

THE SEQUENCING OF CHEMOTHERAPY AND RADIATION THERAPY AFTER CONSERVATIVE SURGERY FOR EARLY-STAGE BREAST CANCER

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Abstract *Background.* Patients with early-stage breast cancer who are at substantial risk for systemic metastases are increasingly treated with breast-conserving therapy and adjuvant chemotherapy. However, the optimal sequencing of chemotherapy and radiation therapy is not clear.

Methods. Two hundred forty-four patients with stage I or II breast cancer who were at substantial risk for distant metastases were randomly assigned to receive a 12-week course of chemotherapy either before or after radiation therapy. All had had breast-conserving surgery. The median length of follow-up in surviving patients was 58 months (range, 10 to 124).

Results. The five-year actuarial rates of cancer recurrence at any site and of distant metastases in the radiotherapy-first group and the chemotherapy-first group were

38 percent and 31 percent ($P=0.17$) and 36 percent and 25 percent ($P=0.05$), respectively. Overall survival was 73 percent and 81 percent ($P=0.11$), respectively. The five-year crude rates of first recurrence according to site in the radiotherapy-first and chemotherapy-first groups, respectively, were 5 percent and 14 percent for local recurrence and 32 percent and 20 percent for distant or regional recurrence or both. This difference in the pattern of recurrence was of borderline statistical significance ($P=0.07$).

Conclusions. This study suggests that for patients at substantial risk for systemic metastases, it is preferable to give a 12-week course of chemotherapy followed by radiation therapy, rather than radiation therapy followed by chemotherapy. (N Engl J Med 1996;334:1356-61.)

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THE temporal order in which patients with early-stage invasive breast cancer receive chemotherapy and radiation therapy after breast-conserving surgery may affect the clinical outcome.¹⁻³ To our knowledge, no previous randomized trial has addressed this issue directly, although two trials comparing different chemotherapy schedules may also yield information about the effect of the timing of radiation therapy after surgery.^{4,5}

We conducted a randomized trial to test whether the sequence of administration of chemotherapy and radiation therapy after breast-conserving surgery influences the outcome among patients at substantial risk for systemic metastases. We found that giving chemotherapy first had better overall results but was associated with an increased risk of local recurrence.

METHODS

Study Design and Selection of Patients

From June 1984 to December 1992, 244 patients with clinical stage I or II breast carcinoma⁶ were randomly assigned after surgery to receive chemotherapy either before or after radiotherapy. Before June 1988, patients had to have pathologic involvement of the axillary nodes to be eligible; after that date, patients with uninvolved nodes were eligible if the primary tumor tested negative for the estrogen-receptor protein (less than 10 fmol per milligram) or if lymphatic vessels had been invaded. Patients were excluded if they had gross residual disease in the breast or axilla, previous cancer (excluding non-melanoma skin cancer), previous radiotherapy or chemotherapy, or

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serious coexisting illnesses. Written informed consent was obtained in accordance with institutional and federal requirements.

Characteristics of Patients

Table 1 lists the relevant features of the patients and their breast tumors. Patients were considered premenopausal if at the time of diagnosis they had had at least one menstrual period in the previous 12 months. Histopathologic features of the primary tumor were recorded on the basis of the original reports; a central review was not performed. We defined a "negative" microscopical resection margin as the presence of more than 1 mm of uninvolved breast tissue between the tumor and the inked edge, a "close" margin as 1 mm or less, and a "positive" margin as the presence of tumor (either invasive or intraductal) at the inked resection margin.⁷ Prognostic factors were distributed uniformly in the two treatment groups, except for a greater number of tumors containing extensive intraductal components⁸ in the radiotherapy-first group.

Treatment

Surgery

In most patients, the initial diagnostic and therapeutic procedure was excision of the tumor along with a small rim of normal breast tissue. Re-excision was commonly performed (Table 1). A level I or II axillary dissection was recommended, although the actual operation performed was left to the discretion of the surgeon.

Radiation Therapy

Radiotherapy technique has been described elsewhere.⁹ The entire breast received a dose of 45 Gy in 25 fractions, with an allowable variation of 10 percent. This was followed by a boost to the primary tumor site of 16 to 18 Gy, with an allowable variation of 20 percent, delivered with either an electron beam or interstitial brachytherapy. Regional lymph nodes (supraclavicular, axillary, or internal mammary nodes, or a combination of these) were irradiated to a maximal dose of 50 Gy at the discretion of the radiation oncologist. Treatment procedures were similar in both groups (Table 1). All treated patients received doses that were within protocol guidelines, except one who received a planned total dose of 50.4 Gy and one who received a dose of only 3.6 Gy because of the discovery of distant metastases during irradiation.

Chemotherapy

Prescribed drug doses were based on ideal body weight. The drugs were administered according to the following doses and schedules:

Table 1. Clinical and Pathological Features of the Two Groups of Patients.*

FEATURE	RADIOTHERAPY-FIRST GROUP (N = 122)	CHEMOTHERAPY-FIRST GROUP (N = 122)
Patients		
Age (yr)		
Median	45	45
Range	25–66	20–68
Percent premenopausal	74	75
Tumors		
Extensive intraductal component (%)		
Present	25	11
Absent	61	71
Unknown	15	17
Lymphatic-vessel invasion (%)		
Present	50	52
Absent	16	17
Indeterminate	18	11
Unknown	16	20
Estrogen-receptor protein (%)		
Present	45	41
Absent	42	44
Unknown	13	15
Margins (%)		
Negative	50	51
Close	23	16
Positive	16	25
Unknown	11	8
Nodal status		
Negative (%)	14	15
Positive		
1–3 nodes (%)	60	61
≥4 (%)	26	23
Median no.†	2 (range, 1–20)	2 (range, 1–20)
Treatment		
Re-excision (%)	69	67
Median no. of recovered axillary nodes	11	11
Radiotherapy‡		
Dose to primary site (Gy)	61	61
Nodal irradiation (%)	36	35
Median duration (days)	49	49
Median duration of chemotherapy§	84	84

*See the Methods section for definitions of menopausal status, presence of the estrogen-receptor protein, and resection-margin categories. Percentages may not add to 100 because of rounding.

†Only women with node-positive disease were included.

‡Radiotherapy values exclude data on two patients receiving 0 to 3.6 Gy only.

§Chemotherapy values exclude data on patients with major protocol violations.

methotrexate — 200 mg per square meter of body-surface area administered intravenously on days 1 and 15; leucovorin — 10 mg per square meter orally every six hours for 12 doses, starting on day 2 and day 16; fluorouracil — 500 mg per square meter intravenously on day 1; cyclophosphamide — 500 mg per square meter intravenously on day 1; prednisone — 40 mg per square meter per day orally for five days, starting on day 1; and doxorubicin, 45 mg per square meter intravenously on day 3. Cycles were repeated every 21 days for a total of four cycles. Complete blood counts were performed on days 1 and 15 of each cycle. The doses of cyclophosphamide and doxorubicin were reduced by 25 percent for the next cycle if the granulocyte count on either day 15 or day 22 (i.e., day 1 of the next cycle) was 300 to 499 per cubic millimeter. If either of these granulocyte counts was 299 per cubic millimeter or less, or if the platelet count was less than 50,000 per cubic millimeter, the doses were reduced by 50 percent. At the beginning of each cycle, the doses were based on the lowest granulocyte and platelet counts of the previous cycle; if a treatment cycle

with reduced doses did not again result in a need for dose modification, the doses were increased to the original starting level. If the granulocyte count on day 22 was less than on day 15, the next cycle was delayed one week. Methotrexate was not given on day 15 if the granulocyte count on that day was less than 500 per cubic millimeter, if the serum creatinine concentration had increased by 50 percent or more above the pretreatment value, or if active mucositis was present. The dose of doxorubicin was reduced by 50 percent if the bilirubin concentration on day 1 was greater than twice the upper limit of the institution's normal reference value. No patient failed to complete the chemotherapy protocol because of toxicity, but two patients (both in the radiotherapy-first group) in whom distant metastases were discovered during chemotherapy were switched to other regimens.

Tamoxifen

After June 1988, 10 mg of tamoxifen was given orally twice daily for five years after completion of both radiotherapy and chemotherapy to 7 patients in the radiotherapy-first group and 10 patients in the chemotherapy-first group, all of whom were postmenopausal and had estrogen-receptor-positive tumors.

Intervals between Treatments

Ninety-five percent of the patients in the chemotherapy-first group and 80 percent in the radiotherapy-first group began treatment within six weeks of the last surgical procedure, as required. Patients assigned to radiotherapy first were to start chemotherapy two weeks after completing radiotherapy, and vice versa. In one patient in the radiotherapy-first group and two patients in the chemotherapy-first group, these treatments overlapped by one or two days. The median interval between the last breast surgery and the start of radiotherapy was 36 days (range, 14 to 234) in the radiotherapy-first group and 126 days (range, 98 to 185) in the chemotherapy-first group. This interval between surgery and radiotherapy was more than 112 days (16 weeks) in 1 percent of the radiotherapy-first group and 84 percent of the chemotherapy-first group. The median interval between the first breast excision and the start of chemotherapy was 119 days (range, 48 to 179) in the radiotherapy-first group and 52 days (range, 15 to 119) in the chemotherapy-first group.

Compliance with Protocol Guidelines

In the radiotherapy-first group, one patient had had a previous cancer, one received nonprotocol chemotherapy, two refused their assigned sequence (one of these also received nonprotocol chemotherapy), and three declined to begin or complete chemotherapy. In the chemotherapy-first group, three patients had had previous cancers, one received nonprotocol chemotherapy and also underwent mastectomy electively without radiotherapy, and one declined to complete chemotherapy.

Statistical Analysis

Patients were registered centrally, and treatment was randomly assigned after stratification for the combination of menopausal status, presence or absence of the estrogen-receptor protein, and number of involved nodes (0, 1 to 3, or 4 or more). The number of participants was originally set at 200 patients (to be enrolled over four years), which was thought to balance the competing interests of practicality and study power. With the use of Pocock boundaries, a sequential analysis was expected to be able to detect a ratio of 1.67 or more for the medians of disease-free survival in the two groups (e.g., 4.8 vs. 8 years) with a two-sided test of significance of 0.05 and a power of 80 percent. When patients with histologically negative nodes were made eligible, the number of participants was increased to 230 to maintain the same power.

Overall outcome and patterns of cancer recurrence were analyzed according to the intention-to-treat principle; all enrolled patients were included, including ineligible patients and those who did not follow the protocol. Actuarial curves of the length of time until the first recurrence, the length of time until distant recurrence (whether before, simultaneously with, or after local or regional nodal recurrences), and

survival time (the length of time until death from any cause) were calculated by the Kaplan–Meier method. Neither the development of a contralateral breast cancer (4 patients in the radiotherapy-first group and 10 patients in the chemotherapy-first group) nor the development of a primary cancer not in the breast (1 patient in each group) was scored as a distant recurrence, nor were data on such patients censored in calculations of the time until the first recurrence or distant recurrence. All times were calculated from the day of randomization. The median follow-up time for surviving patients was 58 months (range, 10 to 124). Four patients lost to follow-up without recurrence at 10 to 39 months were scored as being alive without recurrence.

The site of first recurrence was categorized as “local” (within the parenchyma or skin of the treated breast, with or without simultaneous regional or distant recurrence), “regional” (in the ipsilateral axillary, infraclavicular, or internal mammary lymph nodes without evidence of local recurrence, with or without simultaneous distant recurrence), or “distant” (at other sites, occurring without simultaneous local or regional recurrence). Local recurrence after distant recurrence developed in one patient in the radiotherapy-first group and in two patients in the chemotherapy-first group; these events were excluded from the analysis. Because of the problems of competing risks,¹⁰ patterns of recurrence were described with the use of the crude five-year incidence rates of recurrence rather than actuarial statistics.

Statistical tests used to analyze treatment differences were the exact multinomial test for the site of the first recurrence and toxic effects, the Wilcoxon rank-sum test for dose, and the log-rank test for censored time variables. Polychotomous logistic regression¹¹ (a form of multivariate analysis that does not suffer from the problem of competing risks) was used to create two models to examine the way different variables affected the risk of recurrence at different sites during the five years after treatment (that is, whether a patient would be free of recurrence, or whether a local recurrence or a regional or distant recurrence would be the first to develop). Statistical significance for these models was tested by the Wald test. The first model (the “main effect” model) included the treatment-sequence assignment as one of the variables, as well as such factors as the status of the margin and nodes. The corresponding P values for the effects of each of these variables in the model are shown in Table 2. The second model (the “sequence interaction” model) examined whether other variables affected the relation that was found between the pattern of recurrence and the treatment sequence in the first model. (For example, would both premenopausal and postmenopausal patients have more local recurrences when treated with chemotherapy first and more distant recurrences when treated with radiotherapy first? Or would menopausal status affect the patterns of recurrence in these two groups?) The P values for each variable in this model are listed in Table 2.

RESULTS

Outcome of Therapy

Treatment failed in 45 patients in the radiotherapy-first group and 34 patients in the chemotherapy-first group over the entire period of observation, from 2 to

Table 2. Crude Five-Year Incidence of First Recurrence in the Two Treatment Groups, According to Site.*

VARIABLE	NO. OF PATIENTS ABLE TO BE EVALUATED		LOCAL RECURRENCE		DISTANT OR REGIONAL RECURRENCE		P VALUE FOR MAIN EFFECT	P VALUE FOR SEQUENCE INTERACTION
	RT	CT	RT	CT	RT	CT		
	<i>percent</i>							
Treatment group	78	79	5	14	32	20	0.05	NA
Age of patients							0.08	0.24
≤45 yr	45	46	7	15	24	20		
≥46 yr	33	33	3	12	42	21		
Menopausal status							0.18	0.21
Premenopausal	57	59	5	10	26	22		
Postmenopausal	21	20	5	25	48	15		
Tumor size							0.11	0.43
≤2 cm	48	39	6	10	27	10		
>2 cm	28	39	4	18	39	28		
Unknown	2	1	0	0	50	100		
Extensive intraductal component							0.58	0.57
Present	14	9	7	22	21	11		
Absent	64	70	5	13	34	21		
Lymphatic-vessel invasion							<0.001	0.28
Present	34	44	6	11	35	27		
Absent	7	5	0	0	14	0		
Indeterminate	22	14	9	14	27	14		
Unknown	15	16	0	25	40	13		
Re-excision							0.06	0.50
No	28	30	7	27	39	17		
Yes	50	49	4	6	28	22		
Estrogen-receptor protein							0.93	0.23
Present	35	35	3	17	26	23		
Absent	29	27	10	11	38	19		
Unknown	14	17	0	12	36	18		
Margins							0.09	<0.001
Negative	36	33	6	0	25	18		
Close	15	13	0	23	33	23		
Positive	14	23	14	26	36	17		
Unknown	13	10	0	20	46	30		
Nodal status							0.49	<0.001
Negative	5	5	0	20	40	0		
Positive								
1–3 nodes	51	50	4	10	24	22		
≥4 nodes	22	24	9	21	50	21		

*RT denotes the radiotherapy-first group, CT the chemotherapy-first group, and NA not applicable. See the Methods section for definitions of menopausal status, presence of the estrogen-receptor protein, and resection-margin categories.

118 months after the start of therapy ($P=0.17$). The numbers of patients in whom distant recurrences appeared at any time during follow-up in the radiotherapy-first and chemotherapy-first groups were 42 and 28, respectively ($P=0.07$), and there were 35 and 24 deaths, respectively (including 1 patient in the chemotherapy-first group who died of ovarian cancer without evidence of recurrent breast cancer) ($P=0.13$). The five-year actuarial incidences of any recurrence, distant recurrence, and overall survival in the radiotherapy-first and chemotherapy-first groups were 38 percent and 31 percent ($P=0.17$), 36 percent and 25 percent ($P=0.05$), and 73 percent and 81 percent ($P=0.11$), respectively (Fig. 1). The hazard ratios (and their 95 percent confidence intervals) were 1.37 (0.88 to 2.14) for the time until the first recurrence in the radiotherapy-first group as compared with the chemotherapy-first group, 1.62 (1.01 to 2.62) for the time until distant

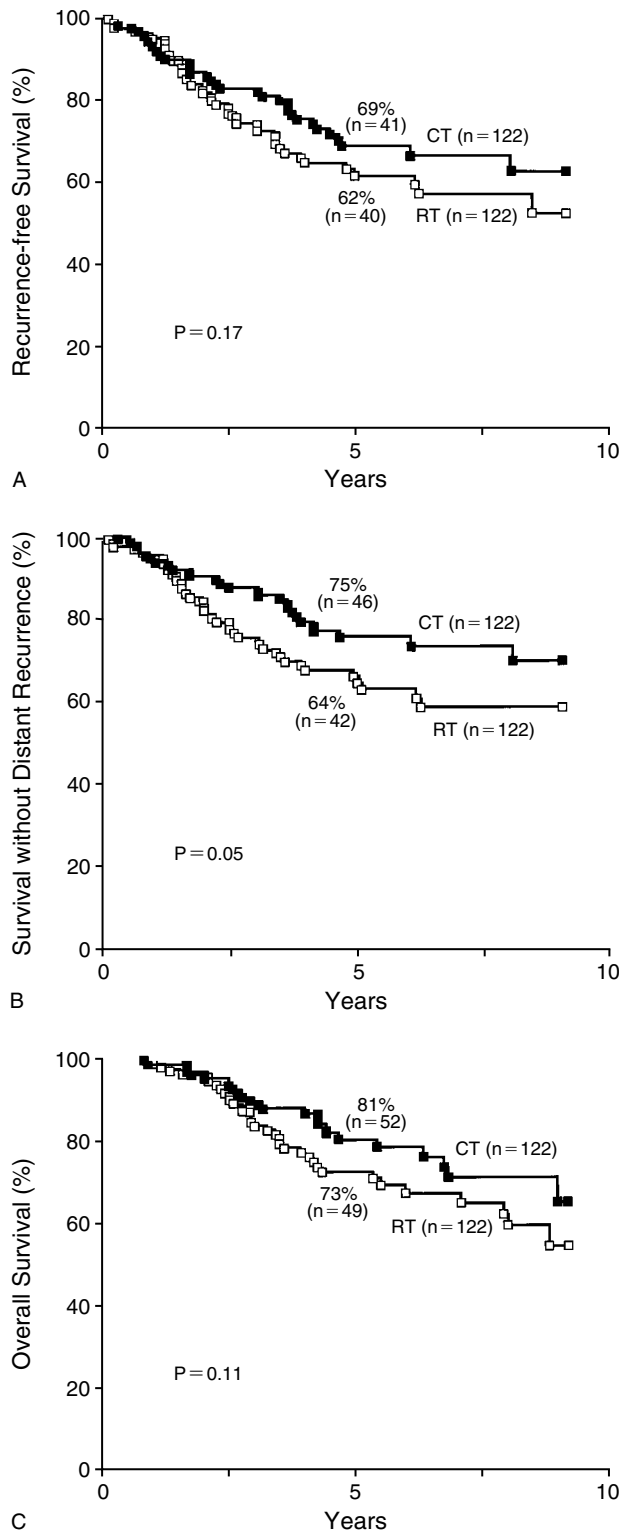


Figure 1. Actuarial Curves for Rates of Recurrence-free Survival (Panel A), Survival without Distant Recurrence (Panel B), and Overall Survival (Panel C), According to the Assigned Treatment Group.

CT denotes the chemotherapy-first group, and RT the radiotherapy-first group. The percentages shown are those at five years.

metastases were found, and 1.52 (0.90 to 2.56) for survival time.

Recurrences

First sites of recurrence for all the patients who could be evaluated five years after randomization are shown in Table 2. There was an increased risk of local recurrence in the chemotherapy-first group (14 percent vs. 5 percent) and of distant recurrence in the radiotherapy-first group (32 percent vs. 20 percent). This difference between the two groups in the pattern of where disease first recurred within five years after treatment was of borderline statistical significance ($P=0.07$, by the exact multinomial test). It is noteworthy that one of the local recurrences in the radiotherapy-first group happened 41 months after treatment began in one of the two patients who refused their assigned sequence and received the reverse; she had an interval of 140 days between surgery and radiotherapy. To compare the two groups in another manner, the relative risk for local or distant recurrence (as compared with no recurrence at all, or in comparison with one another) was calculated for each group. Then, the ratio of these relative risks was calculated by dividing the relative risk in the radiotherapy-first group by that in the chemotherapy-first group. The ratios of relative risks (and their 95 percent confidence intervals) were 0.39 (0.12 to 1.29) for having a local recurrence as compared with no recurrence, 1.66 (0.79 to 3.47) for having a distant recurrence as compared with no recurrence, and 0.23 (0.06 to 0.86) for having a local recurrence as compared with a distant one.

The first site of recurrence within five years after treatment was examined with regard to treatment group and certain features of the patients and the tumors (Table 2). In the first polychotomous logistic model, in which we examined the way variables (including treatment assignment) affected the risks of recurrence at various sites within five years after treatment, sequence assignment ($P=0.05$), invasion of the lymphatic vessels ($P<0.001$), and re-excision ($P=0.06$) had effects that were statistically significant or nearly significant (Table 2). In the second model, we examined the way other variables affected the relation between the pattern of recurrence and the treatment sequence that was found in the first model. Only the status of the tumor margin and the number of axillary lymph nodes with metastases significantly affected the result ($P<0.001$) (Table 2). For example, in patients with negative tumor margins there was little difference in the risks of recurrence, regardless of sequence assignment, and in patients with close, positive, or unknown tumor margins, the higher incidence of local recurrence in the chemotherapy-first group and the higher incidence of distant recurrence in the radiotherapy-first group persisted. For patients with one to three positive nodes, the sequence assignment made little difference in the risk of recurrence, but for patients with either negative nodes

or four or more positive nodes there was a higher local-recurrence rate in the chemotherapy-first group and a higher distant-recurrence rate in the radiotherapy-first group.

Chemotherapy

The median dose of chemotherapy delivered (as a percentage of the cumulative planned dose) was lower in the radiotherapy-first group than in the chemotherapy-first group for cyclophosphamide (81 percent vs. 88 percent, $P=0.01$), doxorubicin (81 percent vs. 88 percent, $P=0.01$), and methotrexate administered on day 15 (50 percent vs. 75 percent, $P<0.001$). There were no differences in the median dose of methotrexate administered on day 1 or fluorouracil (100 percent of each planned drug dose was delivered in each group). The median time required to complete chemotherapy was the same in both groups (84 days).

Side Effects of Therapy

The short-term and long-term toxic effects of either chemotherapy or radiotherapy (within six months of the completion of treatment) are listed in Table 3. There were no deaths. Nadir granulocyte counts of less than 500 per cubic millimeter after chemotherapy were more common in patients in the radiotherapy-first group during the first and third cycles but not the second and fourth cycles, probably because of the dose-reduction rules we used. Fever and neutropenia requiring hospitalization and radiation pneumonitis were more common in patients in the radiotherapy-first group. Complication rates did not vary with the irradiation technique except among patients in the radiotherapy-first group, among whom there was a slightly but not statistically significantly increased risk of radiation pneumonitis for those receiving radiation directed to regional nodes and the breast as compared with those receiving radiation directed to the breast alone. No cardiac events or other long-term complications have occurred as of this writing. Cosmetic results were assessed in patients without recurrence who were seen in follow-up by a radiation oncologist at the Joint Center for Radiation Therapy between 18 and 30 months after treatment. An "excellent" cosmetic result was defined as the virtual absence of changes due to treatment.¹² Results were excellent in 67 percent of the 39 patients who could be evaluated in the radiotherapy-first group and 60 percent of the 38 patients who could be evaluated in the chemotherapy-first group. Only 5 percent of the patients had fair cosmetic results, and only 3 percent had poor results.

DISCUSSION

This randomized study was designed to test the effect of the order in which chemotherapy and radiotherapy were given after conservative surgery and axillary dissection in patients with breast cancer. Local recurrence of cancer was more common when radiation therapy was given after the completion of chemotherapy,

Table 3. Short-Term and Long-Term Toxic Effects of Chemotherapy and Radiotherapy.

EFFECT	RADIOTHERAPY-FIRST GROUP	CHEMOTHERAPY-FIRST GROUP	P VALUE
	<i>percent (number/total)</i>		
Hemoglobin ≤ 6.5 g per deciliter in any cycle	3 (3/114)	3 (4/120)	1.0
Platelets $< 50,000$ per cubic millimeter in any cycle	0 (0/114)	2 (3/120)	0.25
Granulocytes < 500 per cubic millimeter			0.05
In any cycle	80 (91/114)	68 (81/120)	
On day 15			
Cycle 1	76 (77/101)	53 (59/112)	< 0.001
Cycle 2	13 (13/97)	16 (18/111)	0.70
Cycle 3	53 (52/99)	31 (34/109)	0.002
Cycle 4	19 (19/98)	16 (18/111)	0.59
Fever or neutropenia requiring hospitalization	17 (21/122)	7 (8/122)	0.02
Infectious pneumonia	5 (6/122)	1 (1/122)	0.12
Radiation pneumonitis*	4 (5/122)	0 (0/119)	0.06
Breast only	1 (1/78)	0 (0/77)	1.0
Breast and regional nodes	9 (4/44)	0 (0/42)	0.12
Moderate or extensive moist desquamation	15 (17/115)	11 (12/112)	0.43

*Excluded from the denominators of the chemotherapy-first group were two patients who did not receive any radiotherapy and one patient treated with uncertain technique (from the analysis of radiotherapy-technique subgroups only).

whereas systemic recurrence was more frequent when chemotherapy followed radiation therapy.

The rates of distant recurrence may have been higher among the patients treated with radiation therapy before chemotherapy than among those treated with the reverse sequence because of the longer interval between surgery and the start of chemotherapy and because of the lower drug doses in the former group. Retrospective analyses have disagreed about whether the interval between surgery and chemotherapy is important.^{3,13,14} Randomized studies of the effect of starting multidrug chemotherapy within a few hours or days to roughly four weeks after surgery have not found significant differences in outcome.^{15,16} However, the interval before starting "delayed" chemotherapy in our study (a median of 17 weeks) was markedly longer than in those studies. We do not know whether the small differences in delivered doses of drugs between the two groups in this trial account for the difference in rates of distant recurrence. In one randomized study, however, patients who received only one half of the "standard" cumulative drug doses had an increased risk of recurrence as compared with patients given the full dose.¹⁷

The risk of local recurrence is probably related to the number of tumor cells present when radiation therapy is initiated. This risk in turn depends on the tumor burden after surgery and the length of time the tumor cells have to proliferate before radiation therapy. The extent of breast resection, the details of radiotherapy, and the status of the resection margins may also influence the risk of recurrence. These complexities of breast cancer may account for the lack of agreement on the effect of

the interval between surgery and radiotherapy on rates of local recurrence.¹⁸⁻²⁶

Our results suggest that it is preferable to give 12 weeks of chemotherapy before irradiation, rather than radiotherapy first, to patients at substantial risk for systemic recurrence of cancer. However, this study has several limitations. The results of the subgroup analyses must be viewed with special caution. Although our results suggest that the effect of a delay in initiating chemotherapy may be greatest for patients with the highest risk of subclinical systemic disease (i.e., those with four or more positive nodes) and that a delay in initiating radiotherapy may be most detrimental to patients with close or positive margins of the resected tumor, the statistical power of our subgroup analyses is low. In addition, extrapolating the results of this trial to other regimens, particularly those with more prolonged intervals between surgery and radiotherapy (e.g., six months or more), may be misleading. Also, too few patients received tamoxifen (and only late in the study) to allow us to evaluate its effect.

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