

## RECURRENCE RATES AFTER TREATMENT OF BREAST CANCER WITH STANDARD RADIOTHERAPY WITH OR WITHOUT ADDITIONAL RADIATION

HARRY BARTELINK, M.D., PH.D., JEAN-CLAUDE HORIOT, M.D., PH.D., PHILIP POORTMANS, M.D., HENK STRUIKMANS, M.D., PH.D., WALTER VAN DEN BOGAERT, M.D., PH.D., ISABELLE BARILLOT, M.D., ALAIN FOURQUET, M.D., JACQUES BORGER, M.D., PH.D., JOS JAGER, M.D., PH.D., WILLEM HOOGENRAAD, M.D., LAURENCE COLLETTE, M.Sc., AND MARIANNE PIERART, M.Sc., FOR THE EUROPEAN ORGANIZATION FOR RESEARCH AND TREATMENT OF CANCER RADIOTHERAPY AND BREAST CANCER GROUPS

### ABSTRACT

**Background** Radiotherapy prevents local recurrence of breast cancer after breast-conserving surgery. We evaluated the effect of a supplementary dose of radiation to the tumor bed on the rates of local recurrence among patients who received radiotherapy after breast-conserving surgery for early breast cancer.

**Methods** After lumpectomy and axillary dissection, patients with stage I or II breast cancer received 50 Gy of radiation to the whole breast in 2-Gy fractions over a five-week period. Patients with a microscopically complete excision were randomly assigned to receive either no further local treatment (2657 patients) or an additional localized dose of 16 Gy, usually given in eight fractions by means of an external electron beam (2661 patients).

**Results** During a median follow-up period of 5.1 years, local recurrences were observed in 182 of the 2657 patients in the standard-treatment group and 109 of the 2661 patients in the additional-radiation group. The five-year actuarial rates of local recurrence were 7.3 percent (95 percent confidence interval, 6.8 to 7.6 percent) and 4.3 percent (95 percent confidence interval, 3.8 to 4.7 percent), respectively ( $P < 0.001$ ), yielding a hazard ratio for local recurrence of 0.59 (99 percent confidence interval, 0.43 to 0.81) associated with an additional dose. Patients 40 years old or younger benefited most; at five years, their rate of local recurrence was 19.5 percent with standard treatment and 10.2 percent with additional radiation (hazard ratio, 0.46 [99 percent confidence interval, 0.23 to 0.89];  $P = 0.002$ ). At five years in the age group 41 to 50 years old, no differences were found in rates of metastasis or overall survival (which were 87 and 91 percent, respectively).

**Conclusions** In patients with early breast cancer who undergo breast-conserving surgery and receive 50 Gy of radiation to the whole breast, an additional dose of 16 Gy of radiation to the tumor bed reduces the risk of local recurrence, especially in patients younger than 50 years of age. (N Engl J Med 2001;345:1378-87.) Copyright © 2001 Massachusetts Medical Society.

SEVERAL randomized clinical trials<sup>1-5</sup> and a meta-analysis<sup>6</sup> have shown similar survival rates after breast-conserving therapy and after mastectomy in patients with early breast cancer. The B-06 trial of the National Surgical Adjuvant Breast and Bowel Project and other trials demonstrated that after microscopically complete excision, irradiation of the whole breast with a dose of 50 Gy reduced the rate of recurrence in the ipsilateral breast from 35 percent to 10 percent.<sup>4,7-10</sup> However, little is known about the effect of irradiation of the breast at doses higher than 50 Gy.

In the absence of data from randomized trials, there is no uniformity in the dose of radiation and the schedules of fractionation that are used after breast-conserving surgery. To investigate the effect of an additional dose of radiation (a boost) aimed at the tumor bed after the administration of 50 Gy to the whole breast, the European Organization for Research and Treatment of Cancer (EORTC) designed the present trial. We report the first analysis of outcomes in patients with completely excised primary tumors who were randomly assigned to receive the standard therapy — 50 Gy of radiation to the whole breast — or standard therapy plus an additional dose of radiation of 16 Gy directed at the tumor bed.

### METHODS

#### Study Design

Between 1989 and 1996, we enrolled 5569 patients with stage I or II breast cancer who had undergone macroscopically complete surgical removal of the tumor and axillary dissection. The 5318 patients in whom the tumor had been completely excised on micro-

From the Department of Radiation Oncology, the Netherlands Cancer Institute, Amsterdam (H.B., J.B.); the Department of Radiation Oncology, Dr. Bernard Verbeeten Institute, Tilburg (P.P.); the Department of Radiation Oncology, University Hospital Utrecht, Utrecht (H.S.); the Department of Radiation Oncology, Radiotherapeutisch Institute Limburg, Heerlen (J.J.); and the Department of Radiation Oncology, Joint Center for Radiotherapy Arnhem-Nijmegen, St. Radboud Hospital, Nijmegen (W.H.) — all in the Netherlands; the Department of Radiation Oncology, Centre Georges-François Leclerc, Dijon (J.-C.H., I.B.); and the Department of Radiation Oncology, Institut Curie, Paris (A.E.) — both in France; and the Department of Radiation Oncology, University Hospital Gasthuisberg, Leuven (W.V.B.); and the European Organization for Research and Treatment of Cancer, Brussels (L.C., M.P.) — both in Belgium. Address reprint requests to Dr. Bartelink at the Department of Radiation Oncology, Netherlands Cancer Institute, Plesmanlaan 121, 1066 CX Amsterdam, the Netherlands, or at h.bartelink@nki.nl.

scopical examination (as judged on the basis of the pathology report) were randomly assigned to undergo 50-Gy irradiation of the whole breast with or without an additional dose of 16 Gy to the tumor bed; 2661 patients were assigned to the additional-radiation group and 2657 to the standard-treatment group. Patients with a microscopically incomplete excision were assigned to receive booster doses of 10 or 26 Gy; these 251 patients were excluded from the analyses reported here. At randomization, patients were stratified according to age, menopausal status, the presence or absence of an intraductal component in and around the invasive tumor, clinical tumor size, clinical nodal status, and center. The sample size was calculated so as to give the study a 90 percent probability of detecting a 5 percent improvement in 10-year survival. An independent data monitoring committee was convened before 10 years had elapsed. The committee advised that we publish the data on local control of the cancer after a median of five years of follow-up, since a statistically significant effect of the higher dose of radiation on the rate of local recurrence was clearly demonstrated and since it was concluded that these results were unlikely to change with additional follow-up.

### Eligibility

Patients with breast cancer of clinical stage T1–2, N0–1, M0 were eligible for the trial.<sup>11</sup> Patients older than 70 years of age, or those with pure carcinoma in situ, multiple tumor foci in more than one quadrant, a history of other cancers, an Eastern Cooperative Oncology Group (ECOG) performance score higher than 2, residual microcalcifications on mammography, or gross residual disease in the breast after lumpectomy (unless reexcision had been performed) were ineligible. Oral informed consent was obtained according to the guidelines of the EORTC and the local and national rules of the participating centers. Patients came from 31 centers in nine countries. There were major violations of eligibility criteria in the cases of 26 patients — residual microcalcifications on postoperative mammography (6 patients), previous history of a malignant tumor (5 patients), pure intraductal carcinoma in situ (3 patients), stage T3 tumor (2 patients), clinically fixed axillary nodes (2 patients), and various other violations (8 patients). In addition, 107 patients were older than 70 years, and for 343 patients the delay between surgery and the start of radiotherapy was longer than that allowed by the protocol. The latter two groups were considered to have minor deviations from the protocol. All patients, whether eligible or ineligible, were included in the analysis.

### Treatment

The protocol called for patients to undergo surgical excision of the primary tumor, with a 1-cm margin of macroscopically normal tissue (lumpectomy), and an axillary dissection. Any removal of additional breast tissue after the excision of the primary tumor was termed a reexcision, whether it was performed during the same session or later. Postoperative mammography was required if suspicious microcalcifications were seen before lumpectomy. The surfaces of specimens were routinely marked with India ink in the participating centers. Any invasive carcinoma that was found on microscopical examination to have crossed the inked margin was defined as incompletely excised. Patients with a microscopically incomplete excision underwent randomization separately to an additional dose of radiation of either 10 Gy or 26 Gy. Patients with axillary lymph-node involvement received adjuvant systemic therapy: premenopausal patients received chemotherapy, and postmenopausal patients received tamoxifen. Patients not given adjuvant chemotherapy began radiotherapy within nine weeks after lumpectomy. For patients who received adjuvant chemotherapy, a delay of up to six months before irradiation was allowed. Irradiation of the whole breast was performed with the use of two tangential megavoltage photon beams (high-energy x-ray or tele-cobalt). A total dose of 50 Gy over a five-week period, with a dose of 2 Gy per fraction, was delivered at the intersection of the central axes of the beams.<sup>12</sup> The additional dose of 16 Gy was given to the center of the area from which the tumor had been excised; it was given in eight equal external-beam

fractions with fast electrons or tangential photon fields, or alternatively, by means of an iridium-192 implant with a dose rate of 10 Gy per 24 hours.<sup>12–15</sup>

The target area for the additional dose of radiation was the site of the primary tumor, with a margin of 1.5 cm around the primary tumor after microscopically complete excision and of 3.0 cm after incomplete excision or in case of invasive cancer with extensive ductal carcinoma in situ.

### Quality Assurance

At the start of the trial, the participating physicians received guidelines,<sup>13,14</sup> a quality-assurance program was implemented to confirm that breast irradiation was carried out in a standard fashion in all centers,<sup>14–17</sup> a team of physicists verified the calibration of the beams in the participating centers, and a program was set up for thermoluminescent dosimetry. If a major deviation between the calculated doses and the delivered doses was detected, a local audit was held to identify the reason. A central pathology review was performed by one pathologist at the Netherlands Cancer Institute.

### Statistical Analysis

All analyses were conducted according to the intention-to-treat principle. The randomization was performed centrally at the EORTC Data Center by means of the minimization technique.<sup>18</sup> The time to local recurrence was calculated from the date of randomization. All recurrences in the treated breast, before or after the detection of distant metastases, were taken into account. Data for patients who remained free of local disease were censored as of the date when the last follow-up information was obtained. The primary analysis of time-to-event end points was performed with the use of a two-sided log-rank test at the 5 percent level of significance.<sup>19</sup>

Analysis was performed on subgroups defined by the factors that had been used for stratification before randomization: age, menopausal status, presence or absence of ductal carcinoma in situ, clinical tumor size, and nodal status. The probability of event-free survival was estimated with the Kaplan–Meier technique. For the analysis of prognostic factors, we used a Cox proportional-hazards regression model, stratified according to treatment-group assignment.<sup>20</sup> These latter analyses included all 5569 patients. Univariate and multivariate analyses were conducted to determine which factors were associated with local control of the cancer. A univariate analysis was conducted first, and then a backward-selection procedure was used to determine the composition of the multivariate models. Initially, all the variables that were significant at the 0.05 level in the univariate analysis were entered in the model. The least significant variables were then sequentially removed from the model. The last variables to be removed were checked for reentry into the model, in order to validate the final model. For the multivariate analyses, the models obtained with both the 0.05 and 0.01 levels of significance are described.

## RESULTS

### Characteristics of the Patients, the Tumors, and the Treatments

Characteristics of the patients were similar in the two groups (Table 1). To achieve a microscopically complete resection, reexcision was required in 24 percent of the patients. In 99 percent of the patients, axillary dissection was performed. The median number of axillary nodes examined was 12 (range, 0 to 49), and in 60 percent of the patients more than 10 lymph nodes were examined. A total of 13 percent of the patients had a hematoma or breast infection as a complication. Another 17 percent had a seroma or an infection of the axillary wound. The median interval between lumpectomy and the start of radio-

**TABLE 1.** CHARACTERISTICS OF THE PATIENTS AND THE TUMORS.

CHARACTERISTIC	STANDARD-TREATMENT GROUP (N=2657)	ADDITIONAL-RADIATION GROUP (N=2661)	CHARACTERISTIC	STANDARD-TREATMENT GROUP (N=2657)	ADDITIONAL-RADIATION GROUP (N=2661)
yr					
<b>Patient</b>					
Age					
Median	54.9	54.8			
Range	22.7–83.5	25.6–78.8			
no. (%)			no. (%)		
Age group			<b>Tumor (continued)</b>		
≤35 yr	72 (2.7)	82 (3.1)	Histologic type of carcinoma		
36–40 yr	156 (5.9)	139 (5.2)	Unknown	8 (0.3)	8 (0.3)
41–50 yr	665 (25.0)	669 (25.1)	Invasive ductal	2155 (81.1)	2198 (82.6)
51–60 yr	943 (35.5)	860 (32.3)	Invasive lobular	228 (8.6)	219 (8.2)
>60 yr	821 (30.9)	911 (34.2)	Mixed invasive	65 (2.4)	81 (3.0)
Menopausal status			Tubular	99 (3.7)	71 (2.7)
Unknown	10 (0.4)	8 (0.3)	Medullary	58 (2.2)	49 (1.8)
Premenopausal	999 (37.6)	1004 (37.7)	Colloid	37 (1.4)	33 (1.2)
Postmenopausal	1648 (62.0)	1649 (62.0)	Other	7 (0.3)	2 (0.1)
ECOG performance score*			No. of nodes examined		
Unknown	10 (0.4)	9 (0.3)	Unknown	69 (2.6)	75 (2.8)
0	2335 (87.9)	2335 (87.7)	0	21 (0.8)	16 (0.6)
1–2	312 (11.7)	317 (11.9)	1–5	170 (6.4)	176 (6.6)
<b>Tumor</b>			6–10	813 (30.6)	826 (31.0)
Size determined by palpation			11–15	876 (33.0)	914 (34.3)
Unknown	336 (12.6)	348 (13.1)	>15	708 (26.6)	654 (24.6)
Not palpable	569 (21.4)	581 (21.8)	Number of positive nodes		
<1 cm	315 (11.9)	313 (11.8)	Unknown	25 (0.9)	20 (0.8)
1–1.9 cm	856 (32.2)	829 (31.2)	0	2078 (78.2)	2090 (78.5)
2–3 cm	433 (16.3)	449 (16.9)	1–3	452 (17.0)	449 (16.9)
>3 cm	148 (5.6)	141 (5.3)	≥4	102 (3.8)	102 (3.8)
Size determined by mammography			Hormone-receptor status†		
<1 cm	576 (21.7)	525 (19.7)	Estrogen		
1–1.9 cm	1027 (38.7)	1067 (40.1)	Negative	525 (19.8)	528 (19.8)
2–3 cm	397 (14.9)	436 (16.4)	Positive	1391 (52.4)	1409 (53.0)
>3 cm	110 (4.1)	104 (3.9)	Unknown	741 (27.9)	724 (27.2)
Unknown	547 (20.6)	529 (19.9)	Progesterone		
Tumor stage			Negative	601 (22.6)	625 (23.5)
T1	1379 (51.9)	1373 (51.6)	Positive	1168 (44.0)	1187 (44.6)
T2	1274 (47.9)	1281 (48.1)	Unknown	888 (33.4)	849 (31.9)
T3	4 (0.2)	7 (0.3)	Estrogen and progesterone		
Nodal status			Unknown	893 (33.6)	853 (32.1)
N0	2409 (90.7)	2383 (89.6)	Estrogen positive, progesterone positive	1031 (38.8)	1042 (39.2)
N1–2	182 (6.8)	209 (7.9)	Estrogen positive, progesterone negative	255 (9.6)	267 (10.0)
NX	66 (2.5)	69 (2.6)	Estrogen negative, progesterone positive	133 (5.0)	141 (5.3)
Reexcision			Estrogen negative, progesterone negative	345 (13.0)	358 (13.5)
Unknown	8 (0.3)	8 (0.3)			
No	2003 (75.4)	1991 (74.8)			
Yes	646 (24.3)	662 (24.9)			
Largest diameter of dominant lesion on visual examination					
Unknown	49 (1.8)	62 (2.3)			
<10 mm	683 (25.7)	635 (23.9)			
10–20 mm	1402 (52.8)	1451 (54.5)			
>20 mm	523 (19.7)	513 (19.3)			

\*ECOG denotes Eastern Cooperative Oncology Group.

†Status was determined by local procedures, either by ligand-binding assay (charcoal) or immunohistochemical analysis.

therapy was 39 days (range, 3 to 156) for patients who did not receive postoperative chemotherapy and 52 days (range, 14 to 469) for those who did receive postoperative chemotherapy. The median dose of radiation delivered to the tumor bed was 50 Gy (range, 2 to 73) in the standard-treatment group and 66 Gy (range, 23 to 79) in the additional-radiation group. Axillary irradiation was given to the 272 patients who did not undergo a complete axillary dissection or to patients with positive lymph nodes in the highest level of the axillary surgical specimen. Irradiation of the internal mammary lymph nodes was performed in 1089 of the patients. In the standard-treatment group, 53 (2 percent) nevertheless received an additional dose, and the treatment was not documented in 24 patients (1 percent). In the additional-radiation group, 26 patients (1 percent) received no additional dose and for 21 patients (0.8 percent) the information was missing. These patients' treatments were considered to be protocol violations; however, they were included in the intention-to-treat analysis. In 90 percent of the patients in this group, external irradiation was used for the additional dose (63 percent with electrons and 27 percent with photons), and in 8 percent an interstitial implant was used; no information was available on the method of delivery of the additional dose for the remaining 1 percent. Details regarding systemic adjuvant therapies are presented in Table 2.

**Follow-up**

The median duration of follow-up was 5.1 years (maximum, 10.2 years), by which point 479 of the

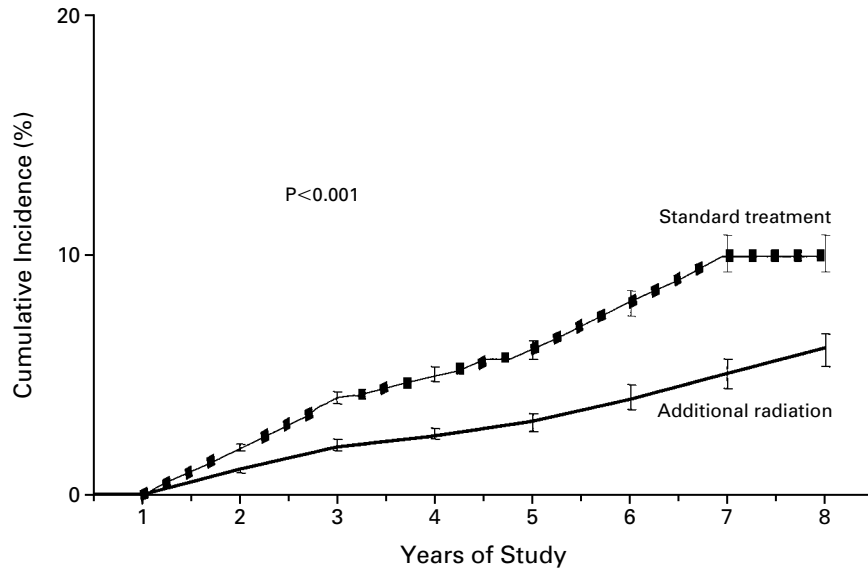
5318 patients with a microscopically complete resection had died and 291 had had local recurrences.

**Local Control**

Local recurrence was observed in 182 of the 2657 patients assigned to receive only the initial 50 Gy of irradiation of the whole breast and in 109 of the 2661 patients assigned to receive 50 Gy plus an additional dose of 16 Gy. This incidence corresponds to five-year actuarial rates of local recurrence of 7.3 percent (95 percent confidence interval, 6.8 to 7.6 percent) and 4.3 percent (95 percent confidence interval, 3.8 to 4.7 percent), respectively (P<0.001), and a hazard ratio for local recurrence of 0.59 (99 percent confidence interval, 0.43 to 0.81) associated with an additional dose (Fig. 1). Local recurrence was the first event in 5.9 percent of the patients in the standard-treatment group and 3.3 percent of those in the additional-radiation group. In the standard-treatment group, 18 local recurrences were reported after another recurrence (i.e., a distant metastasis, a regional metastasis, or contralateral breast cancer); 9 such events occurred in the additional-radiation group. Overall, 47 percent of the local recurrences occurred in the primary tumor bed, 9 percent in the scar, and 29 percent outside the area of the original tumor, and 27 percent were diffuse throughout the breast. Analyses of subgroups defined according to the stratification factors (Table 3) found the largest clinical benefit from the higher dose of radiation in patients 40 years old or younger (Fig. 2). The benefit of the additional dose in local control was independent of whether the patients received adjuvant systemic treatment. The hazard ratio was 0.66

**TABLE 2. ADJUVANT HORMONAL TREATMENT OR CHEMOTHERAPY.**

SUBGROUP	ADJUVANT TREATMENT	STANDARD-TREATMENT GROUP	ADDITIONAL-RADIATION GROUP
		no./total no. with data in subgroup (%)	
Premenopausal, node-negative	Unknown	5/775 (0.6)	5/774 (0.6)
	None	726/775 (93.7)	723/774 (93.4)
	Chemotherapy	44/775 (5.7)	46/774 (5.9)
Premenopausal, node-positive	Unknown	0/221	1/226 (0.4)
	None	47/221 (21.3)	28/226 (12.4)
	Chemotherapy	174/221 (78.7)	197/226 (87.2)
Postmenopausal, node-negative	Unknown	13/1301 (1.0)	12/1316 (0.9)
	None	1072/1301 (82.4)	1062/1316 (80.7)
	Chemotherapy	16/1301 (1.2)	24/1316 (1.8)
	Tamoxifen	189/1301 (14.5)	212/1316 (16.1)
	Chemotherapy and tamoxifen	11/1301 (0.8)	6/1316 (0.5)
Postmenopausal, node-positive	Unknown	5/333 (1.5)	5/325 (1.5)
	None	22/333 (6.6)	22/325 (6.8)
	Chemotherapy	40/333 (12.0)	29/325 (8.9)
	Tamoxifen	231/333 (69.4)	247/325 (76.0)
	Chemotherapy and tamoxifen	35/333 (10.5)	22/325 (6.8)



NO. OF EVENTS/NO. AT RISK

Standard treatment	17/2657	46/2594	44/2464	31/2193	17/1732	15/1197	11/748	1/376
Additional radiation	7/2661	21/2613	22/2501	25/2243	17/1757	8/1196	4/749	2/365

**Figure 1.** Cumulative Incidence of Recurrence of Tumor in the Ipsilateral Breast after Whole-Breast Irradiation at 50 Gy, with or without an Additional Dose to the Tumor Bed.

The P value was calculated by the overall log-rank test for the comparison of the time to local recurrence between the groups. The I bars represent standard deviations.

(99 percent confidence interval, 0.47 to 0.93;  $P=0.002$ ) for patients who received no adjuvant treatment, and 0.40 (99 percent confidence interval, 0.20 to 0.81;  $P=0.001$ ) for patients who received adjuvant treatment.

#### Univariate and Multivariate Analysis of Prognostic Factors for Local Control

In the univariate Cox proportional-hazards regression analysis, patients were stratified according to treatment-group assignment. The following factors had a significant negative effect on local control: young age, premenopausal status, large tumor size (as determined by palpation or as pathologically measured), incomplete first excision of the tumor, absence of estrogen or progesterone receptors, and lack of systemic adjuvant treatment. The variables that reached the 0.05 level of significance in association with age or local control for the overall population were entered in the first step of the multivariate model. Except for the duration of the interval between lumpectomy and the start of radiotherapy, the total dose to the tumor bed, and the use or nonuse of axillary irradiation, all variables were entered in the first step of the multivariate analysis. The backward-elimination process showed that three variables were significant at  $P < 0.05$ : older age ( $P < 0.001$ ; hazard ratio, 0.59 [95 percent confidence interval, 0.48 to 0.71]), the presence of palpable

tumors ( $P=0.007$ ; hazard ratio, 2.14 [95 percent confidence interval, 1.23 to 3.72]), and the presence of a progesterone receptor ( $P=0.004$ ; hazard ratio, 0.66 [95 percent confidence interval, 0.49 to 0.87]), which indicates that the risk of local recurrence was highest in younger patients (Fig. 3), in those in whom the tumor was palpable, and in those who lacked progesterone receptors. At a significance level of 0.01, the model retained the same factors, but at a significance level of 0.001 it retained only age ( $P < 0.001$ ; hazard ratio, 0.56 [99 percent confidence interval, 0.51 to 0.68]).

The multivariate analysis of factors associated with local control was repeated with the additional treatment as a covariate as well as the presence or absence of progesterone receptors, the presence or absence of palpable tumor, and age. This analysis demonstrated that all three clinical factors remained significant at the 0.05 level, but only age and the use of an additional dose of radiation remained significant at a level of 0.001. The effect of the additional dose remained significant in this multivariate analysis (hazard ratio, 0.51; 95 percent confidence interval, 0.37 to 0.70;  $P < 0.001$ ).

#### Salvage Treatment for Local Recurrences

Salvage treatment for local recurrences consisted primarily of total mastectomy; some patients underwent conservative salvage operations. Mastectomy and

TABLE 3. RESULTS OF SUBGROUP ANALYSES OF LOCAL CONTROL ACCORDING TO STRATIFICATION FACTORS.\*

VARIABLE	STANDARD-TREATMENT GROUP		ADDITIONAL-RADIATION GROUP		REDUCTION IN THE ANNUAL ODDS OF LOCAL RECURRENCE (95% CI)	P VALUE
	NO. OF LOCAL RECURRENCES/NO. OF PATIENTS WITH DATA	ACTUARIAL 5-YR LOCAL RECURRENCE RATE (95% CI) percent	NO. OF LOCAL RECURRENCES/NO. OF PATIENTS WITH DATA	ACTUARIAL 5-YR LOCAL RECURRENCE RATE (95% CI) percent		
Age						
≤40 yr	46/228	19.5 (16.5–22.5)	22/221	10.2 (7.9–12.5)	54 (25–71)	0.002
41–50 yr	61/665	9.5 (8.2–10.7)	38/669	5.8 (4.8–6.8)	38 (8–58)	0.02
51–60 yr	43/943	4.2 (3.5–4.9)	25/860	3.4 (2.7–4.1)	36 (0–60)	0.07
>60 yr	32/821	4.0 (3.2–4.7)	24/911	2.5 (1.9–3.2)	32 (0–60)	0.14
Menopausal status						
Premenopausal	106/999	10.3 (9.2–11.4)	61/1004	6.8 (5.8–7.6)	40 (19–56)	0.001
Postmenopausal	76/1648	4.6 (4.1–5.2)	45/1649	2.8 (2.3–3.2)	41 (15–59)	0.004
Tumor stage						
T1	88/1379	5.9 (5.2–6.6)	50/1373	4.0 (3.3–4.6)	42 (19–59)	0.001
T2	94/1274	7.8 (7.0–8.7)	58/1281	4.5 (3.9–5.2)	39 (16–56)	0.002
Nodal status						
N0	169/2409	6.9 (6.4–7.5)	92/2383	4.2 (3.4–4.6)	43 (27–55)	0.001
N1–2†	9/182	5.6 (3.7–7.4)	11/209	5.7 (3.7–7.6)	0 (0–56)	0.89
Ductal carcinoma in situ						
Absent	92/1641	5.4 (4.8–6.0)	56/1644	3.5 (3.0–4.0)	40 (17–56)	0.002
Present	90/1015	9.3 (8.2–10.3)	53/1014	5.6 (4.5–6.5)	41 (17–57)	0.002

\*CI denotes confidence interval.

†The results of this analysis may not be valid, owing to the small number of events in both groups.

lumpectomy were performed in 131 and 24 patients, respectively, among the 182 patients with local recurrence in the standard-treatment group, and 82 and 11 patients, respectively, among the 109 patients with local recurrence in the additional-radiation group; 34 patients received systemic treatment alone or combined with hormonal therapy; and in 9 patients no information was available regarding salvage therapy.

**Side Effects of the Booster Dose**

The higher dose of radiation was expected to increase the incidence and the degree of fibrosis and cause an unsatisfactory cosmetic result. To date, we have not seen a significant difference in the grades of fibrosis, as scored by physicians on a four-point scale (with 0 indicating the absence of fibrosis and 3 indicating severe fibrosis) between the patients who received the additional dose and those who did not. The grades of fibrosis in the whole breast for patients in the standard-treatment and additional-radiation groups were as follows: 1288 patients (48 percent) and 1339 patients (50 percent), respectively, had no fibrosis; 991 (37 percent) and 908 (34 percent), respectively, had minor fibrosis; 236 (9 percent) and 261 (10 percent), respectively, had moderate fibrosis; 24 (1 percent) and 32 (1 percent), respectively, had severe fibrosis; and in 118 (4 percent) and 121 (5 percent), respectively, the grade of fibrosis was unknown. The cosmetic results

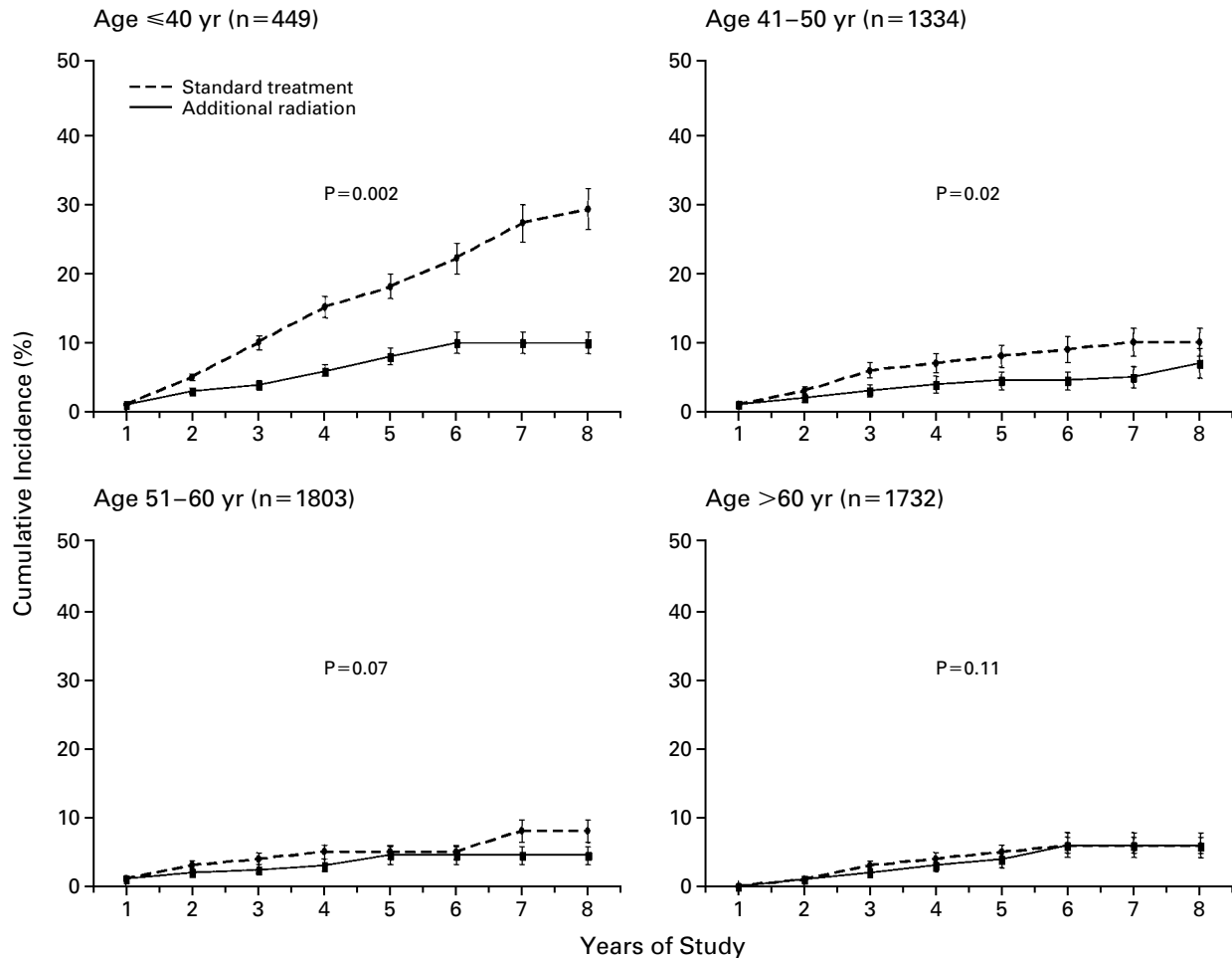
were the subject of separate studies and have been published elsewhere.<sup>21,22</sup> Excellent or good cosmetic results were obtained in 86 percent of the patients in the standard-treatment group, as compared with 71 percent of the patients in the additional-radiation group. No other side effects of the additional dose have been observed.

**Survival and Causes of Death**

Survival free of distant metastases and overall survival were similar in the two treatment groups (P=0.93 and P=0.63, respectively), with five-year rates of 87 percent and 91 percent, respectively, in both groups (Fig. 3). No analysis of subgroups defined according to the stratification factors was conducted. The causes of death were also similar in the two treatment groups. Of the 479 deaths, 361 — 186 in the standard-treatment group and 175 in the additional-radiation group — were due to breast cancer.

**DISCUSSION**

Multiple randomized trials have conclusively demonstrated that breast irradiation markedly reduces the rate of local recurrence after conservation surgery for breast cancer, but these studies did not deal with the dose or fractionation of radiation. The decision to deliver an additional localized dose of irradiation is based on the fact that most local recurrences occur within



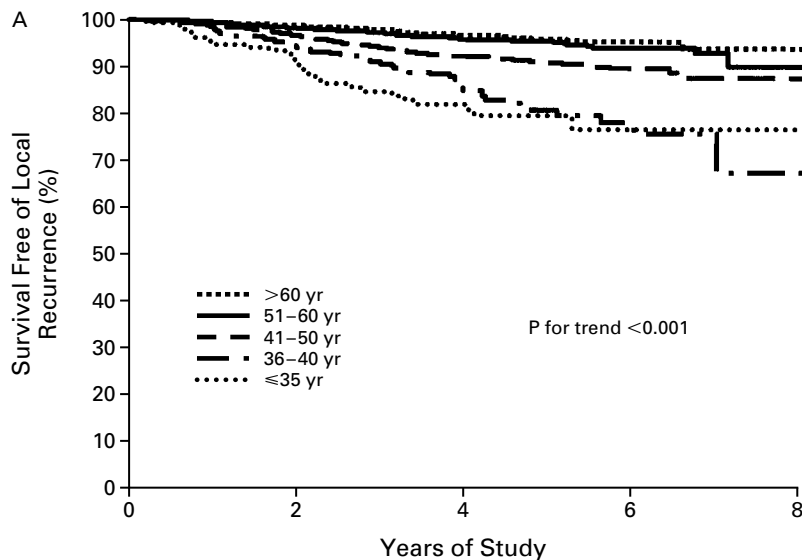
**Figure 2.** Cumulative Incidence of Recurrence of Tumor in the Ipsilateral Breast after Whole-Breast Irradiation at 50 Gy, with or without an Additional Dose to the Tumor Bed, According to Age.

At five years, the rate of local recurrence in patients 40 years old or younger was 10.2 percent in the additional-radiation group, as compared with 19.5 percent in the standard-treatment group (hazard ratio, 0.46 [99 percent confidence interval, 0.23 to 0.89]); in patients 41 to 50 years old, the rates were 5.8 percent (99 percent confidence interval, 4.8 to 6.8 percent) and 9.5 percent (99 percent confidence interval, 8.2 to 10.7 percent), respectively; in patients 51 to 60 years old, the rates were 3.4 percent (99 percent confidence interval, 2.7 to 4.1 percent) and 4.2 percent (99 percent confidence interval, 3.5 to 4.9 percent), respectively; and in patients older than 60 years of age, the rates were 2.5 percent (99 percent confidence interval, 1.9 to 3.2 percent) and 4.0 percent (99 percent confidence interval, 3.2 to 4.7 percent), respectively. P values were calculated by the overall log-rank test for the comparisons of the time to local recurrence between the groups. The I bars represent standard deviations, and N denotes the number of patients in each age group.

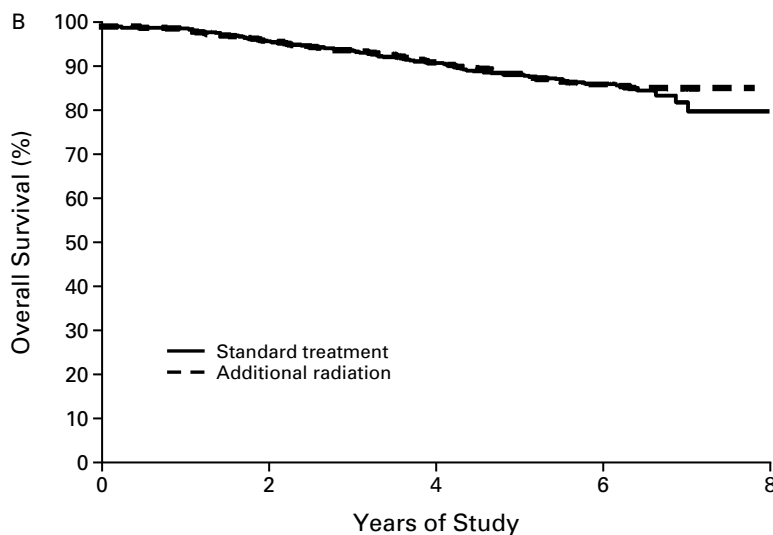
the vicinity of the primary tumor. For this reason, additional treatment was prescribed in all but one of the randomized trials that established the equivalence of breast-conserving and radical surgical therapy.<sup>1-5</sup> However, the National Surgical Adjuvant Breast and Bowel Project trials limited the dose of radiation to 50 Gy when the excised tumor had microscopically negative margins, a practice that has been adopted as standard therapy in published guidelines.<sup>23</sup> Our trial investigated the benefits and risks of adding an additional 16-Gy dose to this standard 50-Gy irradiation of the whole breast in patients with completely excised

early breast cancer. We found that an additional dose to the primary tumor area nearly halved the annual odds of local recurrence (hazard ratio, 0.59). Preliminary data from a smaller trial are similar to ours.<sup>24</sup>

A 41 percent reduction in the rate of local recurrences is substantial in relative terms, but the absolute benefit of additional treatment depends on each patient's risk of recurrence after receiving the initial 50 Gy of radiation. The only factor we could associate with the extent of the benefit of additional treatment was age. Since the unfavorable influence of young age on the risk of local recurrence and overall survival is



No. AT RISK					
>60 yr	1807	1694	1237	518	85
51-60 yr	1885	1768	1220	525	102
41-50 yr	1407	1316	912	407	75
36-40 yr	314	285	200	90	17
≤35 yr	156	137	95	46	9



No. AT RISK					
Standard treatment	2657	2515	1814	795	137
Additional radiation	2661	2524	1806	779	156

**Figure 3.** Survival Free of Local Recurrence According to Age for the Entire Cohort (Panel A) and Overall Survival According to Treatment-Group Assignment (Panel B).

There were a total of 58 local recurrences among patients older than 60 years of age, 75 among those 51 to 60 years of age, 109 among those 41 to 50 years of age, 48 among those 36 to 40 years of age, and 28 among those 35 years of age or younger.

well established,<sup>25-29</sup> it was not unexpected that patients 40 years old or younger would derive the greatest absolute benefit from additional treatment; the cumulative five-year rate of local recurrence was 19.5 percent without an additional dose and 10.2 percent with an additional dose. Our analysis also indicated that breast cancer in younger patients is more responsive to radiation, but there is no clear radiobiologic explanation for this. We do not suggest that additional treatment is ineffective in older patients, but its efficacy does decrease with increasing age, perhaps because in older patients local control after 50 Gy of irradiation of the whole breast alone is excellent. In our opinion, the absolute benefit of the additional dose justifies its use in patients 50 years old or younger.

The excellent local control found in this study was probably due, at least in part, to the intensive quality-assurance program that monitored surgical and radiotherapy procedures and the evaluation of pathology specimens. Unlike many other breast-cancer trials, this study did not involve the use of systemic adjuvant therapy in most patients, although such therapy has been shown to improve local control. We found that systemic adjuvant treatment reduced the rate of local recurrence (hazard ratio, 0.75), although its significance disappeared in the multivariate analysis. The contribution of the additional dose to improved local control was similar regardless of whether patients received systemic adjuvant treatment. Nevertheless, since the patients were not stratified according to the use or nonuse of such treatment, it cannot be considered a substitute for the additional dose, particularly in young patients.

There are indications that the improvement in local control associated with breast irradiation after breast-conserving surgery or mastectomy translates into a survival advantage.<sup>6,30-32</sup> In our trial, however, the five-year survival rate was identical in the two treatment groups. We believe that a follow-up period of at least 10 years would be needed to find a difference in overall survival, and we plan to follow our patients for at least 10 years.

Soft-tissue sarcomas are rarely seen after breast irradiation (incidence, less than 0.5 percent).<sup>33</sup> A slight increase in the incidence of contralateral breast cancer was observed in women treated with radiation after mastectomy, probably as a result of the small dose of "scatter" radiation to the other breast.<sup>34</sup> An increase in the incidence of second malignant tumors as a consequence of the higher additional dose has not yet been observed in our trial. However, it is unlikely that the delivery of an additional 16-Gy dose to a limited volume of tissue, with the use of modern irradiation techniques, will lead to a measurable increase in the risk of such tumors from that associated with 50 Gy of irradiation of the whole breast.

We found no significant increase in the degree of fibrosis in the treated breast among women who re-

ceived an additional dose of radiation. However, a panel consisting of surgeons, radiation oncologists, and laypersons concluded that excellent or good cosmetic results were obtained in 86 percent of the patients in the standard-treatment group at three years, as compared with 71 percent of those in the additional-radiation group. The additional dose was, however, not the only factor with a negative influence on the cosmetic outcome. Other factors included the location of the primary tumor, the size of the tumor, the volume of tissue excised, and any complications of surgery.<sup>21,22</sup> A 5-year follow-up period is too short to allow a definitive analysis of late effects of radiation,<sup>35</sup> and a further analysis will be performed at 10 years. The reduction in the incidence of local recurrences associated with the additional dose far outweighs the slight increase in the poorer cosmetic outcome, especially in patients younger than 50 years of age.

Supported by grants (5R10-CA11488 through 5U10-CA11488-30) from the National Cancer Institute. The content of the article is solely the responsibility of the authors and does not necessarily reflect the official views of the National Cancer Institute.

*We are indebted to the following persons for their help in the concept and design of the trial and their active participation: E. van der Schueren, Leuven, Belgium; B. Pierquin, Paris; R.P. Müller, Cologne, Germany; J. Kurtz, Geneva; D. Morgan, Nottingham, United Kingdom; J.B. Dubois, Montpellier, France; E. Salamon, Namur, Belgium; R.O. Mirimanoff, Lausanne, Switzerland; J.W.H. Leer, Leiden, the Netherlands; M. Bolla, Grenoble, France; A. Kuten, Haifa, Israel; A. Renaud, La Louvière, Belgium; U. Schulz, Krefeld, Germany; P.C.M. Koper, Rotterdam, the Netherlands; D. Van den Weyngaert, Antwerp, Belgium; G.A. Storme, Brussels, Belgium; G.H.M. Calitchi, Creteil, France; W. Budach, Berlin, Germany; S. Roth, Düsseldorf, Germany; M. Poulsen, Brisbane, Australia; M.A. Dominguez, Pamplona, Spain; E. Monpetit, Vannes, France; F. Kovner, Tel Aviv, Israel; A. Biete Sola, Barcelona, Spain; P. Calvo, Madrid, Spain; and C. Vrieling, Amsterdam, the Netherlands; and to J.L. Peterse for pathology review.*

## REFERENCES

1. Sarrazin D, Le MG, Arriagada R, et al. Ten-year results of a randomized trial comparing a conservative treatment to mastectomy in early breast cancer. *Radiother Oncol* 1989;14:177-84.
2. Blichert-Toft M, Rose C, Andersen JA, et al. Danish randomized trial comparing breast conservation therapy with mastectomy: six years of life-table analysis. 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, 1992:19-25. (NIH publication no. 90-3187.)
3. Veronesi U, Salvadori B, Luini A, et al. Breast conservation is a safe method in patients with small cancer of the breast: long-term results of three randomised trials on 1,973 patients. *Eur J Cancer* 1995;31A:1574-9.
4. 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. *N Engl J Med* 1995; 333:1456-61.
5. van Dongen JA, Voogd AC, Fentiman IS, et al. Long-term results of a randomized trial comparing breast-conserving therapy with mastectomy. *European Organization for Research and Treatment of Cancer 10801 trial*. *J Natl Cancer Inst* 2000;92:1143-50.
6. 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.]
7. Forrest AP, Stewart HJ, Everington D, et al. Randomised controlled tri-

- al of conservation therapy for breast cancer: 6-year analysis of the Scottish trial. *Lancet* 1996;348:708-13.
8. 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.
  9. Uppsala-Orebro Breast Cancer Study Group. Sector resection with or without postoperative radiotherapy for stage I breast cancer: a randomized trial. *J Natl Cancer Inst* 1990;82:277-82.
  10. Clark RM, Whelan T, Levine M, et al. Randomized clinical trial of breast irradiation following lumpectomy and axillary dissection for node-negative breast cancer: an update. *J Natl Cancer Inst* 1996;88:1659-64.
  11. International Union against Cancer. TNM clinical classification. In: Hermanek P, Sobin LH, eds. TNM classification of malignant tumors. 4th ed. rev. Berlin, Germany: Springer-Verlag, 1987:95-6.
  12. Prescribing, recording, and reporting with photon beam therapy. Report 50. Bethesda, Md.: International Commission of Radiation Units and Measurements, September 1993.
  13. Bartelink H, Garavaglia G, Johansson KA, et al. Quality assurance in conservative treatment of early breast cancer: report on a consensus meeting of the EORTC Radiotherapy and Breast Cancer Cooperative Groups and the EUSOMA (European Society of Mastology). *Radiother Oncol* 1991;22:323-6.
  14. Van Tienhoven G, Van Bree NAM, Mijnheer BJ, Bartelink H. Quality assurance of the EORTC trial 22881/10882: "assessment of the role of the booster dose in breast conserving therapy": the Dummy Run. *Radiother Oncol* 1991;22:290-8.
  15. Hamers HP, Johansson KA, Venselaar JLM, de Brouwer P, Hansson U, Moudi C. Entrance and exit TL-dosimetry in the conservative treatment of breast cancer: a pilot study for the EORTC-Radiotherapy Cooperative Group. *Radiother Oncol* 1991;22:280-4.
  16. Heukelom S, Lanson JH, van Tienhoven G, Mijnheer BJ. In vivo dosimetry during tangential breast treatment. *Radiother Oncol* 1991;22:269-79.
  17. van Tienhoven G, Leunens G, Vantongelen K, et al. Quality assurance of EORTC trial 22881/10882: "assessment of the role of the booster dose in breast conserving therapy": the individual case review. *Radiother Oncol* 1992;24:Suppl:S35. abstract.
  18. Pocock SJ, Simon R. Sequential treatment assignment with balancing for prognostic factors in the controlled clinical trial. *Biometrics* 1975;31:103-15.
  19. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc* 1958;53:457-81.
  20. Cox DR, Oakes D. Analysis of survival data. London: Chapman & Hall, 1984.
  21. Vrieling C, Collette L, Fourquet A, et al. The influence of the boost in breast-conserving therapy on cosmetic outcome in the EORTC "boost versus no boost" trial. *Int J Radiat Oncol Biol Phys* 1999;45:677-85.
  22. Vrieling C, Collette L, Fourquet A, et al. The influence of patient, tumor and treatment factors on the cosmetic results after breast-conserving therapy in the EORTC "boost vs no boost" trial. *Radiother Oncol* 2000;55:219-32.
  23. The Steering Committee on Clinical Practice Guidelines for the Care and Treatment of Breast Cancer. Breast radiotherapy after breast-conserving surgery. *CMAJ* 1998;158:Suppl 3:S35-S42.
  24. Romestaing P, Lehingue Y, Carrie C, et al. Role of a 10-Gy boost in the conservative treatment of early breast cancer: results of a randomized clinical trial in Lyon, France. *J Clin Oncol* 1997;15:963-8.
  25. de la Rochefordiere A, Asselain B, Campana F, et al. Age as prognostic factor in premenopausal breast carcinoma. *Lancet* 1993;341:1039-43.
  26. Albain KS, Allred DC, Clark GM. Breast cancer outcome and predictors of outcome: are there age differentials? In: Breast cancer in young women. Journal of the National Cancer Institute monographs. No. 16. Washington, D.C.: Government Printing Office, 1994:35-42. (NIH publication no. 93-03559.)
  27. Borger J, Kemperman H, Hart A, Peterse H, van Dongen J, Bartelink H. Risk factors in breast-conservation therapy. *J Clin Oncol* 1994;12:653-60.
  28. Voogd AC, Nielsen M, Peterse JL, et al. Differences in risk factors for local and distant recurrence of breast-conserving therapy or mastectomy for stage I and II breast cancer: pooled results of two large European randomized trials. *J Clin Oncol* 2001;19:1688-97.
  29. Elkhuizen PHM, van Slooten HJ, Clahsen PC, et al. High local recurrence risk after breast-conserving therapy in node-negative premenopausal breast cancer patients is greatly reduced by one course of perioperative chemotherapy: a European Organization for Research and Treatment of Cancer Breast Cancer Cooperative Group Study. *J Clin Oncol* 2000;18:1075-83.
  30. Overgaard M, Hansen PS, Overgaard J, et al. Postoperative radiotherapy in high-risk premenopausal women with breast cancer who receive adjuvant chemotherapy. *N Engl J Med* 1997;337:949-55.
  31. Overgaard M, Jensen MB, Overgaard J, 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.
  32. Ragaz J, Jackson SM, Le N, et al. Adjuvant radiotherapy and chemotherapy in node-positive premenopausal women with breast cancer. *N Engl J Med* 1997;337:956-2.
  33. Huang J, Mackillop WJ. Increased risk of soft tissue sarcoma after radiotherapy in women with breast carcinoma. *Cancer* 2001;92:172-80.
  34. Shapiro CL, Recht A. Side effects of adjuvant treatment of breast cancer. *N Engl J Med* 2001;344:1997-2008.
  35. Curran D, van Dongen JP, Aaronson NK, et al. Quality of life of early-stage breast cancer patients treated with radical mastectomy or breast-conserving procedures: results of EORTC Trial 10801. *Eur J Cancer* 1998;34:307-14.

Copyright © 2001 Massachusetts Medical Society.

**CORRECTION**

**Recurrence Rates after Treatment of Breast Cancer with Standard Radiotherapy with or without Additional Radiation**

Recurrence Rates after Treatment of Breast Cancer with Standard Radiotherapy with or without Additional Radiation . On page 1378, the last sentence of the Results paragraph of the abstract should have read, "In patients 41 to 50 years old, the rates were 9.5 percent and 5.8 percent, respectively (P=0.02). At five years, no differences between treatment groups were found in the rates of metastasis or overall survival (which were 87 and 91 percent, respectively)."