patients with such lesions was too small to draw a conclusion (Fig. 6).

The patients with Stage III carcinoma with no lymph node involvement were also studied in a similar manner. Although these 58 patients represent a relatively small percentage (11.9%) of the total sample of patients, some striking differences are apparent. First, although classified as having Stage III carcinoma, these patients had an excellent overall survival rate. At five years, 82.2% of the patients were still alive, and 75.3% of the patients survived ten years (Fig. 7). Second, the grave signs did not have the same effect on survival rates in patients with negative axillary lymph nodes as they did in the patients with positive axillary lymph nodes. Twelve patients had one or more grave signs. No patient had chest wall fixation and only one patient had carcinoma invasion of the pectoral muscle without at least one of the other grave signs. Their survival rate was compared, as a group, with those patients with negative axillary lymph

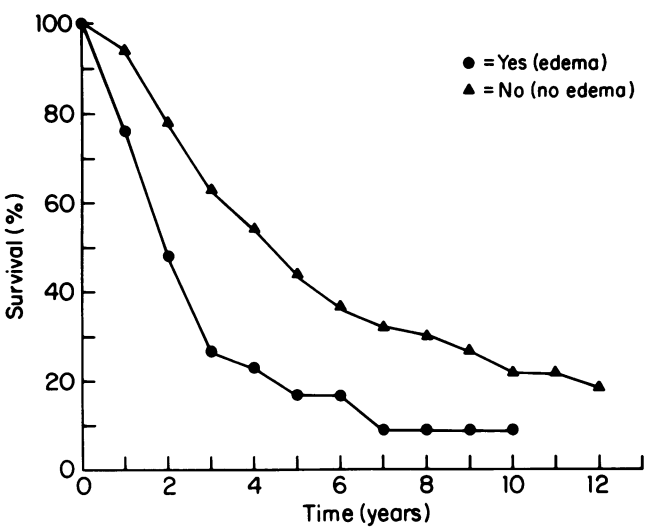

FIG. 5. Effect of skin edema on survival in Stage III patients with positive nodes.

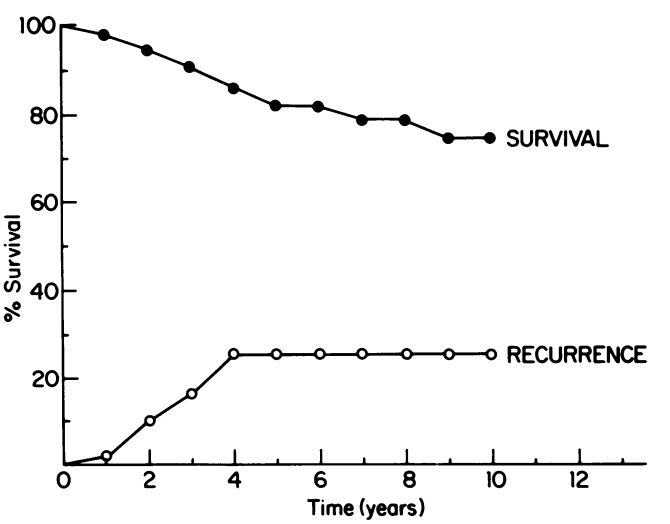

FIG. 7. Stage III patients with negative nodes actuarial survival and recurrence curves.

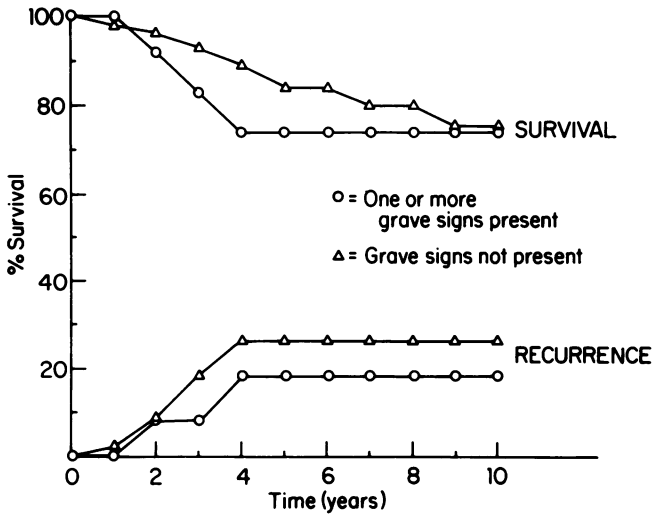

FIG. 8. Stage III with negative nodes comparison of patients with and without grave signs.

nodes who had no grave signs. As demonstrated in Figure 8, the presence of grave signs (which here really means skin edema or infiltration) in patients with large lesions but negative lymph nodes does not adversely affect recurrence or survival rates.

Two other significant differences between this group and those with axillary lymph node metastases should also be noted. First, a higher percentage of histologic types other than infiltrating duct carcinoma is present. Eleven of the 58 patients (19%) had either papillary, lobular, or medullary carcinomas. However, the survival rate in the 47 patients with infiltrating duct carcinomas was also excellent. Second, of the patients without axillary lymph node invasion in whom estrogen receptor assays were done, ten of 11 (91%) were estrogen receptor positive (ERP). In a small group of patients with involved axillary lymph nodes, the estrogen receptors were positive in only 48% of 75

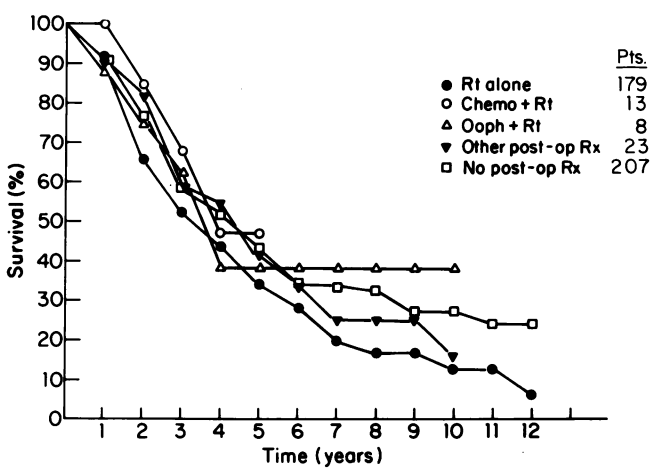

FIG. 9. Effect of prophylactic postoperative therapy on Stage III patients with positive nodes. Survival curves.

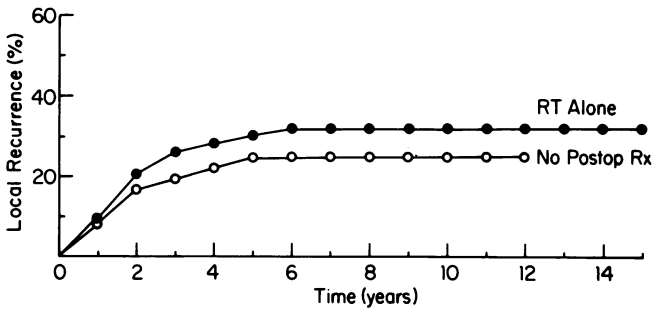

FIG. 10. Local recurrence for Stage III patients with positive nodes. Comparison of postoperative radiotherapy versus no postoperative radiotherapy.

patients. The favorable prognosis in the group of patients with no lymph node involvement correlates well with estrogen receptor positivity.

Standard radical mastectomy was the surgical procedure of choice in patients with Stage III breast carcinoma. At times the responsible physician elected to give postoperative prophylactic (adjuvant) radiation therapy. This was usually 4000–5500 rads given in "Hockey Stick portals" to the supraclavicular and internal mammary regions. The practice of performing prophylactic oophorectomy had essentially been abandoned by this time, because it had shown no improvement in survival rates.[7–9] Adjuvant chemotherapy had not been administered to a sufficient number of patients during this study to provide any meaningful five-year follow-up data. In comparing the group of patients who had postoperative irradiation with the group who had no postoperative irradiation, there was no change in survival rates. The patients treated by irradiation had five- and ten-year survival rates of 34.3 and 13.0%, as opposed to 43.0 and 27.1% for the untreated group of patients. These differences were not significant (Fig. 9). Strangely, the incidence of local recurrence was not reduced by postoperative irradiation (Fig. 10).

Discussion

The treatment of locally advanced adenocarcinoma of the breast is currently changing. In selecting a form of ancillary postoperative therapy, initial sites of recurrences or metastases must be considered. As Figure 11 shows, the site of initial recurrence is more frequently systemic (bone, viscera, and multiple areas) than local. Trials with some form of systemic chemotherapy would, therefore, appear more beneficial than regional treatment. A major factor to be considered in designing such trials is that the staging does not always correlate with the prognosis. For example, we have identified a subgroup of patients (those with negative axillary lymph nodes) with Stage III breast carcinoma whose prognosis is better than a significant

number of patients with Stage II disease, and approaches the prognosis of some patients with Stage I disease. At the other end of the spectrum is a group of patients (large primary tumors with skin edema or infiltration and positive axillary lymph nodes) whose ten-year survival rate of 9–13% is relatively poor, but is better than those patients with Stage IV breast carcinoma.[10] These findings create two problems. First, it is clear that adjuvant therapy (cytotoxic or endocrine manipulation), designed to treat all these patients, might either overtreat those patients with a good prognosis or undertreat those patients with a poor prognosis. Adjuvant therapy with drugs that are more effective but are often associated with potential irreversible side effects, such as doxorubin HCl, seems justified in this latter group. In addition, adjuvant forms of endocrine manipulation need to be tested, particularly in those patients with positive estrogen receptors. Efforts should also be directed toward identifying the 20–30% of the patients in the negative lymph node group whose carcinoma recurs and who might benefit from less toxic adjuvant therapy. Steroid hormone receptor assays, immunologic evaluation, tumor associated serum antigens, or histologic criteria (such as lymphatic invasion) should be investigated for such prognostic value.

The second problem created by this lack of correlation between stage and prognosis relates to the interpretation of the results of clinical trials. It is possible that the differences to be detected between treated and untreated controls in a prospective, randomized trial may be small, yet medically significant. If the treated or untreated group is compared with a group of patients with a better prognosis, the conclusions drawn may be erroneous. In addition, small differences noted on one study might be inapparent in another study, whose treatment groups were not strictly comparable. This would lead to contradictory or equivocal information. The overall ten-year survival rate in our study, for example, could be changed from 20% to 27% merely by the inclusion of those patients who had no axillary lymph node metastases, which constitute only 12% of the total sample. Therefore, a plea is made to separate these subgroups of patients so that we can intelligently compare the results of different methods of treatment.

In identifying such subgroups of patients, numerous factors correlate with prognosis. The dominant factor, in our study, however, was the status of the axillary lymph nodes. Carcinoma invasion into the pectoral muscle does not appear to worsen the prognosis in those patients with axillary lymph node involvement, assuming that the local therapy is adequate. Although infiltration of the skin by the disease or edema appear

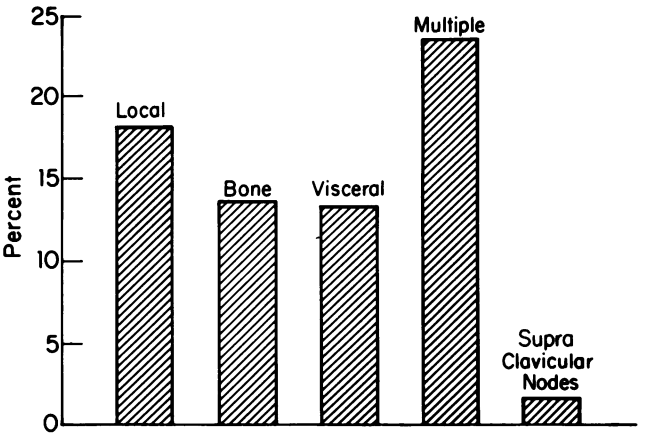

FIG. 11. Initial site of recurrence or metastases. Four hundred and thirty patients Stage III breast cancer with positive nodes.

to adversely affect prognosis in those patients with lymph node involvement, they do not signify more advanced disease in those patients without lymph node involvement. The finding of skin edema or infiltration per se, therefore, should not be a sufficient criterion to classify a patient's carcinoma as Stage III.

In selecting a form of primary treatment for Stage III breast carcinoma, the choice is between irradiation or radical mastectomy. A common characteristic of Stage III breast carcinomas is that they are usually large. The irradiation employed must be intense with an added booster dose to the tumor. Interstitial irradiation is sometimes added and irradiation of the tumor approaches at times 8000, 9000 and 10,000 rads. Because of these high doses of radiation, marked reactions occur, with inflammation and soft tissue necrosis being the most common. Underlying pulmonary fibrosis, rib fractures, and brachial plexus neuropathies are not uncommon. All this could be set aside were the results similar. Primary irradiation for Stage III breast carcinoma has been reported by Bruckman et al.[11] to result in a 25% five-year survival rate and reported by Rubens[12] to result in a 13% five year survival rate. In our total series of Stage III breast carcinomas treated by radical mastectomy with or without supplementary irradiation, we attained a 45% five-year survival rate, which is almost twice the reported figure. Primary operative therapy, therefore, appears to be preferable.

The 25% local recurrence rate following radical mastectomy in the group of patients with positive axillary lymph nodes leaves sufficient room for improvement in the treatment of these patients with advanced primary lesions. This relatively high incidence was not significantly altered by the type of postoperative irradiation used in this group of patients. However, it must be stated that these patients were

not randomly selected and, it may be that patients with the worst prognosis were chosen for postoperative radiation therapy. Another possible explanation is that the postoperative radiation technique of "Hockey Stick portals" used in this series entraps cancer cells left behind on the chest wall following radical mastectomy. These cancer cells, blocked by the searing effect of supravoltage therapy to supraclavicular and internal mammary areas, were delayed from disseminating and were forced to grow upward, increasing the incidence of local recurrence. When this was recognized in 1974, tangential portals to the chest wall were incorporated in treatment planning.

The reason for this high incidence of local failure and the influence of still other methods of treatment need to be further studied, as this can frequently become the most significant management problem in the patient with recurrent, advanced disease.

References

1. Patchefsky AS, Shaber GS, Schwartz GF, et al. The pathology of breast cancer detected by mass population screening. Cancer 1977; 40:1659–1703.
2. Shapiro S. Evidence on screening for breast cancer from a randomized trial. Cancer 1977; 39:2772–2782.
3. Strax P. Evaluation of screening programs for the early diagnosis of breast cancer. Surg Clin North Am 1978; 58:667–679.
4. Fisher B, Montague E, Redmond C. Comparison of radical mastectomy with alternative treatments for primary breast cancer. Cancer 1977; 39:2827–2839.
5. American Joint Committee for Cancer Staging and End-Results Reporting. Manual for Staging of Cancer. 1978.
6. Haagensen CD, Stout AP. Carcinoma of the breast, criteria of operability. Ann Surg 1943; 118:859–870 and 1032–1051.
7. Fracchia AA, Murray DR, Farrow JH, Balachandra VK. Comparison of prophylactic and therapeutic castration in breast carcinoma. Surg Gynecol Obstet 1969; 129:270–276.
8. Kennedy BJ, Mielke PW, Fortuny IE. Therapeutic castration vs prophylactic castration in breast cancer. Surg Gynecol Obstet 1964; 118:524–540.
9. Ravdin RG, Lewison EF, Slack NH, et al. Results of a clinical trial concerning the worth of prophylactic oophorectomy for breast carcinoma. Surg Gynecol Obstet 1970; 31:1055–1064.
10. Pearlman NW, Guerra O, Fracchia AA. Primary inoperable cancer of the breast. Surg Gynecol Obstet 1976; 143:909–913.
11. Bruckman JE, Harris JR, Levene MD, et al. Results of treating stage III carcinoma of the breast by primary irradiation therapy. Cancer 1979; 43:985–993.
12. Rubens RD, Armitage P, Winter PJ, et al. Prognosis in inoperable stage III carcinoma of the breast. Eur J Cancer 1977; 13: 805–811.