

ORIGINAL ARTICLE

Long-Term Results of Hypofractionated Radiation Therapy for Breast Cancer

Timothy J. Whelan, B.M., B.Ch., Jean-Philippe Pignol, M.D., Mark N. Levine, M.D., Jim A. Julian, Ph.D., Robert MacKenzie, M.D., Sameer Parpia, M.Sc., Wendy Shelley, M.D., Laval Grimard, M.D., Julie Bowen, M.D., Himu Lukka, M.D., Francisco Perera, M.D., Anthony Fyles, M.D., Ken Schneider, M.D., Sunil Gulavita, M.D., and Carolyn Freeman, M.D.

ABSTRACT

BACKGROUND

The optimal fractionation schedule for whole-breast irradiation after breast-conserving surgery is unknown.

METHODS

We conducted a study to determine whether a hypofractionated 3-week schedule of whole-breast irradiation is as effective as a 5-week schedule. Women with invasive breast cancer who had undergone breast-conserving surgery and in whom resection margins were clear and axillary lymph nodes were negative were randomly assigned to receive whole-breast irradiation either at a standard dose of 50.0 Gy in 25 fractions over a period of 35 days (the control group) or at a dose of 42.5 Gy in 16 fractions over a period of 22 days (the hypofractionated-radiation group).

RESULTS

The risk of local recurrence at 10 years was 6.7% among the 612 women assigned to standard irradiation as compared with 6.2% among the 622 women assigned to the hypofractionated regimen (absolute difference, 0.5 percentage points; 95% confidence interval [CI], -2.5 to 3.5). At 10 years, 71.3% of women in the control group as compared with 69.8% of the women in the hypofractionated-radiation group had a good or excellent cosmetic outcome (absolute difference, 1.5 percentage points; 95% CI, -6.9 to 9.8).

CONCLUSIONS

Ten years after treatment, accelerated, hypofractionated whole-breast irradiation was not inferior to standard radiation treatment in women who had undergone breast-conserving surgery for invasive breast cancer with clear surgical margins and negative axillary nodes. (ClinicalTrials.gov number, NCT00156052.)

From McMaster University and Juravinski Cancer Centre, Hamilton, ON (T.J.W., M.N.L., J.A.J., S.P., H.L.); Odette Cancer Centre (J.-P.P., R.M.) and Princess Margaret Hospital (A.F.) — both in Toronto; Cancer Centre of Southeastern Ontario, Kingston (W.S.); Ottawa Regional Cancer Centre, Ottawa (L.G.); Northeastern Regional Cancer Centre, Sudbury, ON (J.B.); London Regional Cancer Centre, London, ON (F.P.); Windsor Regional Cancer Centre, Windsor, ON (K.S.); Northwestern Regional Cancer Centre, Thunder Bay, ON (S.G.); and McGill University and Montreal General Hospital, Montreal (C.F.) — all in Canada. Address reprint requests to Dr. Whelan at the Juravinski Cancer Centre, 699 Concession St., Hamilton, ON L8V 5C2, Canada, or at tim.whelan@jcc.hhsc.ca.

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IN WOMEN WITH BREAST CANCER WHO UNDERGO breast-conserving surgery, whole-breast irradiation reduces the risk of local recurrence and can prevent the need for mastectomy.¹⁻⁴ An update of a meta-analysis conducted by the Early Breast Cancer Trialists' Collaborative Group showed that breast irradiation after breast-conserving surgery reduces mortality from breast cancer.⁵ However, up to 30% of women in North America who undergo breast-conserving surgery do not undergo breast irradiation, in part because of the inconvenience of the therapy and its cost.⁶

In the original trials that evaluated whole-breast irradiation after breast-conserving surgery, 50.0 Gy of radiation was commonly given in 25 fractions over a period of 5 weeks in daily fractions of 2.0 Gy.^{1,2} Radiobiologic models suggest that a larger daily dose (hypofractionation) given over a shorter time (accelerated therapy) might be just as effective⁷; this regimen may also be more convenient for patients and less resource-intensive than the standard schedule. Low rates of local recurrence and limited radiation-induced morbidity have been reported with such approaches.⁸⁻¹⁰ Schedules used in these studies ranged from 40.0 to 44.0 Gy given in 15 to 16 fractions over a 3-week period, with daily fractions of 2.5 to 2.7 Gy.

In 2002, we reported the 5-year results of a randomized trial in which whole-breast irradiation at a dose of 50.0 Gy given in 25 fractions over a period of 35 days was compared with accelerated, hypofractionated whole-breast irradiation, at a dose of 42.5 Gy given in 16 fractions over a period of 22 days, after breast-conserving surgery in women with axillary lymph node-negative breast cancer.¹¹ Local recurrence rates were 3% and cosmetic outcomes, which reflect radiation-related morbidity, were similar in both groups. Toxic effects of radiation, in particular toxicity related to large doses per fraction, can increase over time^{12,13}; this raised concerns that inhibited the universal adoption of the hypofractionated approach.^{14,15} In this article, we describe the results of our trial at a median follow-up of 12 years.

METHODS

PATIENTS

Details of the study design have been described elsewhere.¹¹ Briefly, the participants had invasive

carcinoma of the breast with negative axillary nodes and were treated by means of breast-conserving surgery and axillary dissection. Exclusion criteria were invasive disease or ductal carcinoma in situ involving the margins of excision, tumors that were larger than 5 cm in diameter, and a breast width of more than 25 cm at the posterior border of the medial and lateral tangential beams, which could increase the heterogeneity of the radiation dose to the breast.

The participating centers were the Cancer Care Ontario cancer centers in Hamilton, Toronto, Ottawa, Sudbury, London, Windsor, Kingston, and Thunder Bay; Princess Margaret Hospital in Toronto; and Montreal General Hospital in Montreal. The study protocol was approved by the institutional review board of each participating center, and all patients provided written informed consent. All authors contributed to the design, data collection, and interpretation of the analysis. All authors vouch for the accuracy and completeness of the reported data.

TREATMENT REGIMENS

Randomization was performed centrally through the Ontario Clinical Oncology Group coordinating center in Hamilton, Ontario. Patients were stratified according to age (<50 years or ≥50 years), tumor size (≤2 cm or >2 cm), systematic adjuvant therapy (tamoxifen, any chemotherapy, or no therapy), and center. A computer-generated randomization schedule assigned patients to standard whole-breast irradiation at a dose of 50 Gy given in 25 fractions over a period of 35 days (the control group) or accelerated, hypofractionated whole-breast irradiation at a dose of 42.5 Gy given in 16 fractions over a period of 22 days (the hypofractionated-radiation group). Radiation was delivered by means of two opposed tangential fields, with treatment provided daily from Monday through Friday. No attempt was made to treat the axilla or the supraclavicular or internal mammary nodes, and boost irradiation of the tumor bed was not used.

FOLLOW-UP AND OUTCOMES

After completion of radiation therapy, patients were seen every 6 months for 5 years and then yearly. At each visit, a history was taken, and physical examination was performed. If a participant was unable to attend a scheduled follow-up visit, the family doctor was contacted regarding recur-

rence, new cancer, or death. Mammography was performed 6 months after radiation therapy and then yearly. Late toxic effects of radiation were assessed 3, 5, and 10 years after randomization. Cosmetic outcomes were assessed at baseline and at these same subsequent time points.

The primary outcome was any local recurrence of invasive cancer in the treated breast. Secondary outcomes were a distant (including regional) recurrence of breast cancer; second cancers, including contralateral breast cancer; breast cosmesis; late toxic effects of radiation; and death. The cause of death (cancer, a cardiac-related cause, or another cause) was also evaluated as a possible indicator of radiation-associated morbidity. Two physicians independently adjudicated the cause of death with supporting documentation. If there was disagreement in attribution, a third physician reviewed the case.

Radiation-related toxic effects were assessed by a clinical-trials nurse with the use of the Late Radiation Morbidity Scoring Scheme, developed by the Radiation Therapy Oncology Group and the European Organization for Research and Treatment of Cancer (EORTC).¹⁶ The treatment assignment was not concealed from the clinical-trials nurse. Effects of radiation therapy on skin and subcutaneous tissue were graded on a scale of 0 to 4 (with 0 indicating no toxic effects and grade 4 indicating skin ulceration or soft-tissue necrosis). A trained clinical-trials nurse assessed the cosmetic outcome using the EORTC cosmetic rating system.¹⁷ Nurses compared the treated breast with the untreated breast and graded a number of characteristics, including the size and shape of the breast and the location of the areola and nipple, telangiectasia, and the global cosmetic result. Characteristics were graded on a scale of 0 to 3 (with 0 indicating no difference between the treated and untreated breasts or an excellent result and grade 3 indicating a large difference or a poor result). We report only the global cosmetic outcome. Cosmesis and toxic effects were not evaluated after recurrence or a second cancer.

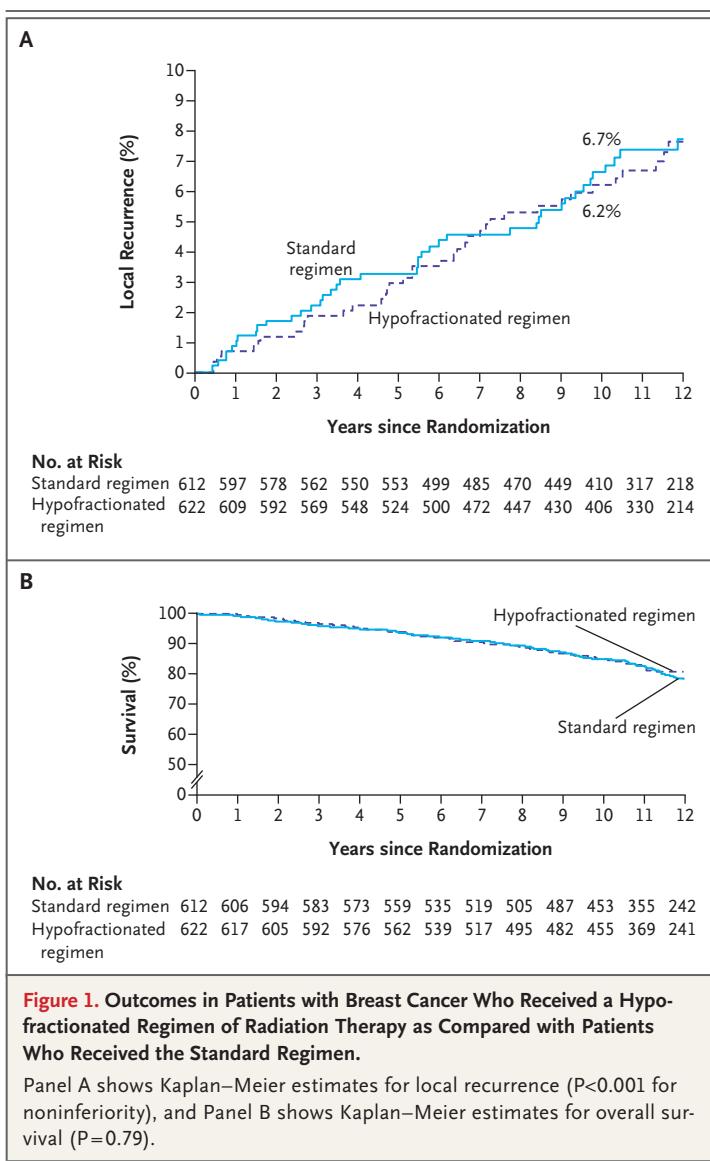
STATISTICAL ANALYSIS

The study was designed to assess the noninferiority of the hypofractionated regimen relative to the standard schedule for radiation therapy. The rate of local recurrence at 5 years in the control group was assumed to be 7%. On the basis of the

results of an earlier trial in which the rate of local recurrence at 5 years was 8% with the use of breast irradiation as compared with 30% with no further treatment³ (absolute difference, 22 percentage points; 99% confidence interval [CI], 15 to 29), we accepted a maximum loss of efficacy of 5 percentage points in the hypofractionated-radiation group. This noninferiority margin was determined through consultation with radiation oncologists. The sample size for the trial, 600 patients per group, was based on these assumptions and a power of 80% with a one-sided alpha level of 5%. The first analysis, performed at 69 months, showed relatively low event rates, and a second analysis was planned when all patients had completed a 10-year assessment.

Analysis of the primary end point was performed according to the intention-to-treat principle. The time to local recurrence was defined as the number of days from randomization to local recurrence as a first event. Data were censored at the time of distant recurrence, last contact, or death, whichever occurred first. Overall survival was defined as the time to death from any cause. Rates of local recurrence and overall survival were determined according to the Kaplan-Meier method. The difference in the 10-year local-recurrence rates (the rate in the control group minus the rate in the hypofractionated-radiation group) was calculated with a two-sided 95% confidence interval (a one-sided 97.5% confidence interval) by means of the Greenwood formula. The noninferiority hypothesis was tested with the use of a z-test offset by the noninferiority margin. We used the log-rank test to compare overall survival in the two groups, and we used Cox proportional-hazards models to evaluate the consistency of treatment effects by testing for interactions between the treatment group and subgroups of interest. For the subgroup analysis, tumor size was dichotomized as smaller than 2 cm or 2 cm or larger.

Results of the scales used to measure skin and subcutaneous toxic effects were dichotomized and described as the proportion of patients with no toxic effects versus the proportion with toxic effects of any grade. For cosmesis, we report the percentage of patients with one of four levels of cosmesis, and the results were also dichotomized as the proportion of patients with an excellent or a good result versus the proportion with a fair or poor result. Groups were compared with the use



of 95% confidence intervals for the difference between proportions. Repeated-measures logistic-regression models were used to investigate the effect of treatment, time from randomization, and baseline variables on the cosmetic outcome. Results of unplanned and sensitivity analyses and the effect of censoring are included in the Supplementary Appendix, available with the full text of this article at NEJM.org.

RESULTS

STUDY PARTICIPANTS

Between April 1993 and September 1996, a total of 1234 patients underwent randomization, with 612 assigned to the control group and 622 to the

hypofractionated-radiation group. The two groups were similar at baseline: 24.7% of the women were younger than 50 years of age; 31.3% had tumors that were 2 cm or larger in diameter; 26.1% had estrogen-receptor-negative disease and 18.8% had high-grade disease; 41.8% received adjuvant tamoxifen, and 10.9% had received adjuvant systemic therapy, most commonly cyclophosphamide, methotrexate, and fluorouracil. Twenty-one patients (12 in the control group and 9 in the hypofractionated-radiation group) did not receive the specified radiation regimen (1.7%). All 1234 patients were included in the efficacy analysis; 98 (7.9%) were lost to follow-up. For the toxicity analysis, 873 patients were evaluated at 5 years and 455 patients were evaluated at 10 years.

LOCAL RECURRENCE

Local invasive recurrence of breast cancer was the first event in 83 patients (42 patients in the control group and 41 patients in the hypofractionated-radiation group). The cumulative incidence of local recurrence was similar in the two groups (Fig. 1A). At 10 years, the cumulative incidence of local recurrence was 6.7% in the control group as compared with 6.2% in the hypofractionated-radiation group (absolute difference, 0.5 percentage points; 95% CI, -2.5 to 3.5); that is, we have 97.5% confidence that the hypofractionated regimen is no worse than the control regimen by 2.5 percentage points. The test of the null hypothesis that the accelerated regimen would be worse than the standard treatment (by >5 percentage points) was rejected in favor of noninferiority ($P < 0.001$). In addition to the 83 invasive recurrences, there were 13 cases of noninvasive local recurrences (i.e., ductal carcinoma in situ): 6 cases in the control group and 7 in the hypofractionated-radiation group. At 10 years, the cumulative incidence of invasive or noninvasive local recurrence was 7.5% in the control group as compared with 7.4% in the hypofractionated-radiation group (absolute difference, 0.1 percentage points; 95% CI, -3.1 to 3.3). A subgroup analysis showed that the treatment effect was similar regardless of the patient's age, tumor size, estrogen-receptor status, or use or nonuse of systemic therapy (Fig. 2). The hypofractionated regimen appeared to be less effective in patients with high-grade tumors; in this subgroup, the cumulative incidence of local recurrence at 10 years was 4.7% in the control group as compared with 15.6% in the hypofrac-

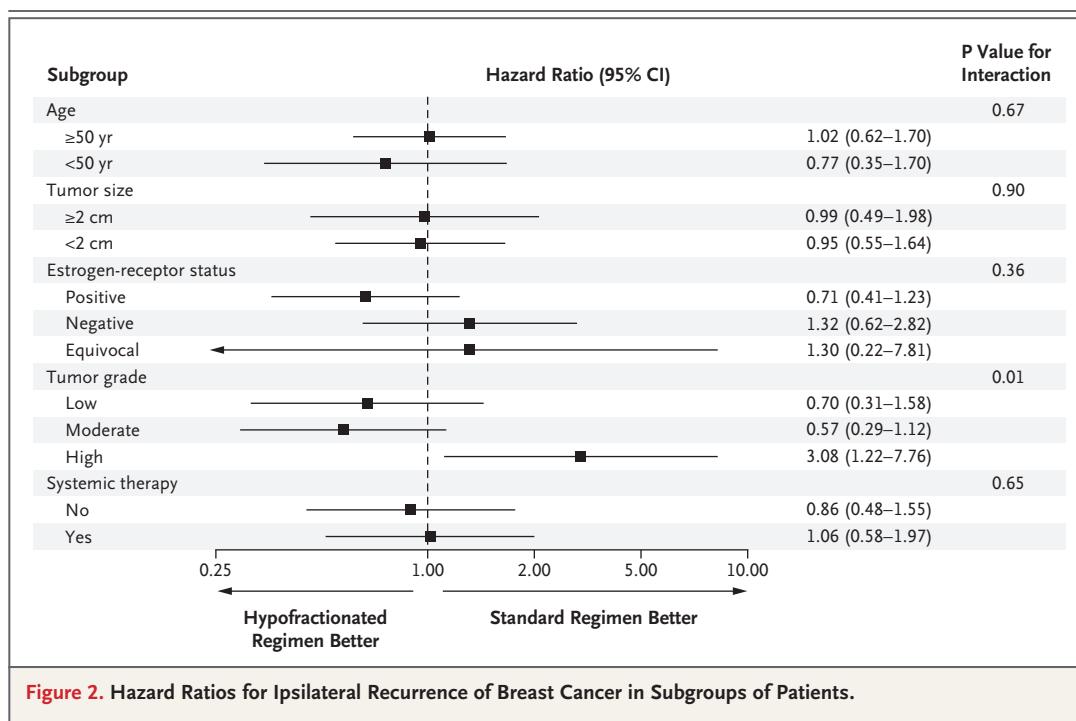


Figure 2. Hazard Ratios for Ipsilateral Recurrence of Breast Cancer in Subgroups of Patients.

tionated-radiation group (absolute difference, -10.9 percentage points, 95% CI, -19.1 to -2.8; test for interaction, $P=0.01$).

MORTALITY

There were 248 deaths (126 in the control group and 122 in the hypofractionated-radiation group). The probability of survival over time was similar in the two groups ($P=0.79$) (Fig. 1B). At 10 years, the probability of survival was 84.4% in the control group as compared with 84.6% in the hypofractionated-radiation group (absolute difference, -0.2 percentage points; 95% CI, -4.3 to 4.0). In the control group of 612 patients, 82 deaths were related to cancer (13.4%), 9 were related to cardiac disease (1.5%), and 35 were due to other causes (5.7%). In the hypofractionated-radiation group of 622 patients, 82 deaths were related to cancer (13.2%), 12 were related to cardiac disease (1.9%), and 28 were due to other causes (4.5%). No significant differences were detected between the groups ($P=0.56$).

TOXIC EFFECTS OF RADIATION AND COSMETIC OUTCOME

Table 1 shows the percentage of patients with toxic effects of irradiation of the skin and subcutaneous tissue 5 and 10 years after randomization. Neither grade 4 skin ulceration nor soft-

tissue necrosis was observed. Although the incidence of late toxic effects of radiation did increase over the follow-up period, at 10 years, the proportion of women with grade 3 radiation-associated morbidity was 4% or less. At 10 years, there were no skin toxic effects in 70.5% of women in the control group as compared with 66.8% of women in the hypofractionated-radiation group (absolute difference, 3.7 percentage points; 95% CI, -4.9 to 12.1). There were no toxic effects in subcutaneous tissue in 45.3% of women in the control group as compared with 48.1% of women in the hypofractionated-radiation group (absolute difference, -2.8 percentage points; 95% CI, -11.7 to 6.5).

Table 2 shows the cosmetic outcome at baseline, 5 years, and 10 years. Although the global cosmetic outcome worsened over time, no significant differences were observed between the groups at any time. At 10 years, 71.3% of women in the control group as compared with 69.8% of women in the hypofractionated-radiation group, had an excellent or good cosmetic outcome (absolute difference, 1.5 percentage points; 95% CI, -6.9 to 9.8). The repeated-measures logistic-regression analysis suggested that the cosmetic outcome was affected by the time from randomization as well as by the patient's age and tumor size, but there was no interaction with treatment (Table 3).

Table 1. Late Toxic Effects of Radiation, Assessed According to the RTOG–EORTC Late Radiation Morbidity Scoring Scheme.*

Site and Grade	5 Yr		10 Yr	
	Standard Regimen (N=424)	Hypofractionated Regimen (N=449)	Standard Regimen (N=220)	Hypofractionated Regimen (N=235)
	percent of patients			
Skin				
0†	82.3	86.1	70.5	66.8
1	14.4	10.7	21.8	24.3
2	2.6	2.5	5.0	6.4
3	0.7	0.7	2.7	2.5
Subcutaneous tissue				
0‡	61.4	66.8	45.3	48.1
1	32.5	29.5	44.3	40.0
2	5.2	3.8	6.8	9.4
3	0.9	0.9	3.6	2.5

* Effects of radiation therapy on skin and subcutaneous tissue were graded on a scale of 0 to 4 (with 0 indicating no toxic effects and grade 4 indicating skin ulceration or soft-tissue necrosis). RTOG–EORTC denotes the Radiation Therapy Oncology Group and the European Organization for Research and Treatment of Cancer.

† The absolute difference at 5 years was –3.8 percentage points (95% confidence interval [CI], –8.7 to 1.0), and at 10 years the absolute difference was 3.7 percentage points (95% CI, –4.9 to 12.1).

‡ The absolute difference at 5 years was –5.4 percentage points (–11.9 to 0.9), and at 10 years the absolute difference was –2.8 percentage points (–11.7 to 6.5).

DISCUSSION

Our goal was to determine whether whole-breast irradiation after breast-conserving surgery could be safe and effective when administered in a larger dose per fraction and in a shorter period of time than in the standard schedule. The 5-year results of our trial reported previously showed no significant differences in efficacy or toxicity between the radiation regimens.¹¹ Nevertheless, because radiation-related microvascular damage increases over time, there was concern that late toxic effects of radiation associated with the hypofractionated regimen could develop.^{14,18}

At a median follow-up of 12 years, the risk of local recurrence at 10 years was low in both groups, and the results with the hypofractionated regimen were not inferior to the results with standard, longer treatment. In an exploratory subgroup analysis, hypofractionation appeared to be less effective for high-grade tumors than for lower-grade tumors. The result of this analysis could be a chance finding, but it may instead reflect a different inherent radiation sensitivity

of high-grade tumors or biologic subtypes of breast cancer that are associated with high-grade tumors.¹⁹

In the long term, radiation therapy may cause skin telangiectasia and fibrosis of subcutaneous tissue, leading to loss of volume and retraction of the breast, all of which can adversely affect the cosmetic outcome. We did see a worsening of the cosmetic outcome over time, which coincided with the increase in toxic effects of irradiation of the skin and subcutaneous tissue. However, we saw no increase in toxic effects in women who received accelerated, hypofractionated radiation therapy as compared with those who received the standard regimen. Although older age and large tumor size were associated with a worse cosmetic outcome, the outcomes of the hypofractionated regimens were similar to those of the standard regimen.

Whole-breast irradiation, particularly on the left side, has been associated with a slightly increased risk of death attributable to coronary artery disease.²⁰ This late effect is not usual until 10 years or more after radiation therapy. In

Table 2. Global Cosmetic Outcome, Assessed According to the EORTC Scale.*

Rating	Baseline			5 Yr			10 Yr		
	Standard Regimen (N=604)	Hypofractionated Regimen (N=616)	Absolute Difference (95% CI) percentage points	Standard Regimen (N=423)	Hypofractionated Regimen (N=448)	Absolute Difference (95% CI) percentage points	Standard Regimen (N=216)	Hypofractionated Regimen (N=235)	Absolute Difference (95% CI) percentage points
Excellent	46.3	46.8	34.3	34.9	36.4	27.8	39.2	30.6	
Good	36.3	37.0	44.9	41.5			43.5		
Fair	15.1	14.6	17.3	19.0			25.5	25.4	
Poor	2.3	1.6	3.5	3.1			3.2	4.8	
Excellent or good	82.6	83.8	-1.2 (-5.4 to 3.1)	79.2	77.9	1.3 (-4.2 to 6.7)	71.3	69.8	1.5 (-6.9 to 9.8)

* Absolute differences were calculated as the value in the group that received the standard regimen minus the value in the group that received the hypofractionated regimen. EORTC denotes European Organization for Research and Treatment of Cancer.

our trial, we observed no significant difference in overall survival between the two treatment groups, and at a median follow-up of 12 years, few cardiac-related deaths were observed and no increase occurred in patients who received the hypofractionated regimen.

Recently, 5-year results were reported from two trials: the UK Standardisation of Breast Radiotherapy (START) Trial A, which compared each of two schedules of hypofractionation given over 5 weeks with conventional whole-breast irradiation, and START Trial B, which compared a hypofractionation schedule given over 3 weeks with conventional treatment (Current Controlled Trials number for both trials, ISRCTN59368779).^{21,22} Although both trials had limited follow-up, the results were consistent with those of our trial.

The potential limitations of our study should be noted. The trial was restricted to women who had node-negative, invasive breast cancer with clear margins of excision after lumpectomy. Although we did include patients with microinvasive breast cancer and women in whom a component of the breast cancer was ductal carcinoma in situ, it is not entirely clear whether our results can be extrapolated to women with ductal carcinoma in situ only. We did not include women with node-positive breast cancer, and for this reason our results are not applicable to patients for whom nodal irradiation is planned. Women with large breasts were also not included, and few women received adjuvant chemotherapy. Such patients can be at increased risk for an adverse cosmetic outcome with standard radiotherapy, so it is unclear whether hypofractionation would lead to an outcome that would be any worse than that with standard treatment. We did not use boost irradiation, because at the time the study was initiated, the efficacy of boost irradiation had not been demonstrated and we wanted to avoid the confounding effect that boost irradiation could have on local recurrence or breast cosmesis. Since the completion of our trial, the results of other trials, providing support for the use of boost irradiation, have been published.^{23,24} Boost irradiation was permitted in both START trials, and adjuvant chemotherapy was used more widely than in our trial. To date, no increase in toxic effects in these trials has been reported.

In conclusion, our long-term results provide support for the use of accelerated, hypofraction-

Table 3. Predictors of an Excellent or Good EORTC Global Cosmetic Rating.*

Variable	Odds Ratio (95% CI)	P Value
Treatment (hypofractionated regimen vs. standard regimen)†	1.00 (0.81–1.25)	0.94
Time from randomization (per yr)	0.93 (0.90–0.95)	<0.001
Age (<50 yr vs. ≥50 yr)	1.64 (1.26–21.5)	<0.001
Tumor size (<2 cm vs. ≥2 cm)	1.26 (0.99–1.62)	0.07
Systemic therapy (yes vs. no)	0.89 (0.70–1.12)	0.30

* Data are based on a repeated-measures logistic-regression analysis. EORTC denotes European Organization for Research and Treatment of Cancer.

† There were no first-order interactions of treatment with time from randomization, age, tumor size, or systemic therapy.

ated, whole-breast irradiation in selected women with node-negative breast cancer after breast-conserving surgery. For women with breast cancer who are similar to the patients in this trial, an abbreviated course of radiation therapy should be more convenient and less costly than standard treatment, and its availability as a treatment option may lead to an increase in the number of women who receive breast irradiation after breast-conserving surgery.

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