ADJUVANT RADIOTHERAPY AND CHEMOTHERAPY IN NODE-POSITIVE PREMENOPAUSAL WOMEN WITH BREAST CANCER

JOSEPH RAGAZ, STEWART M. JACKSON, NHU LE, IAN H. PLENDERLEITH, JOHN J. SPINELLI, VIVIAN E. BASCO, KENNETH S. WILSON, MARGARET A. KNOWLING, CHRISTOPHER M.L. COPPIN, MARILYN PARADIS, ANDREW J. COLDMAN, AND IVO A. OLIVOTTO

ABSTRACT

Background Radiotherapy after mastectomy to treat early breast cancer has been known since the 1940s to reduce rates of local relapse. However, the routine use of postoperative radiotherapy began to decline in the 1980s because it failed to improve overall survival. We prospectively tested the efficacy of combining radiotherapy with chemotherapy.

Methods From 1978 through 1986, 318 premenopausal women with node-positive breast cancer were randomly assigned, after modified radical mastectomy, to receive chemotherapy plus radiotherapy or chemotherapy alone. Radiotherapy was given to the chest wall and locoregional lymph nodes between the fourth and fifth cycles of cyclophosphamide, methotrexate, and fluorouracil.

Results After 15 years of follow-up, the women assigned to chemotherapy plus radiotherapy had a 33 percent reduction in the rate of recurrence (relative risk, 0.67; 95 percent confidence interval, 0.50 to 0.90) and a 29 percent reduction in mortality from breast cancer (relative risk, 0.71; 95 percent confidence interval, 0.51 to 0.99), as compared with the women treated with chemotherapy alone.

Conclusions Radiotherapy combined with chemotherapy after modified radical mastectomy decreases rates of locoregional and systemic relapse and reduces mortality from breast cancer. (N Engl J Med 1997;337:956-62.)

TRIALS of postoperative radiotherapy for breast cancer conducted during the 1960s and 1970s showed significant reductions in rates of locoregional recurrence but no improvement in overall survival.[1,2] This result has been attributed to micrometastases, which determine prognosis regardless of the effect of the locoregional therapy. Additional concern was raised by data suggesting that irradiated patients have reduced survival rates, due to either immune suppression[3] or cardiac complications.[2,4,5]

In the late 1970s, adjuvant chemotherapy became a standard treatment for high-risk premenopausal patients with breast cancer.[6-8] The use of adjuvant radiation subsequently declined, because it did not appear to prolong survival. Nevertheless, there are reasons to reconsider radiotherapy, including the limited value of adjuvant chemotherapy for bulky disease,[9-11] a synergistic effect of chemotherapy plus radiation on residual locoregional tumor,[12-14] and the possibility that eliminating bulky disease with radiation may improve the effect of chemotherapy, because chemotherapy may be more effective when the overall disease burden is low.[9-12,15] To test the hypothesis that adding radiation to adjuvant systemic therapy improves the outcome in patients with breast cancer, we designed a randomized trial in 1978 in British Columbia. This report presents our findings after 15 years of follow-up.

METHODS

From 1979 through 1986, 318 premenopausal women with newly diagnosed stage I or II breast cancer were enrolled in the study after undergoing modified radical mastectomy if, after axillary-node dissection, one or more level I or II lymph nodes were found to be positive on pathological examination. The mastectomy was performed according to standard surgical practice between 1979 and 1986. After written informed consent was obtained, the patients were randomly assigned to one of two groups: those receiving adjuvant chemotherapy plus locoregional radiotherapy in five fields (the chemotherapy–radiotherapy group, with 164 patients) and those receiving chemotherapy alone (the chemotherapy group, with 154 patients). The characteristics of the patients were evenly balanced, as Table 1 shows.

Surgery

All the patients underwent modified radical mastectomy, with dissection of level I and II axillary lymph nodes. The surgery was performed by specialists who referred all the patients to the British Columbia Cancer Agency, the provincial cancer institute, for registration, randomization, and the planning of the chemotherapy and radiation treatments.

Chemotherapy

The chemotherapy consisted of cyclophosphamide (600 mg per square meter of body-surface area), methotrexate (40 mg per square meter), and fluorouracil (600 mg per square meter) (the CMF regimen), given intravenously every 21 days as described by Bonadonna et al.,[7] initially for 12 months (80 patients), and in the case of patients randomized after 1981, for 6 months.

Radiation

The radiation therapy was administered between the fourth and fifth cycles of chemotherapy. Sixteen daily treatments were

From the Departments of Medical Oncology (J.R., I.H.P., M.A.K., C.M.L.C.) and Radiation Oncology (S.M.J., V.E.B., M.P., I.A.O.), the Cancer Control Research Unit (N.L.), and the Cancer Control Strategy Process (A.J.C.), British Columbia Cancer Agency, Vancouver; the Department of Health Care and Epidemiology, University of British Columbia, Vancouver (J.J.S.); the Health Research Centre, St. Paul's Hospital, Vancouver (J.J.S.); and the Department of Medical Oncology, British Columbia Cancer Agency, Victoria (K.S.W.) — all in British Columbia, Canada. Address reprint requests to Dr. Ragaz at Medical Oncology, British Columbia Cancer Agency, 600 W. 10th Ave., Vancouver, BC V5Z 4E6, Canada.

TABLE 1. PROGNOSTIC VARIABLES AT BASE LINE IN THE TWO STUDY GROUPS.

VARIABLE	CHEMOTHERAPY (N = 154)	CHEMOTHERAPY AND RADIOTHERAPY (N = 164)	P VALUE
Median no. of nodes studied	11	11	1.0
	no. of patients (%)		
No. of nodes involved			0.4
1–3	92 (59.7)	91 (55.5)	
≥4	54 (35.1)	58 (35.4)	
Unknown	8 (5.2)	15 (9.1)	
Nodal size			0.5
<2 cm	59 (38.3)	67 (40.9)	
2–5 cm	74 (48.1)	67 (40.9)	
>5 cm	5 (3.2)	6 (3.7)	
Unknown	16 (10.4)	24 (14.6)	
Age			0.8
≤40 yr	36 (23.4)	34 (20.7)	
>40 yr	118 (77.6)	128 (78.0)	
Unknown	1 (0.6)	2 (1.2)	
Grade			0.85
Low (I)	45 (29.2)	44 (26.8)	
Medium (II)	66 (42.9)	75 (45.7)	
Poor (III)	43 (27.9)	45 (27.4)	
Estrogen receptors			0.55
≤10 fmol	60 (39.0)	66 (40.2)	
>10 fmol	82 (53.2)	80 (48.8)	
Unknown	12 (7.8)	18 (11.0)	
Duration of chemotherapy			0.95
6 mo	112 (72.7)	122 (74.4)	
12 mo	40 (26.0)	40 (24.4)	
Unknown	2 (1.3)	2 (1.2)	
Loss to follow-up	3 (1.9)	8 (4.9)	0.15
Receipt of therapy different from that randomized	8 (5.2)	12 (7.3)	0.44
Ovarian ablation	33 (21.4)	35 (21.3)	0.98

delivered over a period of three to four weeks. The postmastectomy chest wall received a dose of 37.5 Gy through two tangential fields. The mid-axilla received a dose of 35 Gy through an anterior supraclavicular–axillary field with a posterior axillary boost. A direct internal mammary field delivered a dose of 35 Gy at a depth of 3 cm. All the fields were treated with cobalt-60. The interval between the fourth and fifth cycles of chemotherapy was five to six weeks. Also, as part of a second randomization, 68 patients with estrogen-positive tumors were treated with radiation-induced ovarian ablation that included 20 Gy over a period of five days plus prednisone (7.5 mg per day) for two years, as described by Meakin et al.[16] Among these 68 patients, 33 were assigned to chemotherapy and 35 were assigned to chemotherapy and radiotherapy.

Statistical Analysis

In the various analyses, we studied the following end points: any relapse of breast cancer (or death without a known relapse of breast cancer), for the analysis of disease-free survival; locoregional recurrence as a first event, before a systemic recurrence (in the ipsilateral chest wall or an axillary, internal mammary, or supraclavicular node), for the analysis of survival free of locoregional disease; any systemic relapse, with or without a locoregional relapse (or death without a known systemic relapse), for the analysis of survival free of systemic disease; death from breast cancer, for the analysis of breast-cancer–specific survival; and any death, for the analysis of overall survival.

Survival curves were estimated by the Kaplan–Meier method.[17] Significance levels, estimates of relative risk, and 95 percent confidence intervals were calculated with a proportional-hazards regression model.[18] Two-sided P values of less than 0.05 were considered to represent statistical significance. The analysis was done for the whole group of 318 patients and also for subgroups with involvement in either one to three axillary nodes or four or more nodes. Differences between these subgroups with respect to the relative risk associated with the radiation were studied by testing for significant interactions with the proportional-hazards regression model. In the survival analysis, the time to the end points associated with each event was calculated from the date of the tissue diagnosis of breast cancer. Eleven patients (3.5 percent) were lost to follow-up — three (1.9 percent) from the chemotherapy group and eight (4.9 percent) from the chemotherapy–radiotherapy group. All 11 patients were alive and had no recurrences at their last known follow-up. In all the analyses, the data were censored as of the date of that follow-up. Of the 164 patients randomly assigned to chemotherapy and radiotherapy, 12 did not receive radiotherapy and were treated with chemotherapy alone (7 declined radiotherapy, 3 had metastases before radiotherapy, and 2 had postsurgical complications). Eight patients randomly assigned to chemotherapy had radiotherapy at their own request or that of their physicians. All the analyses presented were performed on an intention-to-treat basis (according to the initial randomization).

RESULTS

All Patients

A total of 318 patients were randomized, and among the survivors the median follow-up was 150 months (150 months in the chemotherapy group and 150 in the chemotherapy–radiotherapy group). During the 15 years of follow-up, breast cancer had recurred in 176 patients and 144 patients died. Of the 176 patients with recurrences, the disease returned locoregionally as a first event in 55 and systemically in 169; 14 additional patients had locoregional recurrences after a systemic recurrence. There was no difference with regard to any survival end point between the patients who had 12 months of chemotherapy and those who had only 6 months ($P = 0.60$ for disease-free survival at 15 years; $P = 0.70$ for overall survival).

Study Groups

Table 2 and Figures 1 through 4 show the results in the two groups of patients. In the group treated with chemotherapy plus radiotherapy, 79 of 164 patients had recurrences — locoregional, systemic, or both — as compared with 97 of 154 patients in the group given chemotherapy alone. These values translate into an overall reduction of 33 percent in the rate of recurrence of breast cancer (relative risk, 0.67; 95 percent confidence interval, 0.50 to 0.90; $P = 0.007$), with an improvement of 17 percentage points in disease-free survival at the 15-year follow-up (Fig. 1). There was an overall reduction of 34 percent in the rate of systemic recurrence (relative risk, 0.66; 95 percent confidence interval, 0.49 to 0.89; $P = 0.006$) in the group treated with combined therapy (75 of 164 patients vs. 94 of 154 patients in

TABLE 2. SURVIVAL OUTCOMES AFTER 5, 10, AND 15 YEARS IN THE STUDY GROUPS.*

VARIABLE AND DURATION OF FOLLOW-UP	CHEMOTHERAPY (N=154)		CHEMOTHERAPY AND RADIOTHERAPY (N=164)		P VALUE	RELATIVE RISK (95% CONFIDENCE INTERVAL)
	PERCENT SURVIVING	NO. OF EVENTS	PERCENT SURVIVING	NO. OF EVENTS		
Disease-free survival		97		79	0.007	0.67 (0.50–0.90)
5 yr	52		66			
10 yr	41		56			
15 yr	33		50			
Survival free of systemic disease		94		75	0.006	0.66 (0.49–0.89)
5 yr	56		69			
10 yr	43		58			
15 yr	34		51			
Survival free of locoregional disease		36		19	0.003	0.44 (0.26–0.77)
5 yr	79		90			
10 yr	75		87			
15 yr	67		87			
Breast-cancer–specific survival		76		62	0.05	0.71 (0.51–0.99)
5 yr	70		76			
10 yr	56		65			
15 yr	47		57			
Overall survival		78		66	0.07	0.74 (0.53–1.02)
5 yr	70		76			
10 yr	54		64			
15 yr	46		54			

*P values, relative risks, confidence intervals, and numbers of events shown are for the entire duration of the study.

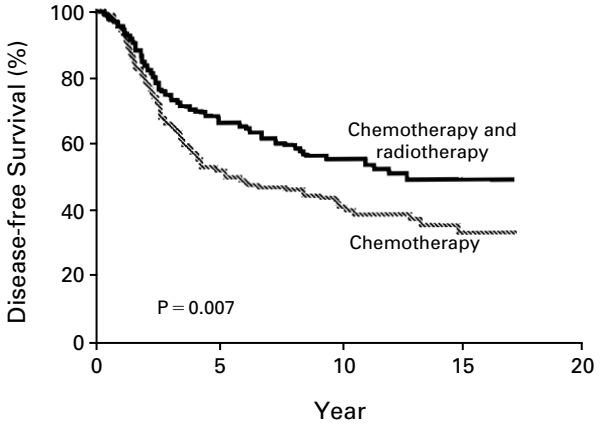

Figure 1. Disease-free Survival in the Study Groups.

In the group receiving chemotherapy combined with radiotherapy, 79 of 164 patients had relapses. The ratio of observed events to expected events was 0.82. In the group receiving chemotherapy alone, 97 of 154 patients had relapses. The ratio of observed events to expected events was 1.20. The relative risk of relapse when the former group was compared with the latter was 0.67 (P=0.007).

the group treated only with chemotherapy), and a 17-percentage-point improvement in systemic disease-free survival (Fig. 2). The rate of locoregional recurrence was reduced by 56 percent (relative risk, 0.44; 95 percent confidence interval, 0.26 to 0.77; P=0.003) in the group given chemotherapy plus radiotherapy (19 events, vs. 36 events in the group treated with chemotherapy only), for an absolute improvement of 20 percent in survival free of local disease. Mortality from breast cancer was reduced by 29 percent in the chemotherapy–radiotherapy group (relative risk, 0.71; 95 percent confidence interval, 0.51 to 0.99; P=0.05), with 62 deaths, as compared with 76 in the chemotherapy-only group, which represented an improvement of 10 percentage points in breast-cancer–specific survival (Fig. 3). There were 66 deaths in the group given the combined treatment and 78 deaths in the chemotherapy group, for a 26 percent reduction in overall mortality at 15 years (relative risk, 0.74; 95 percent confidence interval, 0.53 to 1.02; P=0.07) and an 8 percent improvement in overall survival (Table 2 and Fig. 4).

Among the 94 patients who had systemic relapses after chemotherapy alone, 19 were alive at the time of the 15-year analysis, as compared with 9 of the 75 patients with such relapses in the chemotherapy–radiotherapy group. Radiation also improved outcome in the 68 patients randomly assigned to ovar-

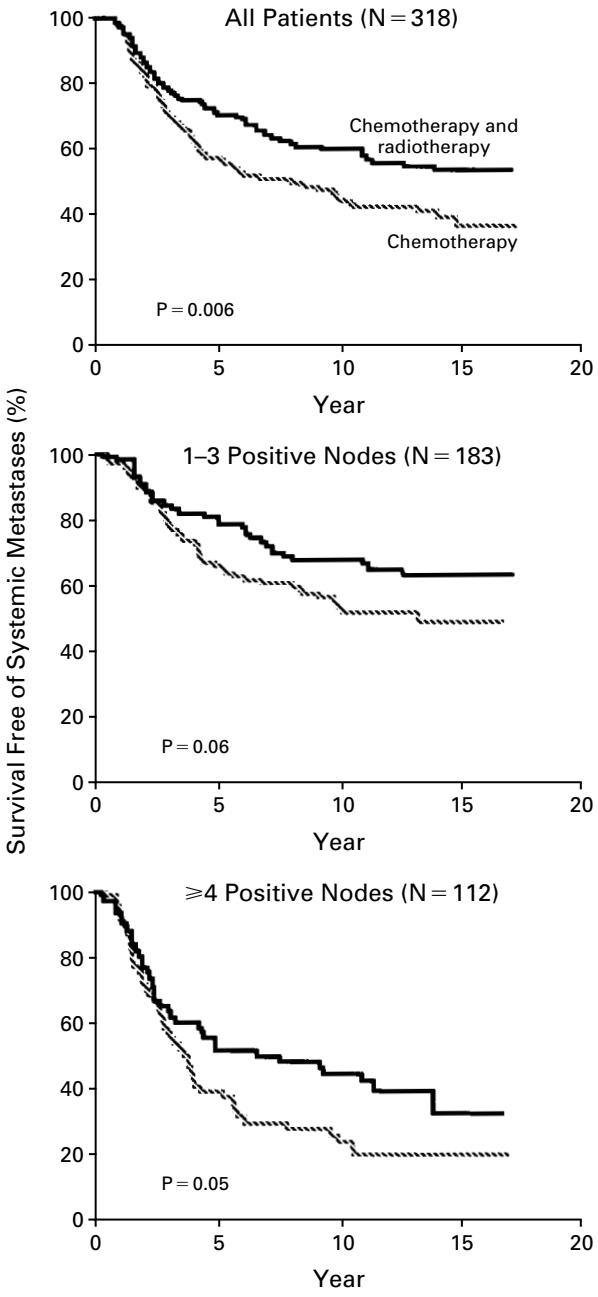

Figure 2. Survival Free of Systemic Disease in the Study Groups.

The top panel shows an analysis of all 318 study patients. In the group receiving chemotherapy combined with radiotherapy, 75 of 164 patients had systemic recurrences or died. The ratio of observed events to expected events was 0.81. In the group receiving chemotherapy alone, 94 of 154 patients had systemic recurrences or died. The ratio of observed events to expected events was 1.23. The relative risk of a systemic recurrence or death when the former group was compared with the latter was 0.66 (P = 0.006).

The middle panel shows an analysis of the 183 study patients with one to three involved lymph nodes each. In the group receiving chemotherapy combined with radiotherapy, 32 of 91 patients had systemic recurrences or died. The ratio of observed events to expected events was 0.79. In the group receiving chemotherapy alone, 45 of 92 patients had systemic recurrences or died. The ratio of observed events to expected events was 1.23. The relative risk of a systemic recurrence or death when the former group was compared with the latter was 0.65 (P = 0.06).

The bottom panel shows an analysis of the 112 study patients with four or more involved lymph nodes each. In the group receiving chemotherapy combined with radiotherapy, 35 of 58 patients had systemic recurrences or died. The ratio of observed events to expected events was 0.8. In the group receiving chemotherapy alone, 43 of 54 patients had systemic recurrences or died. The ratio of observed events to expected events was 1.25. The relative risk of systemic recurrences or death when the former group was compared with the latter was 0.64 (P = 0.05).

ian ablation, in regard to disease-free survival (relative risk, 0.72), survival free of systemic disease (relative risk, 0.76), and overall survival (relative risk, 0.88).

Subgroups Based on Nodal Involvement

The reduction in the relative risk of a recurrence that was obtained by adding radiation to chemotherapy was similar in the subgroup with one to three positive nodes and the subgroup with four or more positive nodes (Table 3). There were no statistically significant differences between these subgroups with regard to either survival free of systemic disease (P for interaction = 0.9) or rates of locoregional recurrence (P = 0.73).

Side Effects of Radiation

Arm edema developed in 15 of the 154 irradiated patients. Interventions were required in six (an elastic sleeve in four, a pump in one, and physiotherapy in one), as compared with five patients in the chemotherapy group, one of whom required physiotherapy. Limited apical lung fibrosis developed in most of the irradiated patients, but only one had interstitial pneumonitis requiring corticosteroids, with full resolution on chest radiography several weeks later. In one patient with a right-sided breast lesion, congestive heart failure developed 14 years after radiotherapy, at the age of 63. We considered this event related not to the adjuvant radiation but rather to treatment with doxorubicin, which was given at a cumulative dose of 540 mg for metastases to the lung and pleura. There were no cases of brachial plexopathy. The incidence of second cancers and the associated mortality were distributed evenly between the two groups (Table 4).

DISCUSSION

This study of premenopausal women with breast cancer demonstrates that locoregional radiotherapy reduces the rates of locoregional and systemic relapses and the chance of dying from breast cancer. There was no excess mortality we could attribute to the long-term side effects of radiotherapy. Our trial did not stratify the patients according to nodal status, but a test for interaction showed no significant difference in the magnitude of the benefit from radiotherapy between the subgroup with three or fewer positive nodes and the subgroup with four or more positive nodes. These data based on a 15-year follow-up indicate that radiation can offer substantial protection from systemic relapse to node-positive patients. It is possible that we will see additional benefit in overall survival, because at this writing 19 patients in the chemotherapy group remain alive with systemic recurrence, as compared with only 9 in the combined-treatment group; most of these 28 patients are expected to die of breast cancer.

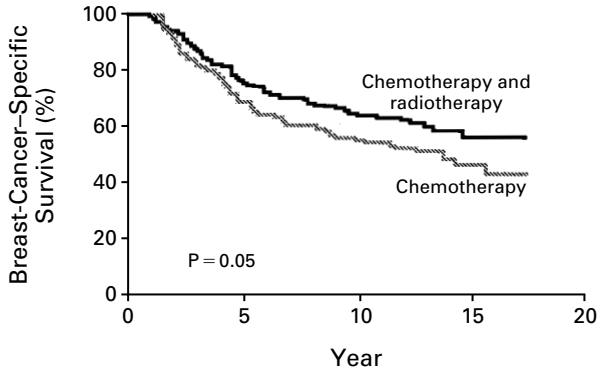

Figure 3. Breast-Cancer–Specific Survival in the Study Groups.
In the group receiving chemotherapy combined with radiotherapy, 62 of 164 patients died of metastatic breast cancer. The ratio of observed events to expected events was 0.84. In the group receiving chemotherapy alone, 76 of 154 patients had metastatic breast cancer or died. The ratio of observed events to expected events was 1.18. The relative risk of death from metastatic breast cancer when the former group was compared with the latter was 0.71 (P = 0.05).

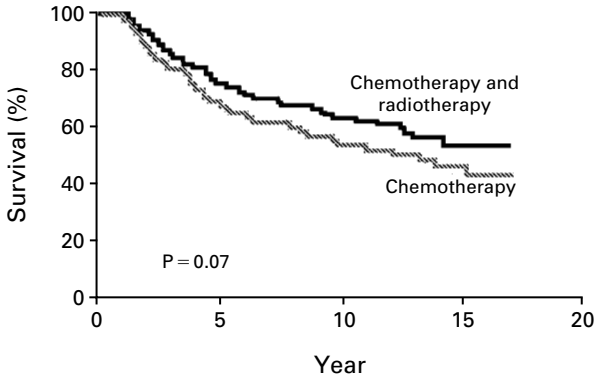

Figure 4. Overall Survival in the Study Groups.
In the group receiving chemotherapy combined with radiotherapy, 66 of 164 patients died. The ratio of observed deaths to expected deaths was 0.86. In the group receiving chemotherapy alone, 78 of 154 patients died. The ratio of observed deaths to expected deaths was 1.16. The relative risk of death when the former group was compared with the latter was 0.74 (P = 0.07).

The benefits of radiotherapy found in our study, but not in most earlier studies, merit comment. The meta-analysis performed by the Early Breast Cancer Trialists' Collaborative Group,[1] which analyzed all the randomized radiation trials begun before 1985, found a 67 percent reduction in rates of locoregional relapse ($P<0.001$) and a 6 percent reduction in mortality from breast cancer ($P = 0.03$), but no improvement in overall survival. There was an important increase in the number of deaths not due to breast cancer among the irradiated patients ($P = 0.002$). A previous meta-analysis and several individual trials found that the latter was due to a substantial increase in mortality from cardiac causes.[2,4,19] These studies, however, included all the radiation trials started in the 1960s, using older equipment and radiation techniques and considered obsolete by present standards. Also, in various past trials different areas were encompassed in the irradiated volume, and the trials differed in techniques of radiation, treatment planning, age, nodal status, and the use of adjuvant chemotherapy. Therefore, the meta-analyses of previous studies may not be relevant to current practice.

There are at least nine reported randomized trials comparing the combined treatment with chemotherapy alone.[20-26] Of these, only the Danish study[20] found that radiotherapy had a benefit of a magnitude similar to that in our trial, and there was a significant survival benefit in favor of radiotherapy ($P = 0.001$). The patients in that study were similar to those in our cohort; there was a large and homogeneous group of premenopausal, node-positive patients treated with chemotherapy and five-field radiotherapy.[20] The other eight studies were not similar to ours or the Danish trial, either because the number of randomized premenopausal patients was small or because the radiotherapy techniques or the chemotherapy schedules were heterogeneous.

Our data suggest that locoregional disease is not only a marker of systemic disease but also, in some patients, a potential source for its future dissemination. The Stockholm trial[27] also provides evidence that locoregional radiotherapy in node-positive patients decreases the risk of systemic metastases. In this context, the interaction with adjuvant chemotherapy may be important, because chemotherapy is expect-

TABLE 3. RATES OF SURVIVAL FREE OF SYSTEMIC AND LOCOREGIONAL DISEASE, ACCORDING TO THE NUMBER OF POSITIVE LYMPH NODES.*

DISEASE CATEGORY AND NODAL STATUS	CHEMOTHERAPY	CHEMOTHERAPY AND RADIOTHERAPY	P VALUE	RELATIVE RISK (95% CONFIDENCE INTERVAL)
	percent surviving			
Systemic disease				
1–3 Positive nodes			0.06	0.65 (0.41–1.02)
5 yr	66	79		
10 yr	53	68		
15 yr	49	63		
≥4 Positive nodes			0.05	0.64 (0.41–1.00)
5 yr	39	52		
10 yr	24	44		
15 yr	20	33		
Locoregional disease				
1–3 Positive nodes			1.17	0.55 (0.23–1.30)
5 yr	84	93		
10 yr	84	90		
15 yr	67	90		
≥4 Positive nodes			0.04	0.45 (0.20–0.98)
5 yr	72	82		
10 yr	59	79		
15 yr	54	79		

*This analysis included 183 patients with one to three positive nodes (92 in the chemotherapy group and 91 in the chemotherapy–radiotherapy group) and 112 patients with four or more positive nodes (54 and 58 patients, respectively). Twenty-three randomized patients with unknown nodal status (8 in the chemotherapy group and 15 in the chemotherapy–radiotherapy group) were not included.

ed to eliminate systemic micrometastases more effectively than locoregional disease.[9-11,15] In node-positive patients, adding locoregional radiotherapy may be essential to prevent secondary dissemination from the residual locoregional metastatic disease, and it could increase the potential for cure.

Because all our patients were uniformly treated with chest-wall and nodal radiation, our results may not apply to patients treated with breast irradiation alone after conservative surgery. Four randomized trials comparing breast irradiation with no irradiation in patients who underwent conservative surgery[28-31] showed significant reductions in the rate of relapse in the breast but no effect on systemic recurrences or overall survival. Therefore, it may be necessary to add nodal radiation to breast irradiation in premenopausal node-positive patients who are treated with partial mastectomy and adjuvant chemotherapy.

Locoregional radiation is not routinely used at present in patients with node-positive breast cancer, although it is coming into use to treat patients with 10 or more positive nodes[32,33] and occasionally those with 4 or more positive nodes. The routine use of radiation in all node-positive patients would represent a substantial shift in treatment for breast cancer. Our data indicate that locoregional disease remaining after definitive surgery may be an important

TABLE 4. INCIDENCE OF SECOND CANCERS AND SIDE EFFECTS OF TREATMENT.*

SITE OF CANCER OR SIDE EFFECT	CHEMOTHERAPY (N = 154)	CHEMOTHERAPY AND RADIOTHERAPY (N = 164)
	no. of patients	
Contralateral breast	10	9*
Ovary	0	1*
Uterine cervix	0	1
Lung†	1*	0
Colon	1	0
Rectum	1*	0
Anus	0	1*
Acute myelogenous leukemia	0	1*
Arm edema		
Without intervention	4	9
Intervention required	1	6
Congestive heart failure	0	1
Pneumonitis	0	1

*The number shown includes one patient who died.

†The single case of lung cancer was identified histologically as adenocarcinoma.

source of systemic disease. The elimination of locoregional cancer cells by radiotherapy added to adjuvant chemotherapy may reduce mortality in selected patients with breast cancer.

We are indebted to the following colleagues at the British Columbia Cancer Agency: Dr. Ann Worth, for assistance with the conduct of the study; and Mr. David Noble, Dr. Ralph Durand, Dr. Joe Connors, and Dr. Nevine Murray, for their review of the manuscript.

REFERENCES

1. Early Breast Cancer Trialists' Collaborative Group. Effects of radiotherapy and surgery in early breast cancer: an overview of the randomized trials. N Engl J Med 1995;333:1444-55. [Erratum, N Engl J Med 1996;334: 1003.]
2. Cuzick J, Stewart H, Rutqvist L, et al. Cause-specific mortality in long-term survivors of breast cancer who participated in trials of radiotherapy. J Clin Oncol 1994;12:447-53.
3. Stjernsward J. Can survival be decreased by post-operative irradiation? Int J Radiat Oncol Biol Phys 1977;2:1171-5.
4. Rutqvist LE, Lax I, Fornander T, Johansson H. Cardiovascular mortality in a randomized trial of adjuvant radiation therapy versus surgery alone in primary breast cancer. Int J Radiat Oncol Biol Phys 1992;22:887-96.
5. Fuller SA, Haybittle JL, Smith RE, Dobbs HJ. Cardiac doses in post-operative breast irradiation. Radiother Oncol 1992;25:19-24.
6. Fisher B, Carbone P, Economou SG, et al. l-Phenylalanine mustard (L-PAM) in the management of primary breast cancer: a report of early findings. N Engl J Med 1975;292:117-22.
7. Bonadonna G, Brusamolino E, Valagussa P, et al. Combination chemotherapy as an adjuvant treatment in operable breast cancer. N Engl J Med 1976;294:405-10.
8. Nissen-Meyer R, Kjellgren K, Malmio K, Mansson B, Norin T. Surgical adjuvant chemotherapy: results with one short course with cyclophosphamide after mastectomy for breast cancer. Cancer 1978;41:2088-98.
9. Schabel FM Jr. Concepts for treatment of micrometastases developed in murine systems. AJR Am J Roentgenol 1976;126:500-11.
10. Skipper HE, Schabel FM Jr, Mellett LB, et al. Implications of biochemical, cytokinetic, pharmacologic, and toxicologic relationships in the design of optimal therapeutic schedules. Cancer Chemother Rep 1970;54: 431-50.
11. Durand RE. Chemosensitivity testing in V79 spheroids: drug delivery and cellular microenvironment. J Natl Cancer Inst 1986;77:247-52.
12. Tubiana M, Arrigada R, Cosset JM. Sequencing of drugs and radiation: the integrated alternating regimen. Cancer 1985;55:2131-9.
13. Fu KK. Biological basis for the interaction of chemotherapeutic agents and radiation therapy. Cancer 1985;55:Suppl:2123-30.
14. Vokes EE, Weichselbaum PR. Concomitant chemoradiotherapy: rationale and clinical experience in patients with solid tumors. J Clin Oncol 1990;8:911-34. [Erratum, J Clin Oncol 1990;8:1447.]
15. Goldie JH, Coldman AJ. A mathematical model for relating the drug sensitivity of tumors to their spontaneous mutation rate. Cancer Treat Rep 1979;63:1727-33.
16. Meakin JW, Alt WEC, Beale FA, et al. Ovarian irradiation and prednisone following surgery for carcinoma of the breast. Can Med Assoc J 1979; 120:1221-9.
17. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. J Am Stat Assoc 1958;53:457-81.
18. Cox DR. Regression models and life-tables. J R Stat Soc [B] 1972;34: 187-220.
19. Haybittle JL, Brinkley D, Houghton J, A'Hern RP, Baum M. Postoperative radiotherapy and late mortality: evidence from the Cancer Research Campaign trial for early breast cancer. BMJ 1989;298:1611-4.
20. Overgaard M, Hansen PS, Rose C, et al. Postmastectomy radiotherapy and adjuvant systemic treatment in high-risk breast cancer patients. Eur J Cancer 1994;30A:Suppl 2:S28. abstract.
21. McArdle CS, Crawford D, Dykes EH, et al. Adjuvant radiotherapy and chemotherapy in breast cancer. Br J Surg 1986;73:264-6.
22. Muss HB, Cooper MR, Brockschmidt JK, et al. A randomized trial of chemotherapy (L-PAM vs CMF) and irradiation for node positive breast cancer: eleven year follow-up of a Piedmont Oncology Association trial. Breast Cancer Res Treat 1991;19:77-84.
23. Griem KL, Henderson IC, Gelman R, et al. The 5-year results of a randomized trial of adjuvant radiation therapy after chemotherapy in breast cancer patients treated with mastectomy. J Clin Oncol 1987;5:1546-55.
24. Blomqvist C, Tiusanen K, Elomaa I, et al. The combination of radiotherapy, adjuvant chemotherapy (cyclophosphamide-doxorubicin-ftorafur) and tamoxifen in stage II breast cancer: long-term follow-up results of a randomised trial. Br J Cancer 1992;66:1171-6.
25. Velez-Garcia E, Carpenter JT Jr, Moore M, 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.
26. Buzdar AU, Blumenschein GR, Smith TL, et al. Adjuvant chemotherapy with fluorouracil, doxorubicin, and cyclophosphamide, with or without Bacillus Calmette-Guerin and with or without irradiation in operable breast cancer: a prospective randomized trial. Cancer 1984;53:384-9.
27. 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.
28. Fisher B, Redmond C. Lumpectomy for breast cancer: an update of the NSABP experience. In: Consensus Development Conference on the Treatment of Early-Stage Breast Cancer. Journal of the National Cancer Institute monographs. No. 11. Washington, D.C.: Government Printing Office, 1992:7-13. (NIH publication no. 90-3187.)
29. Hermann RE, Esselstyn CB Jr, Grundfest-Broniatowski S, et al. Partial mastectomy without radiation is adequate treatment for patients with stages 0 and I carcinoma of the breast. Surg Gynecol Obstet 1993;177:247-53.
30. Clark RM, McCulloch PB, Levine MN, et al. Randomized clinical trial to assess the effectiveness of breast irradiation following lumpectomy and axillary dissection for node-negative breast cancer. J Natl Cancer Inst 1992; 84:683-9.
31. Veronesi U, Luini A, Del Vecchio M, et al. Radiotherapy after breast-preserving surgery in women with localized cancer of the breast. N Engl J Med 1993;328:1587-91.
32. Marks LB, Halperin EC, Prosnitz LR, 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.
33. Diab SG, deMoor CA, Clark GM, Osborne CK, Ravdin PM, Elledge RM. Radiation therapy improves survival by decreasing local failure in breast cancer patients with 10 or more positive axillary lymph nodes treated with mastectomy. Proc Am Soc Clin Oncol 1997;16:130a. abstract.