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CLINICAL INVESTIGATION **Breast**

BENEFIT OF RADIATION BOOST AFTER WHOLE-BREAST RADIOTHERAPY

Lorenzo Livi, M.D.,* Simona Borghesi, M.D.,* Calogero Saieva, M.D.,† Massimiliano Fambrini, M.D.,‡ Alberto Iannalfi, M.D.,* Daniela Greto, M.D.,* Fabiola Paiar, M.D.,* Silvia Scoccianti, M.D.,* Gabriele Simontacchi, M.D.,* Simonetta Bianchi, M.D.,§ Luigi Cataliotti, M.D.,‖ and Giampaolo Biti, M.D.*

*Radiotherapy Unit, University of Florence, Florence, Italy; †Molecular and Nutritional Epidemiology Unit, ISPO, Cancer Prevention and Research Institute, Florence, Italy; and ‡Department of Gynaecology, Perinatology and Human Reproduction; §Department of Pathology, and ‖Department of Surgery, University of Florence, Florence Italy

Purpose: To determine whether a boost to the tumor bed after breast-conserving surgery (BCS) and radiotherapy (RT) to the whole breast affects local control and disease-free survival.

Methods and Materials: A total of 1,138 patients with pT1 to pT2 breast cancer underwent adjuvant RT at the University of Florence. We analyzed only patients with a minimum follow-up of 1 year (range, 1–20 years), with negative surgical margins. The median age of the patient population was 52.0 years (±7.9 years). The breast cancer relapse incidence probability was estimated by the Kaplan-Meier method, and differences between patient subgroups were compared by the log rank test. Cox regression models were used to evaluate the risk of breast cancer relapse.

Results: On univariate survival analysis, boost to the tumor bed reduced breast cancer recurrence ($p < 0.0001$). Age and tamoxifen also significantly reduced breast cancer relapse ($p = 0.01$ and $p = 0.014$, respectively). On multivariate analysis, the boost and the medium age (45–60 years) were found to be inversely related to breast cancer relapse (hazard ratio [HR], 0.27; 95% confidence interval [95% CI], 0.14–0.52, and HR 0.61; 95% CI, 0.37–0.99, respectively). The effect of the boost was more evident in younger patients (HR, 0.15 and 95% CI, 0.03–0.66 for patients <45 years of age; and HR, 0.31 and 95% CI, 0.13–0.71 for patients 45–60 years) on multivariate analyses stratified by age, although it was not a significant predictor in women older than 60 years.

Conclusion: Our results suggest that boost to the tumor bed reduces breast cancer relapse and is more effective in younger patients. © **2009 Elsevier Inc.**

Boost, Radiotherapy, Breast cancer.

INTRODUCTION

Radiotherapy (RT) has an essential role in breast conserving therapy. Several randomized trials have demonstrated similar survival rates after mastectomy or breast-conserving surgery (BCS) in Stage I and II breast cancer (1–3).

The meta-analysis of the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) revealed the need for RT after tumorectomy by showing that breast irradiation reduced the 5-year local recurrence (LR) rate from 26% to 7% (4).

Recently the 10-year results of the European Organisation for Research and Treatment of Cancer (EORTC) 22881-10882 trial demonstrated that a boost dose of 16 Gy significantly reduced the LR rate for patients after a complete lumpectomy only: at 10 years, the cumulative incidence of LR was 10.2% vs. 6.2% for the 0-Gy and the 16-Gy boost groups ($p < 0.0001$), respectively (5).

On the other hand, in patients with microscopically involved surgical margins, no statistically significant difference was found in local control (LC) or survival between the high-dose boost of 26 Gy and the low-dose boost of 10 Gy ($p > 0.1$) (6).

After BCS, the site of failure within the breast is predominantly at the site of the primary tumor removal (7, 8). Until recently, there has been little evidence relating improved LC rates to the additional dose delivered with a tumor bed boost. Recent reports of three prospective randomized trials investigating the application of boost vs. no boost to the tumor bed show statistically significant improvements in LC (9–11).

The purpose of this retrospective analysis was to investigate the effect of the boost to the tumor bed on LC. Moreover, an interesting aspect of this article might be that previous results from randomized trials may in part be reproduced in

Reprint requests to: Lorenzo Livi, M.D., Radiotherapy Unit, University of Florence, Viale Morgagni no. 85, 50134 Florence, Italy. Tel: +39 055 7947719; Fax: +39 055 437930; E-mail: l.livi@dfc.unifi.it

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Table 1. Distribution of 1,138 breast cancer patients according to selected individual characteristics

Characteristic	Patients		
	No boost (N = 399)	Boost (N = 739)	
Age (y)			
<45	90 (22.6)	104 (14.1)	194
45-60	234 (58.7)	526 (71.2)	760
>60	75 (18.7)	109 (14.7)	184
pT (N, %)			
1	203 (50.9)	614 (83.1)	827
2	196 (49.1)	125 (16.9)	321
pN (N, %)			
0	302 (75.7)	533 (72.1)	835
1–3+	71 (17.8)	164 (22.2)	235
>4+	26 (6.5)	42 (5.7)	68
Histotype (N, %)			
Ductal	179 (44.9)	373 (50.5)	552
Lobular	71 (17.8)	118 (16.0)	189
Ductal + lobular	60 (15.0)	89 (12.0)	149
Other types	89 (22.3)	159 (21.5)	248
Multifocal (N, %)*			
No	381 (96.0)	672 (90.9)	1053
Yes	16 (4.0)	67 (9.1)	83
Estrogen receptor (N, %)†			
Negative	86 (49.1)	191 (25.8)	277
Positive	89 (50.9)	548 (74.2)	637
Progesterone receptor (N, %)‡			
Negative	71 (45.5)	307 (41.5)	378
Positive	85 (54.5)	432 (58.5)	517
Tamoxifen (N, %)			
no	320 (80.2)	308 (41.7)	628
yes	79 (19.8)	431 (58.3)	510
CHT (N, %)			
No	363 (91.0)	469 (63.5)	832
Yes	36 (9.0)	270 (36.5)	306
Total	399	739	1,138

* Data missing for 2 cases.
† Data missing for 224 cases.
‡ Data missing for 243 cases.

a general population rather than one selected only for a trial, while including all of the known potential confounding factors.

METHODS AND MATERIALS

Patients

Between January 1980 and December 2001, a total of 1,138 patients with pT1 to pT2 breast cancer underwent postoperative RT at the Radiotherapy Department of the University of Florence. All patients were treated with BCS, with a median of 16 axillary nodes removed.

In the current analysis we included only patients who underwent quadrantectomy with microscopically negative margins and without clinical and radiographic evidence of local or distant recurrence at the time of the first evaluation at the Radiotherapy Unit. We excluded patients who underwent a different type of surgery.

The mean age of the patient population was 52.4 years (±7.5 years). The mean follow-up of the series was 9.0 years (±7.5 years), with a range of 1.1 to 23.3 years. A total of 41 patients (3.6%) were lost to follow-up.

Treatment

Adjuvant chemotherapy (CT) was recommended in 306 patients (26.8%). Of these, 30% received anthracycline-based CT, and 90% received four courses of epidoxorubicin (100 mg/m^2) followed by 4 courses of intravenous (i.v.) CMF (cyclophosphamide 600 mg/m^2, methotrexate 40 mg/m^2 and 5-fluorouracil 600 mg/m^2) and 10% were treated with six courses of FEC (5-fluorouracil 500 mg/m^2, epidoxorubicin 75 mg/m^2, cyclophosphamide 500 mg/m^2).

Of the patients, 62% received six courses of i.v. CMF (cyclophosphamide 600 mg/m^2, methotrexate 40 mg/m^2, and 5-fluorouracil 600 mg/m^2) and 8% other types of CT. Tamoxifen was prescribed in 510 patients (44.8%).

A median total dose of 50 Gy (range, 46–52 Gy) of whole-breast irradiation was delivered with wedged tangential megavoltage photon beams over a period of 5 weeks, with a dose of 2 Gy per fraction, in agreement with ICRU report 50 (12). All patients received RT only to the whole breast. In fact, according to the protocol followed at our institution, RT was not given to the supraclavicular fossa even in patients with positive axillary nodes.

The boost to the tumor bed was administrated with a direct electron beam given in daily fractions of 2 Gy, for total dose of 10 Gy, according the protocol followed at our department for patients with microscopically negative margins. The boost target was determined clinically and using presurgery mammogram for most patients; only for a small number of patients in the last period was the boost volume determined radiologically using radiopaque clips in the tumor bed. The electron energy was determined clinically or, if available, using a CT scan to measure the tumor bed depth.

The group of patients who were not prescribed the boost to the tumor bed at the discretion of the radiation oncologist were treated in the earlier period when the evidence supporting the role of the boost were lacking.

The main pathologic features of patients are listed in Table 1.

Statistical analysis

For the survival analysis, the date of surgery was used as the start of observation. Disease-free survival (DFS) was calculated from the date of BCS to the date of ipsilateral breast cancer recurrence. The crude probability of breast cancer relapse was estimated by using the Kaplan-Meier method, and differences between patient groups were assessed by the log-rank test. Incidence comparisons were carried out using Cox proportional hazard ratio (HR) and corresponding 95% confidence intervals (95% CIs). Univariate models were performed to evaluate the effect of each specific parameter. The variables used in the univariate regression analyses were listed in Table 2.

Multivariate models with stepwise selection was performed to identify the major significant local relapse predictors. The stepwise selection is a model selection method in which variables added to the model may later be removed if they become insignificant because of the specified criteria (the significance levels for entry to and removal from the model is $p < 0.05$). Effects are entered into and removed from the model in such a way that each forward selection step may be followed by one or more backward elimination steps. The stepwise selection process terminates if no further effect can be added to the model or if the effect just entered into the model is the only effect removed in the subsequent backward elimination.

Because the study spans a 20-year period, further regression analyses were performed, taking into account also the period of the surgery (1981–1990, 1991–2000, or 2001–2005). Finally, the regression analyses were also carried out on subgroups of patient with different follow-up (>3 years, and >5 years).

Table 2. Local disease-free survival in 1,138 breast cancer cases according to selected individual characteristics

Variable	*n* at Start	*n LR*	Cumulative incidence	*p* Value	HR (95% CI)
Age (y)					
<45	194	21	0.245		1
45-60	760	34	0.104	0.01	0.45 (0.26–0.78)
>60	184	11	0.130		0.61 (0.29–1.27)
pT					
1	817	38	0.195	0.28	–
2	321	28	0.145		
pN					
0	835	52	0.133		–
1–3 +	235	8	0.237	0.11	
>4 +	68	6	0.152		
Histotype					
Ductal	552	36	0.14		
Lobular	189	13	0.188		–
Ductal + lobular	149	8	0.172	0.20	
Other	248	9	0.126		
Multifocal*					
No	1053	63	0.148	0.71	–
Yes	83	3	0.132		
Estrogen receptor†					
Negative	277	19	0.16	0.07	–
Positive	637	17	0.14		
Progesterone receptor‡					
Negative	378	19	0.155	0.19	–
Positive	517	16	0.12		
Tamoxifen					
No	628	53	0.145	0.014	1
yes	510	13	0.106		0.47 (0.25-0.87)
Boost					
No	399	54	0.185	<0.0001	1
Yes	739	12	0.04		0.26 (0.13-0.49)
	1,138	66	0.147		

Abbreviation: HR = hazard ratio (1 = HR of the reference category used in the regression analysis).
* Data missing for 2 cases.
† Data missing for 224 cases.
‡ Data missing for 243 cases.

Statistical results were considered significant at a value of $p < 0.05$. All statistical tests were performed with SAS software (SAS Institute, Cary, NC).

RESULTS

At the univariate analysis, age at presentation, tamoxifen use, and boost to the tumor bed emerged as significant predictors of breast relapse, as shown in Table 2. Patients more than 45 years of age at presentation were characterized by less breast cancer relapse than patients less than 45 years of age ($p = 0.01$). The use of tamoxifen and the boost to the tumor bed reduced breast cancer recurrence ($p = 0.014$ and $p < 0.0001$, respectively).

Positive estrogen receptor status seemed to be associated with a lower risk of breast cancer relapse but did not reach statistical significance ($p = 0.07$). Other possible prognostic factors such as tumor grading, lymphatic or vascular invasion, and distance of tumor from surgical margins were not included in our analyses because they were available only for a smaller number of patients.

On multivariate analysis, the boost and the medium age (45–60 years) retained statistical significance (respectively, hazard ratio [HR], 0.27, 95% confidence interval [95% CI], 0.14–0.52; and HR, 0.61; 95% CI, 0.37–0.99). Older age at diagnosis (>60 years) did not reach statistical significance, probably because of the small number of patients in this subgroup compared with the medium age group.

Overall, the boost to the tumor bed reduced breast cancer relapse (HR, 0.26; 95% CI, 0.13–0.49; $p < 0.0001$), as shown in Fig. 1. This effect was more evident in younger patients (HR, 0.15; 95% CI, 0.03–0.66 for patients <45 years of age) than in patients 45–60 years of age (HR, 0.31; 95% CI, 0.13–0.71), as evident in the analysis stratified by age. In women older than 60 years, it was not a significant predictor in uni- and multivariate analyses.

Because the study spanned a 20-year period, we carried out further regression analyses adjusting also for the period of the surgery (1981–1990, 1991–2000, or 2001–2005). The boost and the medium age (45–60 years) persisted as significantly related to a reduced incidence of breast cancer relapse ($p < 0.0001$ and $p = 0.044$, respectively). Because there was a difference between the two patient groups (*i.e.,* those with vs. without boost) regarding average follow-up, we adjusted the regression analyses also for the length of follow-up;

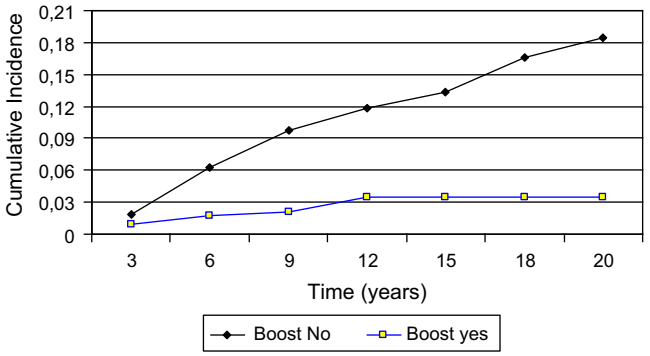

Fig. 1. Cumulative incidence of breast relapses in the 20 years of follow-up of 1,138 breast cancer cases by boost (log-rank test, $p < 0.0001$)

on multivariate analysis, the effect of the boost and the medium age persisted ($p < 0.0001$ and $p = 0.044$, respectively).

Finally, we performed regression analyses on subgroups of patients with different lengths of follow-up. In both the patients with follow-up greater than 3 years and in those with follow-up greater than 5 years, we observed a protective effect of the boost ($p = 0.0001$ and $p = 0.015$, respectively).

DISCUSSION

Breast-conserving therapy is a well-accepted method of treating early breast cancer. After breast-conserving surgery, postoperative RT of the breast has been reported to reduce ipsilateral tumor recurrence (13, 14).

However, it has not been established whether all patients should receive additional boost radiation to the site of tumor resection. In fact, because of logistic and economic burdens and the adverse effects associated with breast irradiation, there have been several attempts to identify a subgroup of patients who might not need RT to achieve an acceptable level of LC (15, 16).

Our study has some potential biases or limitations. It is a retrospective study and thus has the possible bias of this type of epidemiologic study. It is very difficult to restore the medical history of all patients: the recovery of all medical information (clinical, histologic, treatment-related) is difficult to achieve in all patients, particularly for those referred to the hospital during the early years. Thus, it is possible to have missing data for some parameters for many subjects.

There are numerous differences between the two patient groups in regard to some parameters, as shown in Table 1. However, the multivariate analyses, taking into account some potential confounding variables, should provide adjusted results. There is also a difference between the two patient groups regarding the average follow-up and thus the period at risk. However, by adding the variable ''length of follow-up'' in the regression models, the results were unchanged. Furthermore, our study spans a 20-year period, and it is possible that there were differences in type of treatment. However, by performing regression analyses adjusted also for the period of the surgery we obtained the same results (*i.e.,* protective effect of the boost and medium age). In our series, some patients have been lost to follow-up. This is an important limitation of our study that might distort the results. However, we also carried out regression analyses on subgroups of patients with different lengths of follow-up (>3 and 5 years) and still found the same protective effect of the boost.

In our series, we analyzed retrospectively patients with early-stage breast cancer treated with BCS and RT to the whole breast: on univariate analysis, older age at presentation, tamoxifen use, and boost to the tumor bed were associated with a lower risk of breast cancer relapse. On multivariate analysis, tumor bed boost and age persisted as significant predictors of relapse.

We also have to consider that, in the study period, the boost was administered using electrons and the definition of the target was clinical or using pre-surgery mammography or CT scan, with a risk of geographic miss. At the present time, at our institution, almost all patients have clips in the tumor bed; and it is now evident that in some patients these clips lie very deep and the tumor bed cannot be adequately covered using electrons. These considerations could lead to think that the role of boost would be even higher in reducing breast cancer relapse if we can treat every patient adequately.

These findings confirm the results obtained by some randomized trials that have already demonstrated that additional boost radiation after 50 Gy to the whole breast reduces the risk of breast cancer relapse in patients with negative surgical margins, while having little influence on cosmetic outcomes (10, 11, 17).

In addition, in another series of 137 patients with Stage I to II breast cancer, Notani *et al.* showed that boost radiation reduced LR but that the improvement was not significant ($p = 0.07$). Univariate and multivariate analysis failed to detect any factors that were significantly associated with LC (18).

In our study, another factor that was found to be statistically significant for LR on multivariate analysis was age at diagnosis. Furthermore, the advantage of the boost in reducing LR was more evident for women 45–60 years of age than in those younger than 45 years, whereas it was not a significant predictor in older women (>60 years of age).

It has been postulated that breast cancer recurrence is more common in younger women (19–21), and this may be a reason for the superior effect of the boost in this subpopulation of patients.

In the EORTC 22881-10882 trial, this higher risk for younger patients was seen especially during the first 5 years of follow-up and tended to occur earlier. As younger patients had a higher cumulative risk of local relapse by Year 10, the magnitude of the absolute 10-year risk reduction achieved with the boost decreased with increasing age and was greatest in patients less than 40 years of age (95% CI, 23.9–12.5, $p = 0.0014$) (5, 22).

Antonini *et al.*, using data from the EORTC trial, reported that on multivariate analysis LC increased with age ($p = 0.0003$). There was no evidence that the relative effect of a boost on LC depended on age ($p = 0.97$); however, in

younger patients, the 5-year local failure was higher, and therefore the absolute reduction was greater (23).

In 1,165 patients diagnosed with early breast cancer Algara *et al.* reported administration of a boost dose that was modulated in the presence of risk factors. Patients with one risk factor received a boost of 10 Gy, whereas those with two risk factors received 20 Gy. The mean age of patients was 56.7 ± 10.8 years. The probability of remaining free of LR at 5 and 10 years was 97.7% (95% CI, 96.7–98.7) and 94.5% (95% CI, 92.1–96.9). Only age showed an impact on breast cancer relapse on multivariate analysis. Patients 40 years and younger had a relative risk of local relapse of 5.27, and patients 41 to 50 years of age had a relative risk of 3.7 with respect to patients older than 50 years (24).

In any case, the practical guidelines for RT of breast cancer by the German Society of Radiation Oncology (DEGRO) stated that postoperative RT significantly reduces rates of breast cancer recurrence and that an additional boost provides additional absolute risk reduction for LC irrespective of age, and this remains the policy at our institution. Despite the fact that our study has not been able to show an effect in reducing local DFS in older women, in fact we believe that in regard to tumor bed boost, the more pronounced the achieved reduction is, the more substantially it translates into improved local DFS (25).

In our series, administration of a boost decreased breast cancer relapse in a population of patients with microscopically completely resected early breast cancer. The 2006 National Comprehensive Cancer Network (NCCN) guidelines recommend that whole-breast irradiation with boost radiation should be performed after BCS irrespective of the surgical margin status (26).

Neuschatz *et al.* (27), in a series of 498 women with Stage I/II breast carcinomas, analyzed the difference in breast cancer recurrence with respect to surgical margins. Final margin status (FMS) categories were defined as greater than 5 mm, 2 to 5 mm, 0 to 2 mm, and positive. Final tumor bed boosts as a function of FMS were as follows: no residual on re-excision, no boost performed; FMS greater than 5 mm, boost of 10 Gy; FMS greater than 2 to 5 mm, boost of 14 Gy; FMS greater than 0 to 2 mm or positive, boost of 20 Gy. At 12 years, Kaplan-Meier local failure rates were 17% for FMS positive, 9% for FMS greater than 0 to 2 mm, 5% for FMS greater than 2 to 5 mm, 0% for FMS greater than 5 mm, and 6% for specimens without evidence of residuum on re-excision ($p = 0.009$). Graded tumor bed dose escalation in response to FMS resulted in very low rates of local failure over the first 5 years for all FMS categories. However, tumors with close/positive margins have significantly increased local failure rates after 5 years of follow-up, even with increased radiation boost dose. In addition, graded tumor bed dose escalation does not fully overcome the adverse influence of young age.

In another series published by Vordermark *et al.* (28), positive margins were not associated with a higher risk of breast cancer recurrence. In this series of 118 patients, 65% had no tumor cells at the initial margin, 35% had a positive or questionable margin. Re-excisions were performed in 42%. The LC was calculated by the Kaplan-Meier method and compared between subgroups. The 5-year LC for the whole group was 94%. The rates for selected subgroups were as follows: less than 56 years, 89.4% vs. more than 56 years, 98.1% ($p = 0.073$, univariate analysis); pT1 95.9% vs. pT2 88.6% (not significant, NS); pN0 96.6% vs. pN+ 90.8% (NS); initial margins free of tumor cells, 95.5% vs. initial margin involved or questionable, 90.7% (NS); no re-excision, 96.7% vs. one or more re-excisions, 90.6% (NS); adjuvant CT, 81.7% vs. no adjuvant chemotherapy, 100% ($p = 0.007$). These investigators concluded that among patients with close or positive margins, older patients achieved high LC rates with a median tumor bed boost to 66 Gy. Younger patients and patients who received adjuvant chemotherapy (because of the presence of histopathologic risk factors) were at increased risk for breast cancer relapse and thus should be considered for intensified local treatment.

In our series, this type of analysis was impossible because of the lack of data regarding the distance of the tumor from surgical margins; this information was available for our patients from 2001. Furthermore, at our institution, most patients with positive margins undergo re-excision, and we have few patients who underwent irradiation with positive margins because of patient refusal of a second operation.

CONCLUSION

Although the results of our study should be interpreted with caution because of the lack of a randomized design, they suggest that administration of a radiation boost to the tumor bed significantly reduced breast cancer relapse, and that younger patients benefit more from such boosts.

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