Randomized Clinical Trial of Breast Irradiation Following Lumpectomy and Axillary Dissection for Node-Negative Breast Cancer: an Update

*R. M. Clark, T. Whelan, M. Levine, R. Roberts, A. Willan, P. McCulloch, M. Lipa, R. H. Wilkinson, L. J. Mahoney**

For the Ontario Clinical Oncology Group

Background: Breast-conservation surgery is now commonly used to treat breast cancer. Postoperative breast irradiation reduces cancer recurrence in the breast. There is still controversy concerning the necessity of irradiation of the breast in all patients. _Purpose:_ We present an update of results from a randomized clinical trial designed to examine the efficacy of breast irradiation following conservation surgery in the treatment of women with axillary lymph node-negative breast cancer. The patients were enrolled from April 1984 through February 1989. Initial results were published in 1992 after a median follow-up time of 43 months. It was reported that recurrence of cancer in the breast occurred in 5.5% of the patients who received breast irradiation compared with 25.7% of those who did not. No difference in survival was detected between the two treatment groups. Now that the median patient follow-up has reached 7.6 years, the trial end points have been re-examined and an attempt has again been made to identify a group of patients at low risk for recurrence of cancer in the breast. _Methods:_ Eight hundred thirty-seven patients with node-negative breast cancer were randomly assigned to receive either radiation therapy (n = 416) or no radiation therapy (n = 421) following lumpectomy and axillary lymph node dissection. The cumulative local recurrence rate as a first event, distant recurrence (i.e., occurrence of metastasis) rate, and overall mortality rate for the treatment groups were described by the Kaplan–Meier method and compared with the use of the logrank test. The Cox proportional hazards model was used to adjust the observed treatment effect for the influence of various prognostic factors (patient age, tumor size, estrogen receptor level, and tumor histology) at study entry on the outcomes of local breast recurrence, distant recurrence, and overall mortality. All _P_ values resulted from the use of two-tailed statistical tests. _Results:_ One hundred forty eight (35%) of the nonirradiated patients and 47 (11%) of the irradiated patients developed recurrent cancer in the breast (relative risk for patients in the former versus the latter group = 4.0; 95% confidence interval = 2.83-5.65; _P_<.0001). Ninety-nine (24%) of the patients in the former group have died compared with 87 (21%) in the latter group. Age (<50 years), tumor size (>2 cm), and tumor nuclear grade (poor) continued to be important predictors for local breast relapse. On the basis of these factors, we were unable to identify a subgroup of patients with a very low risk for local breast cancer recurrence. Tumor nuclear grade, as previously reported, and tumor size were important predictors for mortality. _Conclusions:_ Breast irradiation was shown to reduce cancer recurrence in the breast, but there was no statistically significant reduction in mortality. A subgroup of patients with a very low risk for local breast recurrence who might not require radiation therapy was not identified. [J Natl Cancer Inst 1996;88:1659-64]

Breast-conservation surgery is now commonly used in the treatment of women with early stage breast cancer. Clinical trials have demonstrated that breast irradiation after surgery substantially reduces the risk for recurrence of cancer in the breast (*1-3*). From April 1984 through February 1989, a clinical trial was conducted in the province of Ontario, Canada, in which women with breast cancer who were treated by lumpectomy and who were determined to be lymph node negative for cancer metastases by axillary dissection were randomly assigned to receive either radiation therapy or no further treatment (*1*). The objectives of this study were to assess the efficacy of breast irradiation in reducing local relapse of cancer in the breast and to identify a group of women at low risk for local breast cancer relapse who might be spared breast irradiation. At a median follow-up time of 43 months, it was reported (*1*) that breast irradia-

**Affiliations of authors:* R. M. Clark, Princess Margaret Hospital, Toronto, Ontario; T. Whelan, M. Levine, Ontario Cancer Treatment and Research Foundation Hamilton Regional Cancer Centre and the Departments of Medicine and Clinical Epidemiology and Biostatistics, McMaster University, Hamilton, Ontario; R. Roberts, A. Willan, Department of Clinical Epidemiology and Biostatistics, McMaster University; P. McCulloch, Hamilton Regional Cancer Centre, Ontario; M. Lipa, Toronto Hospital; R. H. Wilkinson, North York Hospital, Toronto, Ontario; L. J. Mahoney, St. Michael's Hospital, Toronto, Ontario, Canada.

Correspondence to: Mark Levine, M.D., Ontario Cancer Treatment and Research Foundation Hamilton Regional Cancer Centre, 699 Concession St., Hamilton, Ontario, Canada L8V 5C2.

See "Notes" section following "References."

tion reduced relapse in the breast from 25.7% in nonirradiated patients to 5.5% in irradiated patients. No difference in survival was detected between the treatment groups. A low-risk group (<10% chance of relapse of cancer in the breast without irradiation) could not be defined. Since publication of that study, results from a similar randomized trial (*4*) conducted in Italy have been published and results from two earlier randomized trials (*2,3*) have been updated (*5,6*). Despite the results of these studies, the question is still raised as to whether or not there are subgroups of patients who might be spared breast irradiation (*7,8*).

The Ontario study (*1*) is unique in that the patients with node-negative lumpectomy did not receive adjuvant systemic therapy. It is now more than 11 years since the start of the original study and the median follow-up is presently 7.6 years. The purpose of this update is to provide long-term follow-up on the effect of radiation therapy on local recurrence and survival and with additional events to again attempt to identify a low-risk group for local breast cancer relapse.

Methods

Details of the study design have been published previously (*1*) but will be briefly outlined. From April 1984 through February 1989, consecutive patients with breast cancer treated by lumpectomy and axillary lymph node dissection who had been referred to the Princess Margaret Hospital in Toronto, Ontario, Canada, or the Ontario Cancer Treatment and Research Foundation Regional Cancer Centre in the cities of Hamilton, London, Ottawa, Windsor, and Thunder Bay were approached for entry in the study. For patients to be eligible for inclusion in the study, their tumors must have been less than or equal to 4 cm in diameter and the local excision microscopically complete. Histologic evidence of negative axillary lymph nodes was required. Written informed consent was obtained from all study participants. The study protocol was approved by the institutional review boards of all participating institutions. Patients were assigned according to a prescribed randomized arrangement to one of two regimens: 1) breast irradiation or 2) no irradiation. The randomization was done at each center with the use of sealed envelopes that were maintained in the clinical trials departments of the participating centers. Stratification was by center, patient age (<50 and ≥50 years), and tumor size (≤2 and >2 cm). Patients did not receive postoperative adjuvant systemic therapy.

Surgical Technique

Patients underwent lumpectomy and axillary lymph node dissection. Lumpectomy consisted of complete removal of the tumor and an additional 0.5-1 cm margin of normal surrounding tissue. The resection margins were required to be microscopically free of in situ as well as infiltrating tumor. The incision was to be placed immediately over the tumor to facilitate localization of the primary site, and excessively wide resections were to be avoided.

Staging axillary dissection was done through a separate axillary incision with removal of lymph nodes at levels 1 and 2. Following local breast cancer relapse, further lumpectomy was recommended if feasible and cosmetically sound, although this procedure was not mandatory. In the nonirradiated (control) group, following repeat lumpectomy, radiation therapy was recommended in accordance with the protocol.

Radiation Therapy

Those patients assigned to the radiation therapy regimen received a dose of 4000 cGy given by cobalt 60 over a period of 3 weeks with 16 daily fractions to the entire breast. Subsequently, a boost was given to the primary site using a direct field to give a dose of 1250 cGy in five daily fractions. The breast was irradiated by means of a parallel opposed tangential, partially wedged plane of fields. Bolus irradiation was not used. Radiation therapy was started within 12 weeks of surgery.

Follow-up Studies

Following random assignment to treatment, patients in both groups were seen every 3 months until the end of the second year and every 6 months thereafter. Chest x rays and mammograms were performed yearly.

Statistical Analysis

The cumulative local cancer recurrence rate as a first event, distant recurrence rate, and overall mortality rate for the treatment groups were described by the Kaplan–Meier method and compared with the use of the logrank test. For the analysis of cumulative local recurrence, if a woman had a distant recurrence (i.e., metastasis) prior to local breast recurrence, her follow-up time was censored at the time of distant recurrence.

The Cox proportional hazards model was used to adjust the observed treatment effect for the influence of various prognostic factors at study entry, e.g., age, tumor size, estrogen receptor level, and tumor histology, on the outcomes of local breast recurrence, distant recurrence, and overall mortality. All *P* values resulted from the use of two-tailed statistical tests.

Results

Eight hundred thirty-seven patients were randomly allocated to receive either radiation therapy (n = 416) or no radiation therapy (n = 421) (control group). The treatment groups were comparable in terms of base-line characteristics, such as patient age, tumor size, levels of estrogen and progesterone receptors, and tumor differentiation and nuclear grade (*1*).

Recurrence

One hundred twenty-three (30%) of the 416 patients treated with radiation therapy have experienced recurrent breast cancer compared with 207 (49%) of the 421 control patients (Table 1). In the radiation therapy group, 47 patients experienced local breast recurrence and 97 experienced a distant recurrence; the corresponding numbers of patients for the control group were 148 and 128, respectively (Table 1).

The cumulative rate of local breast cancer recurrence as a first event was greater in the no treatment group than in the radiation therapy group (*P*<.001) (Fig. 1). The Cox regression analysis showed that there was a statistically significant increase in relative risk (RR) for a local breast recurrence as the first event for the no radiation therapy group compared with the radiation therapy group (RR = 4.0; 95% confidence interval [CI] = 2.8-5.7; *P*<.0001) (Table 2). Age, tumor size, and tumor grade were

Table 1. Rates of breast cancer recurrence and death

	No. of patients (%)	
Recurrence	Radiation therapy (n = 416)	Control (n = 421)
Local only	26 (6.3)	79 (18.8)
Local then distant	18 (4.3)	62 (14.7)
Distant only	76 (18.3)	59 (14.0)
Distant then local	3 (0.7)	7 (1.7)
Local as a first event	44 (10.6)	141 (33.5)
Any local	47 (11.3)	148 (35.2)
Any distant	97 (23.3)	128 (30.4)
Any recurrence	123 (29.6)	207 (49.2)
Death	87 (20.9)	99 (23.5)

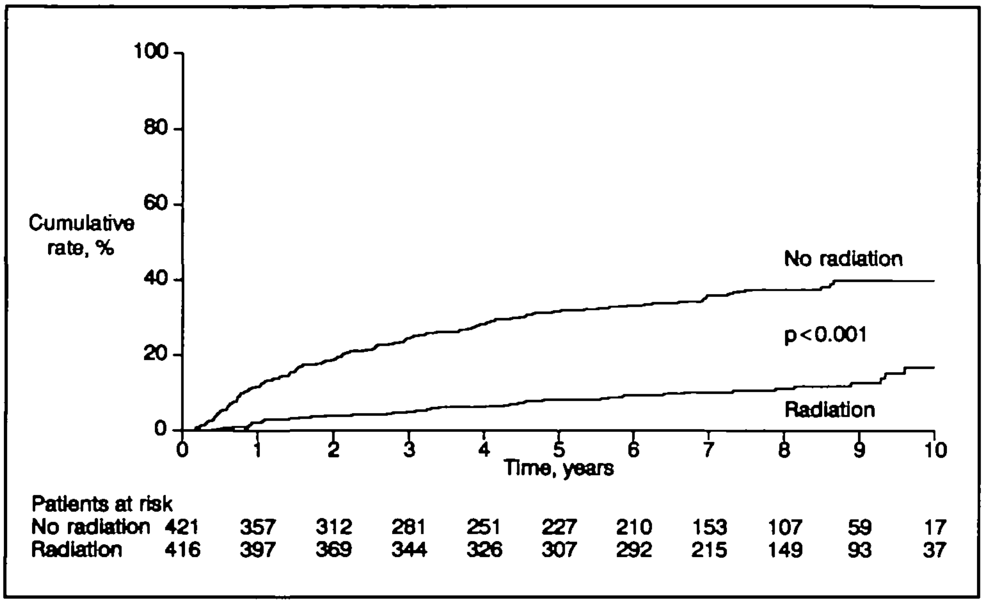

Fig. 1. Cumulative rate of local breast cancer recurrence as a first event for patients with node-negative breast cancer who were assigned to receive or not to receive breast irradiation following lumpectomy and axillary lymph node dissection.

also independent predictors of local breast cancer recurrence (Table 2).

The study protocol did not specify a mandatory treatment approach for the local management of cancer relapse in the breast. In the control patients who had a local breast recurrence, 62 patients underwent a mastectomy, 70 had a lumpectomy plus breast irradiation, 10 had a lumpectomy alone, and six received systemic therapy or no further treatment because of widespread disease. In the radiation therapy group, 26 patients had a mastectomy, 13 had a lumpectomy, and eight received systemic therapy or no further treatment.

The cumulative rate of distant failure (i.e., occurrence of metastasis) was also greater in the no treatment group than in the radiation therapy group ($P<.02$) (Fig. 2). The Cox regression analysis showed a statistically significant increase in RR for distant recurrence for patients in the no radiation therapy group compared with patients in the radiation therapy group (RR = 1.4; 95% CI = 1.07-1.8; P = .01) (Table 2). Tumor size and grade were also independent predictors of distant failure (Table 2).

Survival

Eighty-seven (21%) of the patients treated with radiation therapy have died compared with 99 (24%) control patients. There continues to be no difference in the cumulative mortality between the two treatment groups (P = .33) (Fig. 3). The Cox regression analysis showed an RR for mortality of 1.17 (95% CI = 0.87-1.57; P = .29) for no radiation therapy versus radiation therapy. Tumor size and nuclear grade were important predictors for mortality (Table 2). In the radiation therapy group, 66 patients died of breast cancer and 21 patients died of other causes. The corresponding values for the control group were 81 and 18, respectively. The mortality from breast cancer was not different between treatment groups (P = .19).

Definition of a Low-Risk Group

On the basis of the results of the Cox model, we considered patients who did not receive radiation therapy and attempted to define a group of patients at relatively low risk of cancer recurrence in the breast. The cumulative rate of local breast recurrence in the 207 patients who were 50 years of age or older and who had tumors of 2 cm or less in diameter was 22% (Table 3). Similarly, the cumulative rate of local recurrence in the 209 patients who were 50 years of age or older and who had tumors of nuclear grade 1 or 2 was 24% (Table 3). There were 93 women with tumors of 1 cm or less in diameter. The cumulative rate of local recurrence was 28.5% in this group.

Discussion

The results of this trial at almost 8 years of follow-up are consistent with those reported earlier (*1*). They indicate that in women with node-negative breast cancer who have undergone

Table 2. Cox regression analysis for local breast cancer recurrence, distant metastasis, and survival*

Prognostic factor	Local breast recurrence RR (95% CI)	P	Distant metastasis RR (95% CI)	P	Death RR (95% CI)	P
Treatment (no radiation versus radiation therapy)	4.00 (2.83-5.65)	<.0001	1.40 (1.07-1.84)	.014	1.17 (0.87-1.57)	.29
Age, y (<50 versus ≥50)	1.82 (1.34-2.47)	.0001	1.16 (0.88-1.55)	.29	0.84 (0.61-1.16)	.29
Tumor size, cm (>2 cm versus ≤2 cm)	1.73 (1.26-2.37)	.0006	1.59 (1.20-2.10)	.0013	1.42 (1.04-1.93)	.028
Nuclear grade (poor versus other)	1.44 (1.05-2.00)	.026	1.43 (1.07-1.92)	.015	2.00 (1.47-2.73)	.00001

*RR = relative risk; CI = confidence interval.

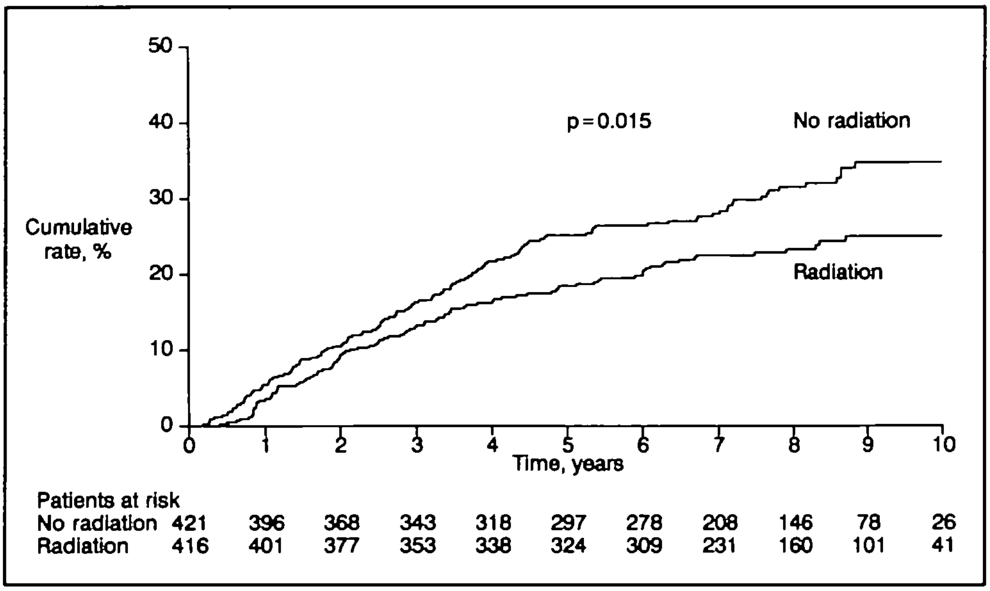

Fig. 2. Cumulative rate of distant failure (i.e., occurrence of metastasis) for patients with node-negative breast cancer who were assigned to receive or not to receive breast irradiation following lumpectomy and axillary lymph node dissection.

lumpectomy, breast irradiation significantly reduces the recurrence of cancer but has no impact on overall survival. Consequently, the reduction in local recurrence resulted in an increase in breast preservation. In this trial, there was also a statistically significant reduction in distant failure associated with radiation therapy. Whether this implies a real effect of radiation therapy on systemic recurrence or a potential bias, whereby a local recurrence precipitated a search for metastatic disease, cannot be determined, since no difference in overall or cause-specific survival was detected (*1,2*).

Other trials (*2-6*) that evaluated breast irradiation in women who had undergone lumpectomy also showed a reduction in local breast recurrence but were unable to detect a difference in overall survival between the two study arms. The National Surgical Adjuvant Breast and Bowel Project recently published the 12-year update of trial B-06 (*5*). The cumulative incidence of tumor recurrence in the breast in women with lymph node-negative breast cancer was 32% in the group treated with lumpectomy alone and 12% in the group treated with lumpectomy and breast irradiation.

A Swedish trial, with a median follow-up of approximately 64 months, reported a recurrence rate in the irradiated group of 2.3% versus 18.4% with no radiation therapy (*6*). The main differences between this study and ours were that in the Swedish study patients had tumors of less than 2 cm in size and 45% of patients were derived from mammography screening. Surgical resection of the primary tumor was described as a sector resection in which at least one third of the breast was dissected free and the pectoral fascia was removed.

A study from Milan, Italy, compared quadrantectomy versus quadrantectomy plus radiotherapy for the treatment of women with localized cancer of the breast (*4*). At a median follow-up of 39 months, quadrantectomy patients had a breast recurrence rate of 8.8% compared with 0.3% in the quadrantectomy plus radiation therapy group. In that trial, patients with positive lymph nodes were entered and received adjuvant therapy. Thus, in both

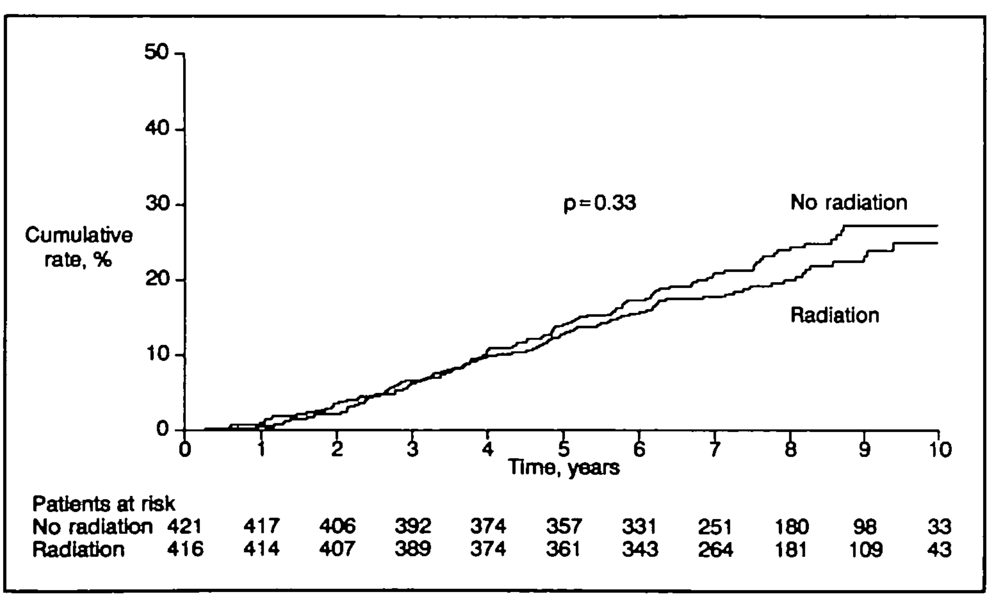

Fig. 3. Cumulative mortality rate for patients with node-negative breast cancer who were assigned to receive or not to receive breast irradiation following lumpectomy and axillary lymph node dissection.

Table 3. Local breast cancer recurrence rates for the low-risk group

Variable	No. of patients	Recurrence rate (%)*	95% confidence interval
≥50 y, ≤2 cm	207	22.4	(14.7-26.1)
≥50 y, ≤1 cm	68	18.4	(9.0-27.9)
≥50 y, grade 1 or 2	209	23.5	(17.6-29.4)
≤1 cm, grade 1 or 2	75	26.0	(15.9-36.0)
≥50 y, ≤1 cm, grade 1 or 2	56	18.8	(8.2-29.4)
≤1 cm	93	28.5	(19.2-37.8)

*Actuarial 7-year cumulative risk.

the Swedish and Italian studies, patients were treated with a wider surgical excision than that normally defined by lumpectomy. The results of those studies suggest that more extensive excision is associated with lower relapse rate, but the cosmetic result would be potentially sacrificed.

The fact that radiation therapy reduced the risk of local recurrence, but did not appear to affect overall survival in all of the above studies, remains difficult to explain. It may be that the reduction of local recurrence does, in fact, prevent further systemic spread, leading to a small increase in survival, but because of the limited power of each individual study, a statistically significant difference has yet to be detected. Alternatively, it may be that while radiation therapy reduces breast cancer-specific mortality, it may increase mortality due to non-breast cancer causes, such as ischemic heart disease (*9,10*). Finally, it may well be that despite reducing local recurrence, the high metastatic potential of breast cancer prevents any real benefit from radiation therapy for survival.

The Early Breast Cancer Trialists Collaborative Group (*11*) recently published a meta-analysis of clinical trials of radiotherapy and surgery in early breast cancer. For the subgroup of patients treated with breast-conserving surgery and randomly assigned to receive radiation or not, they identified four trials (*1,5,6*) consisting of more than 3000 patients. Radiation therapy resulted in a reduction of 75% (standard deviation of 9%) in the odds of recurrence in the breast and a reduction of 12% (±9%) in the odds of death. The effect on mortality was not statistically significant ($P = .2$). Thus, the meta-analysis suggests that the effect of radiation therapy on survival is likely to be small.

The meta-analysis also examined the effect of radiotherapy following any type of surgery, including mastectomy, on cause-specific survival. There appeared to be a reduced risk for death from breast cancer but an increased risk for death from other causes in patients who received radiation therapy. While it is tempting to assume that this may explain the inability to detect a benefit of radiation therapy on overall survival, in the subgroup of patients treated with breast irradiation following lumpectomy, no increase in non-breast cancer deaths was identified consistent with the findings in our study.

In our previous report (*1*) of this trial, radiation therapy, patient age, and tumor size predicted for local breast cancer recurrence. In the present analysis, tumor nuclear grade was an additional independent predictor for local breast recurrence. On subgroup analysis, we still could not identify a group of patients who are at such low risk for breast recurrence that they could be spared breast irradiation. For example, in women 50 years or older with tumors of 2 cm or less in diameter, the rate of local breast recurrence at 7 years was 22% without radiation therapy. These results are consistent with the findings from a recent prospective cohort study (*12*) of 82 similarly selected patients treated by lumpectomy alone, where the annual local recurrence rate was 3.6%. It is often stated (*8,13*) that tumors less than 1 cm in diameter may have a low relapse rate in the breast. In our trial, in patients with tumors of 1 cm or less in diameter, 28 (30%) of 93 control patients developed a breast recurrence. It is important to note that, even if a low-risk group could be identified, radiation therapy is still likely to be effective, and decision making will relate to the degree of benefit that may be gained or foregone.

Since clinical trials still have not demonstrated an impact of breast irradiation on survival, it is imperative that serious long-term morbidity of treatment should be avoided. Excessive skin reactions to radiation therapy will lead to the development of unsightly telangiectasia after 3 or 4 years. Tissue maximums within the treated volume should be carefully noted and kept low. Cardiac irradiation and the inclusion of large volumes of lung within the treated fields should be avoided as much as possible. This can all be accomplished with modern treatment planning and technology. Finally, we have previously reported on the value of tumor size and nuclear grade as predictors of poor prognosis in terms of survival and continue to emphasize that these can be used as prognostic markers for determining the use of adjuvant systemic therapy (*1*).

References

(*1*) Clark RM, McCulloch PB, Levine MN, Lipa M, Wilkinson RH, Mahoney LJ, 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.

(*2*) Fisher B, Bauer M, Margolese R, Poisson R, Pilch Y, Redmond C, et al. Five-year results of a randomized clinical trial comparing total mastectomy and segmental mastectomy with or without radiation in the treatment of breast cancer. N Engl J Med 1985;312:665-73.

(*3*) Sector resection with or without postoperative radiotherapy for stage I breast cancer: a randomized trial. Uppsala-Orebro Breast Cancer Study Group [*see* comment citation in Medline]. J Natl Cancer Inst 1990;82:277-82.

(*4*) Veronesi U, Luini A, Del Vecchio M, Greco M, Galimberti V, Merson M, et al. Radiotherapy after breast-preserving surgery in women with localized cancer of the breast [*see* comment citations in Medline]. N Engl J Med 1993;328:1587-91.

(*5*) Fisher B, Anderson S, Redmond CK, Wolmark N, Wickerham DL, Cronin WM. Reanalysis and results after 12 years of follow-up in a randomized clinical trial comparing total mastectomy with lumpectomy with or without irradiation in the treatment of breast cancer [*see* comment citations in Medline]. N Engl J Med 1995;333:1456-61.

(*6*) Liljegren GG, Holmberg L, Adami HO, Westman G, Graffman S, Bergh J. Sector resection with or without postoperative radiotherapy for stage I breast cancer: five-year results of a randomized trial. Uppsala-Orebro Breast Cancer Study Group [*see* comment citations in Medline]. J Natl Cancer Inst 1994;86:717-22.

(*7*) Fowble B. Is there a subset of patients with early stage breast cancer for whom irradiation may not be indicated after conservative surgery alone? The Breast J 1995;1:79-90.

(*8*) Gelber RD, Goldhirsch A. Radiotherapy to the conserved breast: is it avoidable if the cancer is small? [editorial] [*see* comment citations in Medline]. J Natl Cancer Inst 1994;86:652-4.

(*9*) Cuzick J, Stewart H, Rutqvist L, Houghton J, Edwards R, Redmond C, et al. Cause-specific mortality in long-term survivors of breast cancer who participated in trials of radiotherapy [prior annotation incorrect] [*see* comment citations in Medline]. J Clin Oncol 1994;12:447-53.

(*10*) Rutqvist LE, Johansson H. Mortality by laterality of the primary tumor among 55,000 breast cancer patients from the Swedish Cancer Registry. Br J Cancer 1990;61:866-8.

(*11*) Early Breast Cancer Trialists Collaborative Group. Effects of radiotherapy and surgery in early breast cancer. An overview of the randomized trials. Early Breast Cancer Trialists Collaborative Group [*see* comment citations in Medline]. N Engl J Med 1995;333:1444-55.

(*12*) Schnitt SJ, Hayman J, Gelman R, Eberlein TJ, Love SM, Mayzel K, et al. A prospective study of conservative surgery alone in the treatment of selected patients with stage I breast cancer. Cancer 1996;77:1094-100.

(*13*) Nemoto T, Patel JK, Rosner D, Dao TL, Schuh M, Penetrante R. Factors affecting recurrence in lumpectomy without irradiation for breast cancer. Cancer 1991;67:2079-82.

Notes

We thank Drs. V. Basrur, B. Nair, R. McDermot, C. Wong, P. Corbett, and other investigators; P. Skingley; and trials nurses.

Manuscript received April 29, 1996; revised August 23, 1996; accepted August 28, 1996.