Local Recurrence in Breast Cancer after Conservative Surgery: Timing of Radiotherapy and Sequencing of Chemotherapy

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Abstract. Background: A randomized trial was conducted to determine (a) the role of radiotherapy and chemotherapy on local control and (b) to determine the timing of radiotherapy for early-stage breast cancer. Materials and Methods: Five hundred and ninety patients were treated with both conservative surgery and radiotherapy (group A). The average time interval between surgery and radiation was 90 days for 452 patients and over 90 days for 138 patients. One hundred and ninety-four patients underwent adjuvant therapy based on CMF regimens (group B). Results: Among 396 patients of group A, 8.1% had local failure; we observed 7.2% local recurrences in 363 patients who received therapy before 90 days and 18.2% in patients who received therapy after 90 days. Among patients of group B, 7.7% had local failure; for patients who underwent radiotherapy before 90 days, the local recurrence rate was 6.6%, compared with 12.3% for patients who underwent therapy more than 90 days after surgery.

Conclusion: In patients who are eligible to receive chemotherapy, it is possible to administer radiotherapy after systemic treatment, while in patients who have to be treated with radiotherapy more than 90 days after breast surgery, chemotherapy can reduce the local failure rate.

Conservative surgery and radiation therapy is used as the definitive treatment for early-stage breast carcinoma. Breast-conserving techniques have demonstrated excellent local control rates and survival, equivalent to those observed with mastectomy alone (1-3, 6, 7). Many patients with early-stage breast cancer are currently being treated with both adjuvant chemotherapy and adjuvant radiotherapy. Metastases have demonstrated a survival benefit for both premenopausal and postmenopausal females undergoing adjuvant chemotherapy (4, 5, 8, 11, 21, 26).

In this study, we report the results of a retrospective analysis, investigating the impact of systemic therapy on local recurrence rates after breast-conserving surgery and radiation therapy.

Materials and Methods

From 1973 to 1992, 590 patients with stage I or II invasive breast carcinoma were treated in our Institute with breast-conserving surgery, radiation and with or without chemotherapy.

The mean age of the patients at diagnosis was 57.5 years (range 28-87 years). None of the patients had any evidence of metastases as assessed by physical examination, chest X-ray, blood chemistries and, in most cases, by a bone scan.

The lesions were staged according to the TNM Classification: 369 patients were T1N0, 112 patients T1N1, 62 patients T2N0 and 47 patients T2N1. The tumor site was: for 407 patients upper outer quadrant, for 71 patients lower outer quadrant, for 68 patients upper inner quadrant and for 44 patients lower inner quadrant.

Five hundred and sixty-six patients (96%) underwent surgery (quadrantectomy): the tumor was removed with a 2- to 3-cm cuff of normal breast tissue. Skin, pectoral fascia and the pectoralis minor muscle were also removed; the other 24 patients were submitted to local excision of the tumor with a margin of 1 or 2 cm of normal tissue. Axillary lymph nodes dissection of I and II level was performed in 563 patients (95.5%).

All patients were treated with radiation therapy involving only the ipsilateral breast. The dose to the entire breast was usually 45 to 50.5 Gy, delivered at 1.8 to 2.0 Gy per fraction and administered five times per week. A tumor bed boost (median dose, 10 Gy) was delivered with electrons (9-12 MeV), photons (6 MeV) or 60Co. Patients with axillary metastases (4 or more positive lymph nodes) were further randomly assigned to receive additional radiotherapy to supradivicular and internal mammary nodes (40 to 45 Gy over a period of 4 to 5 weeks).

The average time interval between surgery and radiation was 90 days for 452 patients and over 90 days for 138 patients. Ninety-two patients (15.6%), aged from 35 to 74 years, were treated with Tamoxifene.

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All patients with positive axillary nodes (194 patients) were treated with chemotherapy, according to CMF-based regimens (cyclophosphamide, methotrexate and 5-fluourouracil). Follow-up days and days to failure were calculated from the beginning of radiotherapy using the Kaplan-Meier method. The mean follow-up for surviving patients was 120 months.

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Results

Patients were divided into two groups: lumpectomy, radiotherapy group (A) vs. lumpectomy, radiotherapy and chemotherapy group (B). Each group was then divided into two sub-groups: patients who underwent radiotherapy before 90 days and patients who underwent radiotherapy after 90 days (Table I).

In order to analyze the interaction of these factors, we compared the local failure rates in subgroups categorized by both the interval from last breast surgery and systemic treatment.

Among 396 patients treated with conservative surgery and radiotherapy (group A), 30 (8.1%) had local failure; we observed 26 (7.2%) local recurrences in the 363 patients who received therapy before 90 days and 6 (18.2%) in patients who received therapy after 90 days.

In group B, 89 (45.9%) patients underwent radiotherapy before 90 days and 105 (54.1%) received treatment after 90 days. For patients who underwent radiotherapy before 90 days, the local recurrence rate was 6.6% (30 out of 452), compared with 12.3% (17 out of 138) of patients who underwent therapy more than 90 days after surgery (Table II).

After a mean follow-up of 10 years, the incidence of overall survival in the 590 patients was 78.8% (465 out of 590). Among the women of group A, the survival rate was 78.5% (285 out of 363) for the group treated before 90 days and 54.5% (18 out of 33) for those treated after 90 days; in group B the survival rate was 87.6% (78 out of 89) among the women treated before 90 days and 80% (84 out of 105) among those treated after 90 days. However, on the basis of an analysis with the use of log-rank subtraction, radiotherapy begun before 90 days after surgery as compared with radiotherapy begun more than 90 days after surgery was associated with a decrease of mortality.

Discussion

This study was designed to evaluate (a) the role of radiotherapy and chemotherapy in local control and (b) the timing of radiotherapy after breast conserving surgery in early stage breast cancer.

In the present analysis, recurrent cancer in parenchyma or skin of the treated breast was scored as local failure, providing that this event occurred in the absence of or simultaneously with the discovery of distant metastases. Randomized prospective studies have established that systemic therapy can reduce the incidence of distant metastases for all stages of this disease (4, 5). As a matter of fact, systemic therapy has now become a standard therapy component for breast cancer patients with a clinically relevant life-time risk of distant metastases.

Although systemic therapy cannot be safely used as a substitute for breast irradiation in the treatment of early stage breast cancer (9, 10), in this study we observed how the use of systemic therapy could be a prognostic indicator in achieving local control after treatment with breast conserving surgery and radiation. In fact, among the 590 patients included in our study, 7.7% of those who underwent chemotherapy had a local failure, compared with 8.1% who were treated with surgery and radiotherapy only. Local failure was related to many risk factors such as patients age, margin status, radiation dose, etc.

Kurtz et al. (12, 20) observed that patients younger than 40, in addition to having a higher risk of early local failure, also tend to have a greater incidence of late breast recurrences. In these patients the negative effect of young age could be minimized by the use of systemic therapy. Data from Fowble et al. (13) confirms that, for axillary node-negative women, young age was associated with a statistically significant decreased overall survival, relapse-free survival, cause-specific survival, freedom from distant metastases and a statistically significant increased risk of breast recurrence and regional node recurrence. Anyway, in this study, the adverse effect of young age on the outcome appears to be limited to node-negative patients. Those findings suggest that node-negative early stage breast cancer in young women is a more aggressive disease, with an increased risk for all patterns of failure and a decreased survival.

In addition to patient age, the margin status has been considered by many authors as an independent risk factor for breast cancer recurrence (14-17). In Park et al. (17), patients with close margins and those with negative margins...
both had a rate of local recurrence of 7%. Patients with extensively positive margins had a local recurrence rate of 27%, whereas patients with locally positive margins had an intermediate rate of local recurrence of 14%. Data from the Fox Chase Cancer Center suggest that systemic therapy could delay but not prevent local recurrences in patients with positive resection margins or close resection margins (< or =2 mm) (14).

In our study, we considered time between breast surgery and radiotherapy as a risk factor for local failure in early stage breast cancer. In fact, of 452 patients who received radiotherapy before 90 days, 6.6% had a local recurrence vs. 12.3% who underwent radiotherapy after 90 days. Our data supports the results of a number of randomized trials (18, 22-25). Buchholtz et al. (18) confirm that comparisons of local control, overall survival and disease-free survival between the early radiation patients and delayed radiation patients all favored the early radiation group. Respective 8-year actuarial rates were: local control 98% vs. 76%, p=0.004; overall survival 80% vs. 52%, p=0.016; disease-free survival 71% vs. 48%, p=0.008. However, in contrast to these data, Froud et al. (19) did not find an univariate or multivariate difference in ipsilateral breast cancer recurrence between intervals of 0 to 20 weeks from breast conserving surgery to the beginning of radiation therapy, in a population-based, low-risk group of women who did not receive adjuvant chemotherapy, after controlling for other important factors in predicting ipsilateral breast cancer recurrence. These series differed from ours in which the control group also included III stage patients and none was treated with chemotherapy.

In our study, if we compare patients who received chemotherapy to those who had no systemic treatment, 7.2% of group A who underwent radiation therapy before 90 days had a local failure vs. 18.2% of the same group who received radiotherapy after 90 days; in group B, local failure occurred in 4.5% of patients who received radiotherapy before 90 days compared to 10.5% of those who received radiation therapy after 90 days (p>0.005). Therefore, systemic treatment seems to reduce local recurrence even in patients who received radiotherapy after 90 days, since conservative surgery (10.5% vs. 18.2%) and the percentage of local recurrence gets closer to values observed in patients who were submitted to radiotherapy before 90 days but not to chemotherapy (10.5% vs. 7.2%).

**Conclusion**

Many trials show that a delay in the beginning of radiotherapy after breast-conserving surgery may result in an increased rate of local failure, particularly in patients with positive resection margins or close resection margins (< or =2 mm) and of young age.

In patients with a clinically relevant life-time risk of distant metastases, randomized data have demonstrated the role of chemotherapy in minimizing the development of distant recurrences. In our study we also analyzed the role of systemic therapy in local control after breast-conserving surgery and radiotherapy.

Our results suggest that, in patients who are eligible to receive chemotherapy, it is possible to administer radiotherapy after systemic treatment, while in patients with no risk factors, who have to be treated with radiotherapy more then 90 days after breast surgery, chemotherapy can reduce the local failure rate.

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