Locoregional Radiation Therapy in Patients With High-Risk Breast Cancer Receiving Adjuvant Chemotherapy: 20-Year Results of the British Columbia Randomized Trial

Joseph Ragaz, Ivo A. Olivotto, John J. Spinelli, Norman Phillips, Stewart M. Jackson, Kenneth. S. Wilson, Margaret A. Knowling, Christopher M. L. Coppin, Lorna Weir, Karen Gelmon, Nhu Le, Ralph Durand, Andrew J. Coldman, Mohamed Manji

Background: **The British Columbia randomized radiation trial was designed to determine the survival impact of locoregional radiation therapy in premenopausal patients with lymph node–positive breast cancer treated by modified radical mastectomy and adjuvant chemotherapy. Three hundred eighteen patients were assigned to receive no further therapy or radiation therapy (37.5 Gy in 16 fractions). Previous analysis at the 15-year follow-up showed that radiation therapy was associated with a statistically significant improvement in breast cancer survival but that improvement in overall survival was of only borderline statistical significance. We report the analysis of data from the 20-year follow-up.** ***Methods:*** **Survival was analyzed by the Kaplan–Meier method. Relative risk estimates were calculated by the Wald test from the proportional hazards regression model. All statistical tests were two-sided.** ***Results:*** **At the 20 year follow up (median follow up for live patients: 249 months) chemotherapy and radiation therapy, compared with chemotherapy alone, were associated with a statistically significant improvement in all end points analyzed, including survival free of isolated locoregional recurrences (74% versus 90%, respectively; relative risk [RR] = 0.36, 95% confidence interval [CI] = 0.18 to 0.71; $P = .002$), systemic relapse–free survival (31% versus 48%; RR = 0.66, 95% CI = 0.49 to 0.88; $P = .004$), breast cancer-free survival (48% versus 30%; RR = 0.63, 95% CI = 0.47 to 0.83; $P = .001$), event-free survival (35% versus 25%; RR = 0.70, 95% CI = 0.54 to 0.92; $P = .009$), breast cancer-specific survival (53% versus 38%; RR = 0.67, 95% CI = 0.49 to 0.90; $P = .008$), and, in contrast to the 15-year follow-up results, overall survival (47% versus 37%; RR = 0.73, 95% CI = 0.55 to 0.98; $P = .03$). Long-term toxicities, including cardiac deaths (1.8% versus 0.6%), were minimal for both arms.** ***Conclusion:*** **For patients with high-risk breast cancer treated with modified radical mastectomy, treatment with radiation therapy (schedule of 16 fractions) and adjuvant chemotherapy leads to better survival outcomes than chemotherapy alone, and it is well tolerated, with acceptable long-term toxicity. [J Natl Cancer Inst 2005;97:116–26]**

The use of adjuvant locoregional radiation therapy for high-risk breast cancer received considerable attention in the late 1990s because the results of several recent large, randomized trials and a meta-analysis showed statistically significant reductions in locoregional and systemic relapses and breast cancer mortality *(1–5).* This outcome is in contrast with earlier meta-analyses of postmastectomy radiation therapy trials that showed fewer locoregional events as a result of radiation therapy but no overall survival benefit *(6–8).*

The British Columbia randomized radiation therapy trial was designed to determine the survival impact of locoregional radiation therapy in premenopausal patients with lymph node–positive breast cancer treated by modified radical mastectomy and adjuvant chemotherapy. Three hundred eighteen patients were assigned to receive no further therapy or radiation therapy from January 1, 1979, through December 31, 1986. Radiation therapy (37.5 Gy in 16 fractions) was delivered in the middle of a 6-month chemotherapy course to the chest wall and to all regional lymph node–bearing areas, including bilateral internal mammary chains. All patients had level I and II axillary dissection, with a median of 11 lymph nodes recovered. Outcomes at 15 years of follow-up, reported previously *(3),* were analyzed by Kaplan–Meier methods, with appropriate relative risk (RR) rate estimates from the Cox proportional hazards regression model. The results showed that radiation therapy was statistically significantly associated with reductions in breast cancer mortality (RR = 0.71, 95% confidence interval [CI] = 0.51 to 0.99; $P = .05$) and breast cancer recurrences (RR = 0.67, 95% CI = 0.50 to 0.90; $P = .007$); however, improvement in overall survival was not of statistical significance (RR = 0.74, 95% CI = 0.53 to 1.02; $P = .07$).

This article presents results from the 20-year follow-up analysis of the British Columbia randomized study *(3).* The purpose

Affiliations of authors: McGill University Health Center, Montreal, PQ, Canada (JR); British Columbia Cancer Agency Systemic Therapy (JR, MAK, CMLC, KG, RD), Radiation Therapy (SMJ, LW, MM), and Population and Preventive Oncology (JJS, NP, NL, AJC) Programs of the British Columbia Cancer Agency, Vancouver and Victoria (IAO, KSW), BC, Canada.

Correspondence to: Joseph Ragaz, MD, FRCPC, McGill University Health Center, Royal Victoria Hospital, 687 Pine Ave., Montreal, PQ, Canada H3A 1A1 (e-mail: joseph.ragaz@mcgill.ca).

See "Note" following "References."

DOI: 10.1093/jnci/djh297

Journal of the National Cancer Institute, Vol. 97, No. 2,

of this update was threefold: first, to determine whether the reduction of systemic recurrence rates translates into a long-term survival advantage in irradiated patients that would be reflected in overall survival; second, to determine whether radiation therapy confers a benefit in all patients with involved lymph nodes; and third, to establish whether a paradigm shift in breast cancer management could be solidly confirmed, in which adjuvant radiation therapy after mastectomy would statistically significantly influence not only locoregional recurrences but also the systemic outcome and, thus, curability.

Patients and Methods

Patients

From January 1, 1979, through December 31, 1986, 318 premenopausal women with breast cancer with pathologically positive axillary lymph nodes who were referred to the British Columbia Cancer Agency in Vancouver and Victoria, British Columbia, Canada, after a modified radical mastectomy and axillary lymph node dissection, were randomly assigned to locoregional radiation therapy or to no additional treatment. Patients with breast cancer were randomly allocated to each of the arms by use of a series of even and odd computer-generated numbers, as supervised by the trial headquarters secretary and two principal investigators, one for medical oncology (J. Ragaz) and one for radiation oncology (S. M. Jackson). The CONSORT diagram of the study design is shown in Fig. 1.

Adjuvant chemotherapy with cyclophosphamide (600 mg/m^2), methotrexate (40 mg/m^2), and 5-fluorouracil (600 mg/m^2), all administered intravenously, was given every 3 weeks for a total of nine cycles (the CMF regimen). The CMF regimen was given initially for 12 months (to the first 80 patients), and then the treatment period was reduced to 6 months (for the other 238 patients), after it had been shown that 6 and 12 months of CMF gave equivalent results *(9)*.

Radiation therapy was given by a five-field technique. The postmastectomy chest wall received a dose of 37.5 Gy in 16 daily fractions over 3–4 weeks through tangential fields; the mid-axilla received a dose of 35 Gy in 16 fractions through an opposed anterior supraclavicular/axillary field and a posterior axillary patch. A direct internal mammary-chain field, covering the bilateral internal mammary chains, delivered a dose of 37.5 Gy in 16 fractions to the maximum dose point. Radiation therapy was delivered with a cobalt-60 source between the fourth and fifth chemotherapy cycles (a radiation therapy "sandwich" technique). The chemotherapy interval during radiation therapy was extended for up to 5–6 weeks, to allow recovery of the white blood cell count and recovery from other toxicities.

The first 128 patients with a positive estrogen receptor (ER) status underwent a second random assignment to radiation-induced oophorectomy plus prednisone (7.5 mg/day for 2 years; 63 patients) versus no hormonal manipulation (65 patients). Patients whose disease recurred were treated at the discretion of the attending oncologists. In most instances, patients from the chemotherapy-alone group who had an isolated locoregional recurrence underwent therapeutic radiation therapy according to the same schedule used in the adjuvant setting. ER-positive patients whose disease recurred were treated with a sequential hormonal regimen involving tamoxifen (20 mg/day), megestrol acetate (160 mg/day), or the aromatase inhibitor aminogluteth-

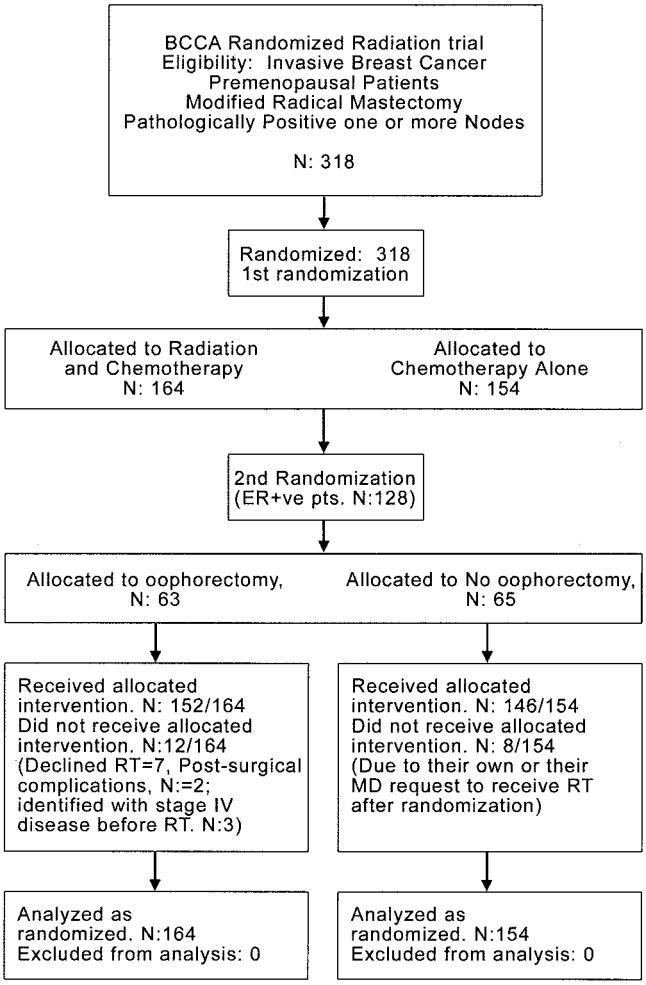


Fig. 1. CONSORT trial flow diagram for the British Columbia Randomized Radiation Trial. Eligibility criteria and outline of treatments in each of the randomized arms are presented. CMF = cyclophosphamide, methotrexate, and 5-fluorouracil. Estrogen receptor–positive (ER+ve) patients were also randomly assigned to no further treatment or to receive adjuvant radiation to ablate the ovaries (radiation oophorectomy), typically delivered at the end of the radiation and chemotherapy program. Oophorectomy in this trial consisted of radiation therapy to the pelvis (20 Gy over five fractions) and prednisone at 7.5 mg/day for 2 years. CT = chemotherapy; RT = radiotherapy.

imide (500–1000 mg/day) plus hydrocortisone (40 mg/day). Most patients whose disease recurred eventually received anthracycline-containing chemotherapy.

Statistical Analysis

In all survival analyses, the time to the end point was calculated from the date of tissue diagnosis of breast cancer until the event date, except for survival after locoregional failure, which was calculated from the date of the locoregional event. The following six end points were analyzed:

1) Event-free survival, was defined as the interval from date of diagnosis until the date of the following events: i. locoregional or systemic breast cancer recurrence, ii. second malignancy, including contralateral breast cancer, and iii. death from any cause.

2) Disease-free survival was defined as the interval between date of diagnosis and the date of the first breast cancer recurrence; with the event being any breast cancer recurrence, locore-

gional or systemic (patients with all other events were censored at the time of the event).

3) Systemic disease–free survival was defined as the interval between the diagnosis and the date of the first systemic breast cancer recurrence, with events being: i) systemic recurrence outside the locoregional area occurring at any time before or after locoregional relapse, ii) systemic recurrence with or without locoregional relapse, or iii) breast cancer death in patients with no information on systemic recurrence (patients with all other causes of death were censored).

4) Breast cancer-specific survival was defined as the interval from diagnosis until the date of death when the underlying cause of death was breast cancer (with or without a prior known date of locoregional or systemic relapse), with patients with all other causes of death censored.

5) Overall survival was defined as the interval from date of diagnosis until the date of death from any cause.

6) Locoregional recurrence was defined as recurrence in the chest wall or regional lymph node areas, including the axillary, supraclavicular, or internal mammary areas. Locoregional recurrence–free survival was calculated in two ways: as survival free of an isolated locoregional recurrence at a minimum of 6 months before a systemic event; or as a survival free of locoregional recurrence occurring at any time before systemic recurrence. For both definitions of locoregional recurrence–free survival, patients with other events were censored at the time of that event.

Analyses compared outcomes in the chemotherapy-alone group with those from the chemotherapy and radiation therapy group for all 318 patients (first analysis). The impact of radiation was also compared for the subgroups of patients with one to three involved lymph nodes (183 patients) and those with four or more involved lymph nodes (112 patients) (the second analysis). The 23 patients who had positive axillary lymph nodes but were missing information on the number of lymph nodes involved were evaluated in the first but not in the second set of analyses.

Survival was calculated by the Kaplan–Meier method. Statistical significance levels and 95% confidence intervals for the relative risk estimates were calculated with the Wald test from the proportional hazards regression model. The proportional hazards assumption was tested by the methods of Grambsch and Therneau, and it was not rejected for any model *(11),* with the smallest $P = .13$. Two-sided P values of less than .05 were considered statistically significant. All statistical tests were two-sided. Differences in the relative risks between subgroups were studied by the test for interaction via a proportional hazards regression model.

Of the 154 patients randomly assigned to the chemotherapy-alone group, eight had radiation therapy at their own request after the randomization. Of the 164 patients randomly assigned to chemotherapy and radiation therapy, 12 did not receive radiation therapy (seven declined, three had metastases before radiation therapy began, and two had postsurgical complications). All analyses were based on "intent to treat" as randomized and not as treated.

RESULTS

The distribution of patient demographic, pathologic, and treatment characteristics was similar in the two arms *(3).* A median of 11 axillary nodes were removed at mastectomy. After 20 years of follow up (a median follow-up of live patients of 249 months), 191 of the 318 patients had suffered a breast cancer relapse, and 190 of the 318 patients had died (170 from breast cancer and 20 from other causes).

Event-Free Survival, Breast Cancer–Free Survival, and Systemic Disease–Free Survival

Among the 154 patients randomly assigned to chemotherapy alone, 116 suffered any event (i.e., as defined by event-free survival) compared with 105 of the 164 patients assigned to chemotherapy and radiation therapy (Table 1), for an event-free survival at 20 years of 25% versus 38%, respectively (RR = 0.70, 95% CI = 0.54 to 0.92; $P = .009$). Analysis of breast cancer recurrences showed that 107 of the 154 patients in the chemotherapy-alone group had a recurrence of breast cancer, either locoregional or systemic, compared with 84 of the 164 patients assigned to chemotherapy and radiation therapy, for a breast cancer–free survival at 20 years of 30% versus 48%, respectively (RR = 0.63, 95% CI = 0.47 to 0.83; $P = .001$) (Fig. 2, A). Systemic recurrence of breast cancer was seen in 104 patients assigned to chemotherapy alone compared with 84 patients assigned to chemotherapy and radiation therapy (Table 1), for a systemic disease–free survival at 20 years of 31% versus 48% survival, respectively (RR = 0.66, 95% CI = 0.49 to 0.88; $P = .004$) (Fig. 3, B).

Breast Cancer–Specific Survival and Overall Survival

Breast cancer was the cause of death for 95 of the 154 patients treated with chemotherapy alone compared with 75 of the 164 patients treated with chemotherapy and radiation therapy (Table 1), for a 20-year breast cancer–specific survival of 38% and 53%, respectively (RR = 0.67, 95% CI = 0.49 to 0.90; $P = .008$). Death from any cause was recorded for 101 of the 154 patients treated with chemotherapy alone compared with 89 of the 164 patients treated with chemotherapy and radiation therapy (Table 1), for a 20-year overall survival of 37% and 47%, respectively (RR = 0.73, 95% CI = 0.55 to 0.98; $P = .03$) (Fig. 4, A).

Locoregional Recurrence

Twenty-seven (18%) of the 154 patients assigned to chemotherapy alone suffered an isolated locoregional recurrence compared with 12 (7%) of the 164 patients assigned to chemotherapy and radiation therapy. Survival free of isolated locoregional disease was 74% for patients assigned to chemotherapy alone and was 90% for those assigned to chemotherapy and radiation therapy (RR = 0.36, 95% CI = 0.18 to 0.71; $P = .002$) (Fig. 5, A). Among all patients, 43 (28%) of the 154 patients assigned to chemotherapy alone, compared with 17 (10%) of the 164 patients assigned to chemotherapy and radiation therapy suffered a locoregional relapse at any time before a systemic relapse. Thus, at 20 years, the survival free of locoregional disease developing at any time before systemic was 61% for patients assigned to chemotherapy alone and was 87% for those assigned to chemotherapy and radiation therapy (RR = 0.32, 95% CI = 0.18 to 0.57; $P < .001$) (Fig. 5, B).

Analysis of 39 patients with isolated locoregional recurrence of breast cancer showed that, in long-term follow-up, 37 of these 39 patients developed a systemic recurrence of breast cancer and died from breast cancer, despite salvage therapy at the time of locoregional relapse (Fig. 6). Specifically, among the 39 pa-

Table 1. Survival outcomes at a follow-up of 20 years*

Outcome	Chemotherapy-alone arm		Chemotherapy and radiation therapy arm		RR (95% CI)	P†
	Survival, %‡	No. of events/ No. of patients	Survival, %‡	No. of events/ No. of patients		
All 318 patients						
Event-free survival	25	116/154	35	105/164	0.70 (0.54 to 0.92)	.009
Breast cancer–free survival	30	107/154	48	84/164	0.63 (0.47 to 0.83)	.001
Survival free of isolated locoregional disease	74	27/154	90	12/164	0.36 (0.18 to 0.71)	.002
Systemic breast cancer–free survival	31	104/154	48	84/164	0.66 (0.49 to 0.88)	.004
Breast cancer–specific survival	38	95/154	53	75/164	0.67 (0.49 to 0.90)	.008
Overall survival	37	101/154	47	89/164	0.73 (0.55 to 0.98)	.03
Comparison by lymph node status						
Event-free survival						
N1–3 (n = 183)	32	62/92	44	51/91	0.71 (0.49 to 1.03)	
N≥4 (n = 112)	12	47/54	26	44/58	0.68 (0.45 to 1.03)	
P for interaction§						.8
Breast cancer–free survival						
N1–3 (n = 183)	41	53/92	57	38/91	0.64 (0.42 to 0.97)	
N≥4 (n = 112)	12	47/54	34	38/58	0.59 (0.38 to 0.91)	
P for interaction§						.7
Survival free of isolated locoregional disease						
N1–3 (n = 183)	79	14/92	91	7/91	0.46 (0.18 to 1.13)	
N≥4 (n = 112)	59	12/54	84	5/58	0.30 (0.10 to 0.85)	
P for interaction§						.6
Systemic breast cancer–free survival						
N1–3 (n = 183)	44	50/92	58	38/91	0.68 (0.45 to 1.04)	
N≥4 (n = 112)	11	47/54	33	38/58	0.63 (0.41 to 0.97)	
P for interaction§						.7
Breast cancer–specific survival						
N1–3 (n = 183)	53	43/92	64	31/91	0.67 (0.42 to 1.06)	
N≥4 (n = 112)	17	46/54	35	37/58	0.66 (0.43 to 1.01)	
P for interaction§						.9
Overall survival						
N1–3 (n = 183)	50	49/92	57	41/91	0.76 (0.50 to 1.15)	
N≥4 (n = 112)	17	46/54	31	40/58	0.70 (0.46 to 1.06)	
P for interaction§						.7

*RR = relative risk; CI = confidence interval.

†*P* values for the two analyses are derived from different tests. For the analysis of all 318 patients; the *P* value reflects the difference between the two arms and was derived from the Wald test from the proportional hazards regression model. Two-sided *P* values of less than .05 were considered to be statistically significant. All statistical tests were two-sided. For the analysis of lymph node status, *P* values were generated from a test for interaction. For comparison by lymph node status, the test for interaction (a proportional hazards regression model) was used to reflect the impact of radiation therapy between the two cohorts with one to three positive lymph nodes (N1–3) and the other with four or more positive lymph nodes (N≥4). (The 23 patients who had positive axillary lymph nodes but were missing information on the number of lymph nodes involved were evaluated in the first but not in the second set of analyses.)

‡Survival values were estimates derived from Kaplan-Meier analyses and do not necessarily reflect the number of events divided by the number of patients.

§P for intraction between subgroups.

tients, a systemic relapse developed subsequently in 25 of the 27 patients treated with chemotherapy alone and in 12 of the 12 patients treated with chemotherapy and radiation therapy (RR = 1.02, 95% CI = 0.50 to 2.08; $P = .96$).

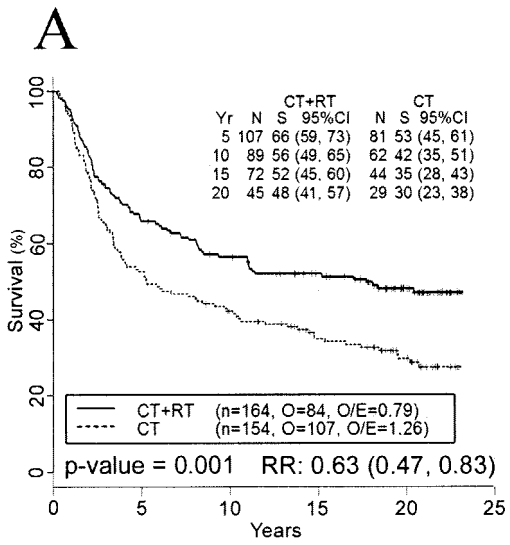
Analysis by Lymph Node Status

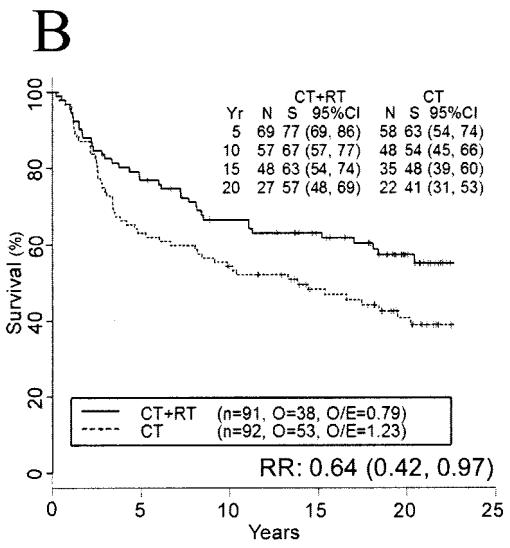
Patients were categorized into two subgroups by lymph node status (one to three involved axillary lymph nodes versus four or more involved lymph nodes), and the association of radiation therapy with all survival end points was analyzed. Table 1 shows that all survival outcomes, including time to isolated locoregional recurrence (Fig. 5, A and B), time to systemic recurrence (Fig. 3, B and C), breast cancer-specific survival, and overall survival (Fig. 4, B and C), were consistently improved with the addition of radiation therapy. Approximately one-third of systemic breast cancer events and breast cancer deaths were reduced by radiation therapy. Moreover, the impact of radiation therapy for all survival outcomes in the subgroup with one to three axillary lymph nodes involved was similar to that in the subgroup with more than four lymph nodes involved, as determined by the test for interaction (Table 1).

Non–Breast Cancer Deaths and Other Toxicities

The rate of non–breast cancer deaths was 8.5% among patients treated with chemotherapy and radiation therapy (14 of 164 patients) compared with 3.8% patients in the chemotherapy-alone group (six of 154 patients; two-sided Fisher's exact test, $P = .11$). Given the magnitude of the benefit associated with radiation therapy for breast cancer, the long-term toxicities of radiation therapy were acceptable. There were three (1.8%) cardiac deaths among the 164 patients treated with chemotherapy and radiation therapy and one (0.6%) among the 154 patients treated with chemotherapy alone (two-sided Fisher's exact test, $P = .622$).

Other toxicities associated with radiation therapy included arm edema among 15 (9.1%) of the 164 patients treated with





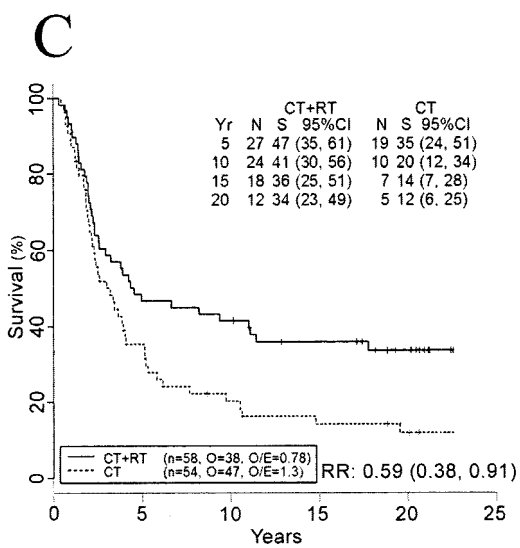
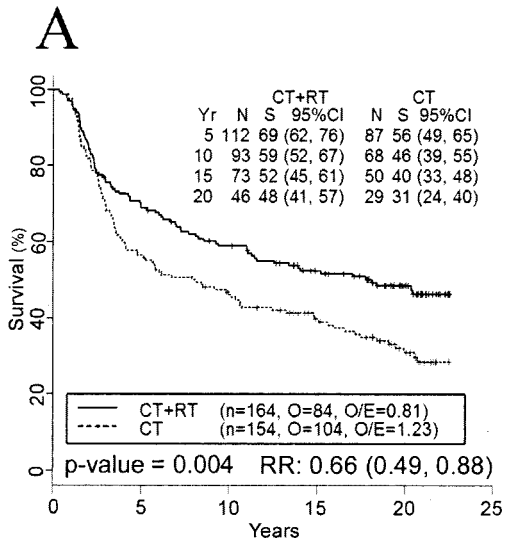
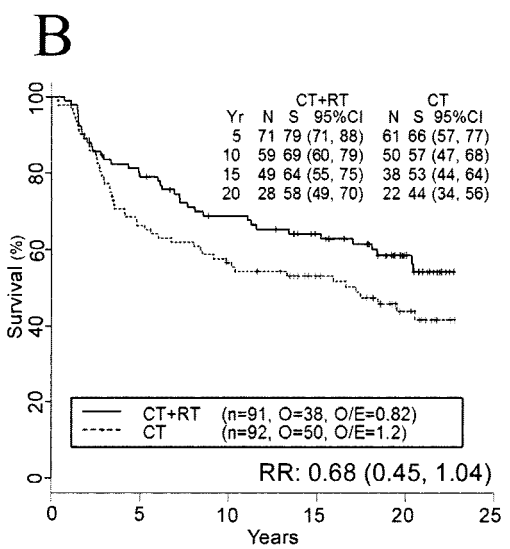


Fig. 2. Breast cancer–free survival. An event is defined as a locoregional or systemic breast cancer recurrence. **A**) All 318 patients. **B**) The 183 patients with one to three positive axillary lymph nodes. **C**) The 112 patients with more than three positive axillary lymph nodes. N or n = number of patients (at risk); S = survival percent with 95% confidence intervals in parentheses; O/E = observed/expected; RR = relative risk, with 95% confidence intervals in parentheses. All statistical tests were two-sided. CT = chemotherapy; RT = radiotherapy.





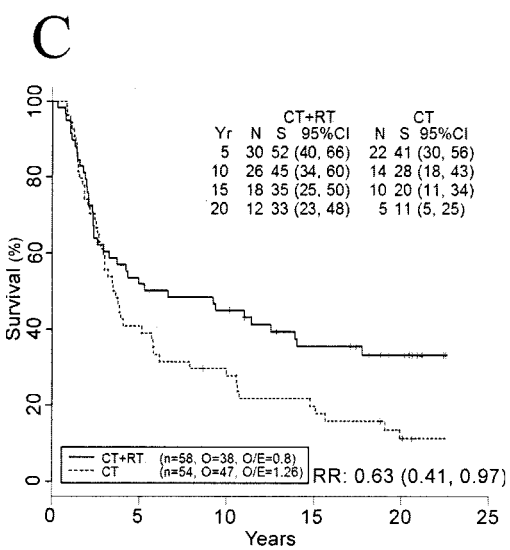


Fig. 3. Systemic breast cancer–free survival. An event is defined as systemic breast cancer recurrence. **A**) All 318 patients. **B**) The 183 patients with one to three positive axillary lymph nodes. **C**) The 112 patients with more than three positive axillary lymph nodes. N or n = number of patients (at risk); S = survival percent, with 95% confidence intervals in parentheses; O/E = observed/expected; RR = relative risk, with 95% confidence intervals in parentheses. All statistical tests were two-sided. CT = chemotherapy; RT = radiotherapy.

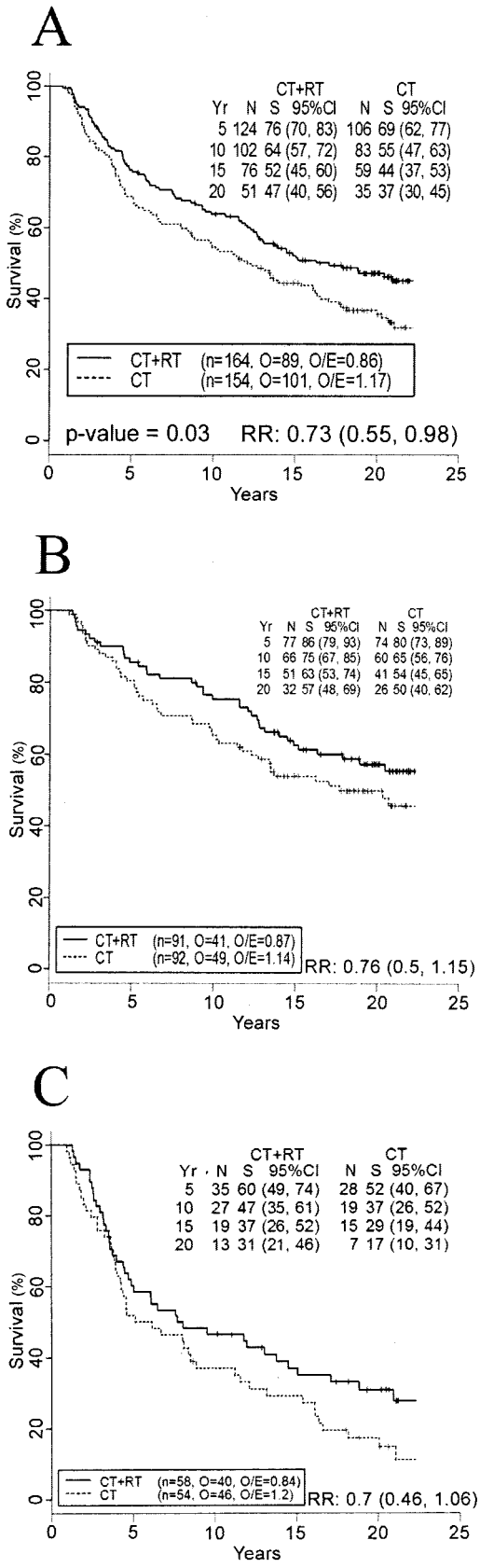


Fig. 4. Overall survival. An event is defined as death from any cause. **A**) All 318 patients. **B**) The 183 patients with one to three positive axillary lymph nodes. **C**) The 112 patients with more than three positive axillary lymph nodes. N or n = number of patients (at risk); S = survival percent, with 95% confidence intervals in parentheses; O/E = observed/expected; RR = relative risk, with 95% confidence intervals in parentheses. All statistical tests were two-sided. CT = chemotherapy; RT = radiotherapy.

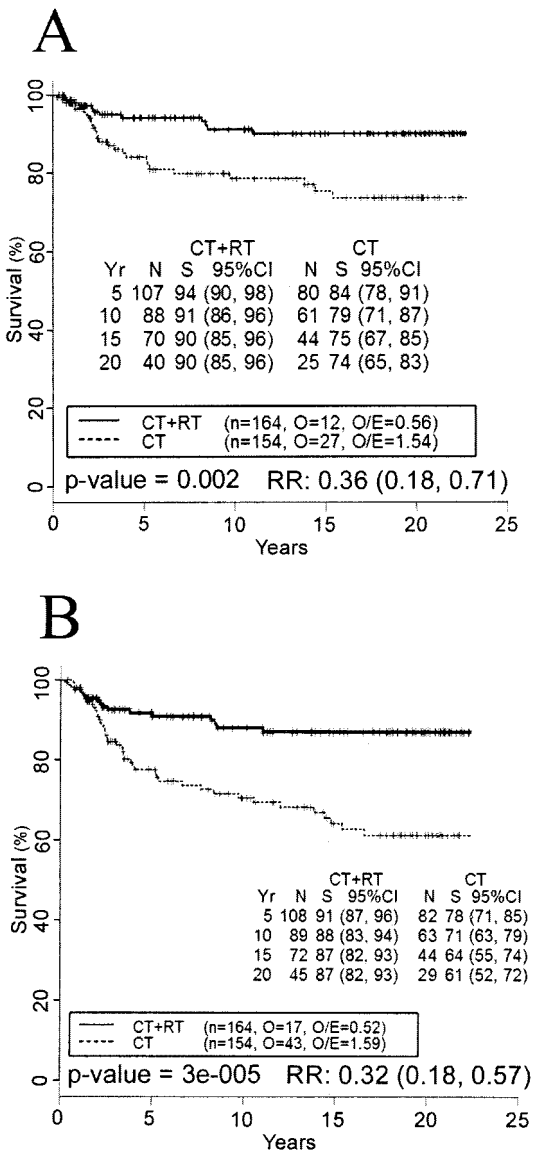


Fig. 5. Survival free of locoregional recurrence (all 318 patients). **A**) Survival free of isolated locoregional recurrence. An event is defined as locoregional recurrence more than 6 months before systemic recurrence. **B**) Survival free of locoregional recurrence before systemic recurrence (an event is defined as locoregional recurrence any time before the systemic recurrence). N or n = number of patients (at risk); S = survival percent, with 95% confidence intervals in parentheses; O/E = observed/expected; RR = relative risk, with 95% confidence intervals in parentheses. All statistical tests were two-sided. CT = chemotherapy; RT = radiotherapy.

chemotherapy and radiation, compared with five (3.2%) of the 154 patients treated with chemotherapy alone (two-sided Fisher's exact test, $P = .035$). Arm edema that required intervention (elastic sleeve, pump, or physiotherapy) occurred in six (3.7%) of the 164 patients in the chemotherapy and radiation therapy group, compared with one (0.6%) of the 154 patients in the chemotherapy-alone group (two-sided Fisher's exact test, $P = .122$). Limited asymptomatic apical lung fibrosis was seen in all patients treated with radiation therapy, with one (0.6%) of the 164 patients in the chemotherapy and radiation group developing interstitial pneumonitis requiring corticosteroids, with full resolution of symptoms confirmed by chest x-ray findings several months later.

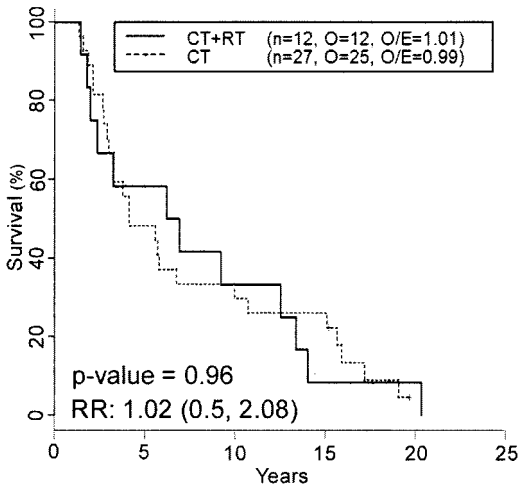


Fig. 6. Survival free of systemic breast cancer recurrence in patients who suffered an isolated locoregional recurrence (n = 39). An event is a systemic breast cancer recurrence. N or n = number of patients (at risk); S = survival percent, with 95% confidence interval in parentheses; O/E = observed/expected; RR = relative risk, with 95% confidence interval in parentheses. All statistical tests were two-sided. CT = chemotherapy; RT = radiotherapy.

Discussion

Impact of Radiation Therapy on Survival

This study found that, with 20 years of follow-up, postmastectomy chemotherapy and radiation therapy encompassing all regional lymph nodes and the chest wall areas statistically significantly reduced the rates of locoregional and systemic breast cancer recurrence, compared with postmastectomy chemotherapy alone. As a result, survival outcomes were substantially improved, with a statistically significant 32% reduction in breast cancer mortality in the chemotherapy and radiation therapy group compared with the chemotherapy-alone group and a statistically significant 27% reduction in overall mortality. Furthermore, the overall survival benefits associated with radiation therapy have now increased with follow-up to 20 years compared with the trial's results after 15 years of follow-up *(3).* Hence, as with adjuvant systemic therapy, adjuvant radiation therapy produces not only delays in breast cancer–related events but also improvements in long-term survival benefits.

These results also confirm that follow-up times of more than 15 years may be required to understand the full survival impact of adjuvant interventions. Our results are consistent with those of the Danish pre- and postmenopausal trials, which also confirmed the survival benefit of radiation therapy in chemotherapy-treated patients *(2,4),* and with a meta-analysis *(5)* of all adjuvant trials in which radiation therapy given in conjunction with chemotherapy was compared with the same chemotherapy alone, confirming statistically significant reduction of overall mortality associated with radiation therapy *(5).*

However, in spite of a reduction in breast cancer mortality, and in systemic and locoregional recurrences in the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) meta-analysis of radiation therapy *(8),* a statistically significant improvement in overall survival was not demonstrated, perhaps because many of its constituent trials, particularly those initiated before 1975 (i.e., 48% of all patients evaluated), used old radiation therapy techniques and now-obsolete treatment schedules with greater cardiotoxicity. In addition, many studies in this meta-analysis included low-risk lymph node–negative patients who had a considerably lower recurrence risk, and thus there was less justification for the side effects of regional radiation. All of these factors can reduce the therapeutic ratio, with increased toxicity rates over the benefits, and may explain the difference between the EBCTCG meta-analysis and our trial. A re-analysis of the 2000 EBCTCG overview showed a statistically significant reduction in all-cause mortality associated with radiation therapy among lymph node–positive patients and among trials started after 1975 *(12).*

Radiation Therapy and Systemic Recurrences

The long-term reduction in the rate of systemic recurrence associated with radiation therapy observed in our trial indicates that the locoregional microscopic disease that survives both mastectomy and chemotherapy is the origin of subsequent systemic metastases and locoregional recurrences. Our data indicate that radiation therapy can effectively eradicate this source of metastases in more than 30% of patients who would otherwise be at risk of systemic dissemination. Thus, radiation therapy, although administered locoregionally, does ultimately have a strong (albeit indirect) systemic effect. This paradigm is a fundamentally new one (Table 2), because most past and present radiation studies have enumerated reductions in locoregional events as the main marker of radiation therapy benefit *(13–15).*

Our data indicate that this approach will underestimate the impact of radiation therapy on systemic dissemination and breast cancer mortality and that to fully characterize the impact of radiation therapy, systemic events and breast cancer mortality must also be evaluated, particularly in medium-risk patients (i.e., breast cancer patients with one to three involved lymph nodes) who have lower rates of locoregional recurrences but still relatively high rates of systemic spread (Table 1). Our results show that, even in these medium-risk patients, approximately one-third of systemic recurrences can be avoided by use of radiation therapy, a benefit that could be missed if only rates of locoregional recurrence are examined. This important observation challenges the conventional view that radiation therapy reduces the locoregional relapse rate but not the systemic relapse rate.

The importance of irradiation added to chemotherapy, as seen in our trial, is consistent with therapy outcomes in other solid tumors, such as lung *(16),* esophageal *(17),* rectal *(18),* and head and neck *(19)* cancers, in which chemotherapy alone, irrespective of dose, regimens, and intensity, cannot successfully eliminate all the residual locoregional disease, the source of subsequent systemic dissemination. This residual disease, although still microscopic, may be sufficiently extensive to be resistant to or to become resistant to chemotherapy. Accordingly, even the best available chemotherapy regimens, including those with high-dose intensification requiring stem cell support, will be ineffective if used alone *(20)* (Table 3), and will require locoregional radiation therapy to optimize outcome.

Applicability of Our Results to Present Clinical Practice

One of the critical questions generated by this trial is its applicability to patients treated with dose-intensive adjuvant chemotherapy regimens, including anthracyclines *(21)* and taxanes *(22).* The CMF regimen in the British Columbia and in the Danish premenopausal trials *(2,3)* is now used infrequently. The

Table 2. New paradigms for postmastectomy radiation therapy in human breast cancer

Old/present paradigm	New paradigm
1. Radiation therapy is primarily aimed at locoregional control.	Although radiation therapy is delivered locoregionally, it has a substantial effect on systemic spread and thus the curability of human breast cancer.
2. Impact of radiation therapy is assessed according to the rate of locoregional recurrence.	Impact of radiation therapy is assessed from the rate of systemic recurrence; otherwise, its impact (on systemic disease and breast cancer cure) may be underestimated.
3. Systemic recurrences originate from locoregional recurrences.	Locoregional recurrences are only a marker for systemic recurrences. Both locoregional and systemic recurrences originate from deep-seated malignant clones; both can be impacted by radiation therapy.
4. Radiation therapy may be effective only if inadequate (low and/or medium dose intensity) chemotherapy is used.	Radiation therapy reduces mortality regardless of the chemotherapy dose intensity. Although absolute benefit of radiation therapy may differ according to chemotherapy dose intensity, the relative risk reduction attributed to radiation therapy is constant.
5. Radiation therapy may be effective only with inadequate (axillary) surgery.	Although the absolute benefit of radiation therapy may be more evident with less adequate surgery, the relative risk reduction attributed to radiation therapy is similar with complete or less complete axillary surgery.

relatively high locoregional recurrence rates reported in both trials *(2,3)* and the adequacy of axillary dissection in the Danish trial (a median of seven lymph nodes removed) have led to speculation that radiation therapy may be effective only in the context of either suboptimal surgery *(23)* or chemotherapy *(24)*.

Axillary surgery and radiation therapy. In the British Columbia trial, patients had a median of 11 axillary lymph nodes removed as part of level I and II axillary lymph node dissections. This type of axillary surgery is considered the present standard of care in patients having modified radical mastectomy or breast-conserving surgery. In our study at 20 years of follow-up, the proportion of patients relapsing with isolated locoregional recurrence (crude estimates) was 18% in patients treated with chemotherapy alone and 7% in patients treated with chemotherapy and radiation therapy. These rates are comparable to those seen with adequate follow-up (i.e., 10 years or more) in ongoing trials of patients with lymph node–positive breast cancer *(25–27)*.

Although the type of axillary surgery and number of recovered axillary nodes in our trial is in accordance with the present standard of care, some evidence that dissection of additional axillary lymph nodes may be of added benefit *(28)* has led to further discussion about the necessity for radiation therapy in the context of axillary lymph node dissection. Axillary radiation fields in our study consisted of a large supraclavicular/axillary field, with a posterior axillary boost (i.e. an extra radiation does focused to the areas of suspected residual tumor).

Current practice in North America is to use a single anterior medial supraclavicular field treating the apex but not the low part of axilla. The limited axillary nodal field is used in an effort to reduce treatment-related morbidity from lymphedema, especially when 10 or more lymph nodes are removed. There are no trials confirming the efficacy of this approach, although several studies have demonstrated that locoregional recurrences are low when limited axillary radiation therapy follows a complete level I and/or II axillary dissection *(29,30)* and that the recurrence rates are inversely proportional to the number of lymph nodes removed *(26)*. These results suggest that radiation therapy techniques that avoid the lateral axilla may be effective when an adequate axillary dissection has been performed. A large Canadian multicenter randomized study, the Canadian National Cancer Institute Trial MA-20, is underway incorporating the selective approach to nodal radiation fields, and the results of this trial should help determine the best approach.

The impact of radiation therapy according to the number of axillary lymph nodes removed is best illustrated in the Danish studies *(2,4)*. Our previous analyses *(31)* of data from these studies show that, although absolute recurrence rates clearly fluctuate from low to high in proportion to the number of axillary lymph nodes removed, the relative benefit of radiation therapy on event reduction remained constant. Thus, in relative terms, radiation therapy impact was substantial, whether the number of lymph nodes removed was three or fewer, four to nine, or 10 or more [data from the Danish premenopausal trial *(2)*] or eight or fewer or more than eight [data from the Danish postmenopausal trial *(4)*], even though absolute recurrence rates were higher in patients with a low number of lymph nodes removed.

The main argument favoring locoregional radiation of all high-risk patients, regardless of the number of axillary lymph nodes removed, however, comes from our data and the Danish data, which show that, even among patients with adequate axillary surgery, recurrence in the chemotherapy-alone arms is more than 30%, with irradiation reducing the recurrences by at least one-third. Therefore, results of the Danish trials, and those of other trials *(28,32–34),* corroborate our conclusions that, in patients with high-risk breast cancer, optimum outcome requires

Table 3. Impact of locoregional radiation therapy on recurrences (locoregional or systemic) in studies of differing chemotherapy dose intensity

Study	No. of patients	Years of follow-up	Chemotherapy dose intensity*	% with no radiation therapy*	% with radiation therapy	Relative risk
Arriagada et al. *(1)*	960	15	0.0	78	55	0.70
Overgaard et al. *(2)*	1708	10	0.4	56	41	0.64
Ragaz et al. *(3)*	318	15	0.6	63	48	0.66
McArdle et al. *(46)*	320	5	0.8	68	55	0.70
Velez-Garcia et al. *(47)*	622	10	1.0	62	47	0.70
Marks et al. *(15)*	49	4	4.0	19	9	0.45

*Chemotherapy dose intensity is reported at mg/m^2 of body surface area per week, as described by Hryniuk et al. *(48)*.

both radiation therapy and adequate axillary surgery in conjunction with chemotherapy.

Chemotherapy dose intensification and radiation therapy. One key ongoing question is whether the observed benefits of radiation therapy would be maintained in the context of contemporary chemotherapy regimens, including anthracyclines and/or taxanes, with higher dose intensity. Although the definitive answer will come only from a new generation of randomized trials testing the impact of radiation therapy and the current chemotherapy regimens (39), data are already available indicating that, even with the highest dose intensity chemotherapy regimens, relapse rates in high-risk patients treated without radiation therapy are substantial and that radiation therapy is beneficial in those situations *(20,35,36).*

In a review of the main randomized trials of radiation therapy for stage I–II breast cancer patients (Table 3) *(35),* the relative risks of locoregional and systemic recurrences were reduced as a result of radiation therapy (RR range = 0.45 – 0.76), independent of the chemotherapy regimen used. Thus, although the absolute relapse rates differ according to the underlying risk rates and chemotherapy dose intensification regimen used, the reductions in the relative risk rates associated with radiation therapy remain constant. These results also indicate that the benefits associated with radiation therapy in absolute terms will remain substantial in patients with a high risk of recurrence, regardless of the chemotherapy schedules used, and that the benefits associated with radiation therapy will be low in cohorts at low risk of recurrence. These data therefore support treatment policies whereby all high-risk patients treated with chemotherapy would be candidates for routine locoregional radiation therapy, whereas patients at low and medium risk may be candidates for either no radiation therapy or for trials assessing its impact on overall outcome.

Irradiation of the internal mammary lymph node chain. The complete five-field technique used in our trial included bilateral internal mammary lymph node chains in addition to axillary and supraclavicular lymph nodes. Most other trials demonstrating a survival advantage in patients treated with radiation therapy also included the internal mammary chain in the treatment volume *(5).* The internal mammary chains are important sites of metastases, particularly for inner and central quadrant tumors, as reported in studies of internal mammary chain scintigraphy *(37).* Thus, an integral component of optimal locoregional therapy of high-risk breast cancer may involve not only adequate axillary surgery and radiation therapy but also adequate radiation therapy delivered to the internal mammary chain. A wider radiation field, however, may be problematic because of cardiotoxicity, as discussed below. It is, however, not known whether the radiation benefit observed in this study would be compromised (and if so, to what extent) if the size of the irradiated fields (e.g., ipsilateral versus bilateral internal mammary chain) is reduced.

The value of radiation therapy to the internal mammary chain and medial supraclavicular area is being tested in the large, randomized European Organisation for Research and Treatment of Cancer (EORTC) trial 22922/10925 *(38).* If the internal mammary lymph nodes are to be treated with radiation, either ipsilateral to the affected breast or bilaterally, as in our study, careful attention to radiation techniques, including the use of three-dimensional treatment planning, is required.

Radiation therapy and cardiotoxicity. The overall survival benefit for patients treated with radiation therapy was observed in spite of slightly more non–breast cancer deaths occurring among patients treated with radiation therapy ($P = .17$). Cardiac events were the primary cause of death in 1.8% of patients treated with chemotherapy and radiation therapy compared with 0.6% of patients treated with chemotherapy alone ($P = .62$). Thus, in contrast to the cardiac mortality reports from the EBCTCG meta-analysis, which reported more cardiac deaths associated with those receiving radiation therapy *(6),* results of our trial suggest that the proportion of cardiac deaths in the radiation therapy arm of this premenopausal patient cohort is relatively low. Moreover, in long-term follow-up, the avoidance of breast cancer deaths outweighs any potential increase of non–breast cancer mortality, including cardiac deaths. Vallis et al. *(40),* using a dose and fractionation regimen similar to those in our trial, also observed low cardiac mortality among the patients treated with radiation therapy. These findings emphasize the need for critical review of the conclusions of the EBCTCG meta-analysis, which includes mainly trials initiated before 1975 that used now obsolete radiation therapy planning and treatment technologies.

Current radiation planning techniques that use three-dimensional computer tomography planning are clearly superior in terms of their ability to shield the heart compared with the radiation therapy used in our trial, which was conducted in the era before such technology. However, cardiac morbidity remains an important issue that may become more evident, particularly for left-side lesions treated with radiation therapy and for radiation therapy used in conjunction with potentially more cardiotoxic schedules of chemotherapy, including anthracyclines, taxanes, and trastuzumab (i.e., Herceptin). Thus, careful attention to avoiding cardiac morbidity and mortality with more sophisticated radiation therapy planning must be a high priority in the new schedules of combined adjuvant chemotherapy and radiation therapy, even though the new radiation techniques provide substantially reduced radiation doses to the heart by use of three-dimensional computed tomography *(41,42).*

Shorter radiation therapy fractionation given with chemotherapy. Short radiation therapy fractionation over 16 days was introduced by our group in the 1970s as a result of observations in earlier studies in the United Kingdom (Jackson S, personal communication) *(3).* The short radiation regimen (42.5 Gy in 16 daily fractions over 3.5 weeks) has been subsequently tested in a randomized trial against the conventional fractionation of 50 Gy in 25 daily fractions over 5 weeks *(43).* This trial showed equal survival, local control, toxicity, and cosmetic outcomes at 5 years in the two arms. Similar results with short fractionation after breast-conserving surgery have been reported in the recent British Columbia Cancer Agency randomized trials of aspirin versus no aspirin that used the short fractionation radiation therapy schedule (i.e., 16 fractions) *(44).* Although the latter two trials were in patients treated with breast-conserving surgery, they support the concept that the short fractionation schedule is acceptable with regard to outcome and preferable with regard to cost and the patient's quality of life. Specifically, the requirement for fewer treatment visits not only substantially reduces strain on the patients but also has clear economic advantages in reducing health care costs.

The short radiation therapy regimen also permits the radiation therapy to be more easily delivered in the middle of a chemo-

therapy course without inordinately long intervals between chemotherapy cycles, which may be an additional advantage. The combined chemotherapy and radiation therapy regimen may provide an important synergistic effect that could be more advantageous than the effect of delayed, sequential radiation therapy, as found in models of other common solid tumors (i.e., gastrointestinal, head and neck, gynecologic, and lung cancers). In addition, the delay with radiation therapy may abrogate the benefits obtained with earlier radiation therapy, as documented in this trial, because of the possible dissemination of chemotherapy-resistant clones while the patient awaits radiation therapy. This point may be particularly evident for high-risk tumors with a high doubling time and a rapidly expanding fraction of chemotherapy-resistant clones that are amenable to radiation therapy cell-kill effect. Hence, a disease that is potentially curable with early radiation therapy may become incurable if radiation therapy is delivered late—a scenario documented with level I evidence in a multicenter, randomized trial of small-cell lung cancer that demonstrated higher recurrence and death rates when radiation therapy was delayed until the conclusion of chemotherapy than when radiation therapy was given earlier *(16,45).*

Summary. This study showed that, in chemotherapy-treated patients with stage I-II breast cancer and involved axillary lymph nodes, locoregional radiation therapy substantially reduced the rates of both locoregional and systemic recurrence. As a result, breast cancer–specific and overall survival rates were substantially improved over a long follow-up of 20 years. Our analyses confirm that the benefits conferred by radiation therapy were of similar relative magnitude for patients with one to three positive axillary lymph nodes and for patients with four or more positive lymph nodes. Our data show that implementing radiation therapy soon after diagnosis in the adjuvant setting is important because patients with locoregional recurrences who were treated with a similar radiation therapy regimen at the time of relapse are generally not curable (Fig. 6). Although the benefits of adjuvant radiation therapy may be measured by both locoregional and systemic recurrence rates, the reduction of systemic recurrences associated with radiation therapy is of substantially higher importance, because systemic recurrence is a surrogate for eventual breast cancer mortality. Furthermore, evaluating the impact of radiation therapy solely according to the number of locoregional events may substantially underestimate its impact on distant metastases and breast cancer mortality.

Although our data were obtained from patients who were treated with relatively low chemotherapy dose intensity, even the highest dose intensity regimens appear to be inadequate to destroy microscopic locoregional disease among high-risk breast cancer patients *(20).* Our results, and those from other groups *(1,2,5,20),* confirm that in situations where residual disease remains, adjuvant chemotherapy alone in high-risk breast cancer patients is suboptimal and that the addition of locoregional radiation therapy is important to achieve the highest cure rate. Furthermore, our results were obtained with a shorter 16-fractionation schedule of radiation therapy that may be clinically equivalent to radiation therapy schedules with 25 or more fractions presently used *(43),* with important cost saving. Although contemporary radiation therapy trials using more dose-intensive chemotherapy regimens are appropriate to determine the therapeutic ratio of radiation therapy, results of our study indicate that in selected high-risk patients with breast cancer, routine use of adjuvant radiation in addition to adjuvant chemotherapy and surgery is indicated, because it substantially reduces mortality.

References

(1) Arriagada R, Rutqvist LE, Mattsson A, Kramar A, Rotstein S. Adequate locoregional treatment for early breast cancer may prevent secondary dissemination. J Clin Oncol 1995;13:2869–78.

(2) Overgaard M, Hansen PS, Overgaard J, Rose C, Andersson M, Bach F, et al. Postoperative radiotherapy in high-risk premenopausal women with breast cancer who receive adjuvant chemotherapy. Danish Breast Cancer Cooperative Group 82b Trial. N Engl J Med 1997;337:949–55.

(3) Ragaz J, Jackson SM, Le N, Plenderleith IH, Spinelli JJ, Basco VE, et al. Adjuvant radiotherapy and chemotherapy in node-positive premenopausal women with breast cancer. N Engl J Med 1997;337:956–62.

(4) Overgaard M, Jensen MB, Overgaard J, Hansen PS, Rose C, Andersson M, et al. Postoperative radiotherapy in high-risk postmenopausal breast-cancer patients given adjuvant tamoxifen: Danish Breast Cancer Cooperative Group DBCG 82c randomised trial. Lancet 1999;353:1641–8.

(5) Whelan TJ, Julian J, Wright J, Jadad AR, Levine ML. Does locoregional radiation therapy improve survival in breast cancer? A meta-analysis. J Clin Oncol 2000;18:1220–9.

(6) Cuzick J, Stewart HJ, Peto R, Baum M, Fisher B, Host H, et al. Overview of randomized trials of postoperative adjuvant radiotherapy in breast cancer. Recent Results Cancer Res 1988;111:108–29.

(7) Effects of radiotherapy and surgery in early breast cancer. An overview of the randomized trials [Erratum in: N Engl J Med 1996;334:1003]. Early Breast Cancer Trialists' Collaborative Group. N Engl J Med 1995;333:1444–55.

(8) Favourable and unfavourable effects on long-term survival of radiotherapy for early breast cancer: an overview of the randomised trials. Early Breast Cancer Trialists' Collaborative Group. Lancet 2000;355:1757–70.

(9) Bonadonna G, Valagussa P. Dose-response effect of adjuvant chemotherapy in breast cancer. N Engl J Med 1981;304:10.

(10) Hosmer DW, Lemeshow S. Applied Survival Analysis: Regression Modeling of Time to Event Data. Wiley, New York, 1999.

(11) Grambsch P, Therneau T. Proportional hazards tests and diagnostics based on weighted residuals. Biometrika 1994;81:515–26.

(12) Ragaz J, Spinelli JJ, Coldman AJ. Breast cancer survival advantage with radiotherapy. Lancet 2000;356:1270.

(13) Ragaz J, Jackson SM. Significance of axillary lymph node extranodal soft tissue extension and indications for postmastectomy irradiation. Cancer 2000;89:223–5.

(14) Mignano JE, Zahurak ML, Chakravarthy A, Piantadosi S, Dooley WC, Gage I. Significance of axillary lymph node extranodal soft tissue extension and indications for postmastectomy irradiation. Cancer 1999;86:1258–61.

(15) Recht A, Bartelink H, Fourquet A, Fowble B, Haffty BG, Harris JR, et al. Postmastectomy radiotherapy: questions for the twenty-first century [Erratum in: J Clin Oncol 1998;16:3211. J Clin Oncol 1998;16:2886–9.

(16) Murray N, Coy P, Pater JL, Hodson I, Arnold A, Zee BC, et al. Importance of timing for thoracic irradiation in the combined modality treatment of limited-stage small-cell lung cancer. The National Cancer Institute of Canada Clinical Trials Group. J Clin Oncol 1993;11:336–44.

(17) Tobias JS. Treatment of oesophageal cancer. J R Soc Med 2002;95:55.

(18) Douglass HO JR, Moertel CG, Mayer RJ, Thomas PR, Lindblad AS, Mittleman A, et al. Survival after postoperative combination treatment of rectal cancer. N Engl J Med 1986;315:1294–5.

(19) Urba SG. Concurrent chemoradiotherapy in head and neck cancer. Curr Oncol Rep 1999;1:105–9.

(20) Marks LB, Halperin EC, Prosnitz LR, Ross M, Vredenburgh JJ, Rosner GL, et al. Post-mastectomy radiotherapy following adjuvant chemotherapy and autologous bone marrow transplantation for breast cancer patients with greater than or equal to 10 positive axillary lymph nodes. Cancer and Leukemia Group B. Int J Radiat Oncol Biol Phys 1992;23:1021–6.

(21) Levine MN, Bramwell VH, Pritchard KI, Norris BD, Shepherd LE, Abu-Zahra H, et al. Randomized trial of intensive cyclophosphamide, epirubicin, and fluorouracil chemotherapy compared with cyclophosphamide, methotrexate, and fluorouracil in premenopausal women with node-

positive breast cancer. National Cancer Institute of Canada Clinical Trials Group. J Clin Oncol 1998;16:2651–8.
(22) Henderson IC, Berry DA, Demetri GD, Cirrincione CT, Goldstein LJ, Martino S, et al. Improved outcomes from adding sequential Paclitaxel but not from escalating Doxorubicin dose in an adjuvant chemotherapy regimen for patients with node-positive primary breast cancer. J Clin Oncol 2003;21:976–83
(23) Wolberg WH, Robins HI. Radiotherapy and chemotherapy in high-risk breast cancer [letter]. N Engl J Med 1998;338:329–333.
(24) Goldhirsch A, Coates AS, Colleoni M, Gelber RD. Radiotherapy and chemotherapy in high-risk breast cancer [letter]. N Engl J Med 1998;338:. 329 – 333.
(25) Pirtoli L, Bellezza A, Pepi F, Tucci E, Crociani M, Crastolla AM, et al. Breast-conserving treatment of early breast cancer. Results in a common clinical trial. Acta Oncol 1993;32:647–51.
(26) Recht A, Gray R, Davidson NE, Fowble BL, Solin LJ, Cummings FJ. Locoregional failure 10 years after mastectomy and adjuvant chemotherapy with or without tamoxifen without irradiation: experience of the Eastern Cooperative Oncology Group. J Clin Oncol 1999;17:1689–700.
(27) Wallgren A, Bonetti M, Gelber RD, Goldhirsh A, Castiglione-Gertsch M, Holmberg SB, et al. Risk factors for locoregional recurrence among breast cancer patients: results from International Breast Cancer Study Group Trials I through VII. J Clin Oncol 2003;21:1205–13.
(28) Zurrida S, Morabito A, Galimberti V, Luini A, Greco M, Bartoli C, et al. Importance of the level of axillary involvement in relation to traditional variables in the prognosis of breast cancer. Int J Oncol 1999;15:475–80.
(29) Katz A, Strom EA, Buchholz TA, Thames HD, Smith CD, Jhingran A, et al. Locoregional recurrence patterns after mastectomy and doxorubicin-based chemotherapy: implications for postoperative radiotherapy. J Clin Oncol 2000;18:2817–27.
(30) Fowble B, Solin LJ, Schultz DJ, Goodman RL. Frequency, sites of relapse, and outcome of regional node failures following conservative surgery and radiation for early breast cancer. Int J Radiat Oncol Biol Phys 1989;17: 703–10.
(31) Ragaz J, Spinelli JJ. Survival impact of locoregional radiation in stage I-II breast cancer: evidence-based review. In: Nabholtz JM, Tonkin K, Reese D, Apro M, Buzdar A, editors. Breast cancer management: application of clinical and translational evidence to patient care. New York (NY): Lippincott Williams & Wilkins; 2002. p. 39–49.
(32) Axelsson CK, Mouridsen HT, Zedeler K. Axillary dissection of level I and II lymph nodes is important in breast cancer classification. The Danish Breast Cancer Cooperative Group (DBCG). Eur J Cancer 1992;28A: 1415–8.
(33) Shukla HS, Melhuish J, Mansel RE, Hughes LE. Does local therapy affect survival rates in breast cancer? Ann Surg Oncol 1999;6:455–60.
(34) Fentiman IS. Long-term follow-up of the first breast conservation trial: Guy's wide excision study. Breast 2000;9:5–8.
(35) Ragaz J, Jackson SM. Survival gains of locoregional radiation in early breast cancer. In: Nabholtz JM, Tonkin K, Aapro MS, Buzdar AU, editors. Breast cancer management. Application of evidence to patient care. London (U.K.): Martin Dunitz; 2000. p. 285–99.
(36) Marks LB, Prosnitz LR. Is there a role for radiotherapy in the "curative" management of patients with metastatic cancer? Int J Radiat Oncol Biol Phys 1994;30:243–4.
(37) Manji M. Internal mammary lymphoscintigraphy in breast carcinoma: possible significance in relation to current treatment. J Can Assoc Radiol 1982;33:10–4.
(38) Poortmans PM, Venselaar JL, Struikmans H, Hurkmans CW, Davis JB, Huyskens D, et al. The potential impact of treatment variations on the results of radiotherapy of the internal mammary lymph node chain: a quality-assurance report on the dummy run of EORTC Phase III randomized trial 22922/10925 in Stage I-III breast cancer (1). Int J Radiat Oncol Biol Phys 2001;49:1399–408.
(39) T. Whelan: The Canadian National Cancer Institute [NCI(C)] randomized trial of locoregional versuss limited breast-on radiation, the MA-20 (ongoing).
(40) Vallis KA, Pintilie M, Chong N, Holowaty E, Douglas PS, Kirkbride P, et al. Assessement of coronary heart disease morbidity and mortality after radiation therapy for early breast cancer. J Clin Oncol 2002;20:1036–42.
(41) Cygler J, Copeland F. Role of CT scanning in radiation therapy with electron beams. Med Dosim 1988;13:69–71.
(42) Kuske RR. Adjuvant irradiation after mastectomy in women with one to three positive axillary nodes: then no; now yes. Semin Radiat Oncol 1999;9:254–8.
(43) Whelan T, MacKenzie R, Julian J, Levine M, Shelley W, Grimard L, et al. Randomized trial of regional irradiation schedules after lumpectomy for women with lymph node-negative breast cancer. J Natl Cancer Inst 2002; 94:1143–50.
(44) Olivotto IA, Kim-Sing C, Bajdik CD, Trevisan CH, Ludgate CM, Weir LM, et al. Effect of acetylsalicylic acid on radiation and cosmetic results after conservative surgery for early breast cancer: a randomized trial. Radiother Oncol 1996;41:1–6.
(45) Murray N. Timing of thoracic irradiation for limited small-cell lung cancer. J Clin Oncol 1998;16:1633–5.
(46) McArdle CS, Crawford D, Dykes EH, Calman KC, Hole D, Russell AR, et al. Adjuvant radiotherapy and chemotherapy in breast cancer. Br J Surg 1986;73:264–6.
(47) Velez-Garcia E, Carpenter JT Jr, Moore M, Vogel CL, Marcial V, Ketcham A, et al. Postsurgical adjuvant chemotherapy with or without radiotherapy in women with breast cancer and positive axillary nodes: a South-Eastern Cancer Study Group (SEG) Trial. Eur J Cancer 1992;28A:1833–7.
(48) Hryniuk W, Levine MN. Analysis of dose intensity for adjuvant chemotherapy trials in stage II breast cancer. J Clin Oncol 1986;4:1162–70.
(49) Ragaz J, Baird R, Rebbeck P. Preoperative versus postoperative adjuvant chemotherapy for stage I-II breast cancer. Long-term analysis of British Columbia randomized trial. Proc ASCO 1997;16:142a.

NOTE

Manuscript received April 1, 2004; revised September 2, 2004; accepted September 16, 2004.