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CLINICAL INVESTIGATION **Breast**

RADIOTHERAPY TIMING IN 4,820 PATIENTS WITH BREAST CANCER: UNIVERSITY OF FLORENCE EXPERIENCE

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Purpose: To analyze the relationship between a delay in radiotherapy (RT) after breast-conserving surgery and ipsilateral breast recurrence (BR).
Methods and Materials: We included in our analysis 4,820 breast cancer patients who had undergone postoperative RT at the University of Florence. The patients were categorized into four groups according to the interval between surgery and RT (T1, <60 days; T2, 61–120 days; T3, 121–180 days; and T4, >180 days).
Results: On multivariate analysis, the timing of RT did not reach statistical significance in patients who received only postoperative RT (n = 1,935) or RT and hormonal therapy (HT) (n = 1,684) or RT, chemotherapy (CHT), and HT (n = 529). In the postoperative RT-only group, age at presentation, surgical margin status, and a boost to the tumor bed were independent prognostic factors for BR. In the RT plus HT group, age at presentation and boost emerged as independent prognostic factors for BR (p = 0.006 and p = 0.049, respectively). Finally, in the RT, CHT, and HT group, only multifocality was an independent BR predictor (p = 0.01). Only in the group of patients treated with RT and CHT (n = 672) did multivariate analysis with stepwise selection show RT timing as an independent prognostic factor (hazard ratio, 1.59; 95% confidence interval, 1.01–2.52; p = 0.045). Analyzing this group of patients, we found that most patients included had worse prognostic factors and had received CHT consisting of cyclophosphamide, methotrexate, and 5-fluorouracil before undergoing RT.
Conclusion: The results of our study have shown that the timing of RT itself does not affect local recurrence, which is mainly related to prognostic factors. Thus, the "waiting list" should be thought of as a "programming list," with patients scheduled for RT according to their prognostic factors. © 2009 Elsevier Inc.

Timing, Radiotherapy, Breast cancer.

INTRODUCTION

The risk of local recurrence after complete surgery is related to the density of the clonogenic tumor cells in the surgical bed (1). A delay in delivering radiotherapy (RT) would seem to favor growth in the clonogenic tumor cells (2) and might be associated with an increased risk of local recurrence (3). However, a recent prospective study revealed that the timing of RT was not an independent risk factor for local recurrence (4). Moreover, RT after breast-conserving surgery has resulted in a significant reduction in the incidence of ipsilateral breast recurrence (BR) (5–7). The optimal interval between breast-conserving surgery and the beginning of breast RT is not known. The Canadian Clinical Practice Guidelines for the Care and Treatment of Breast Cancer recommended "that local breast irradiation should be started as soon as possible after surgery and not later than 12 weeks after, except for patients in whom radiotherapy is preceded by chemotherapy" (8); however, this guideline has not been confirmed by other studies (9).

We have had long waiting lists for RT at the RT department of the University of Florence; therefore, we performed a survival analysis of a series of breast cancer patients who underwent adjuvant RT to evaluate the effect of the timing of RT on the local recurrence rates.

METHODS AND MATERIALS

Between January 1981 and September 2004, 4,820 patients with breast cancer underwent postoperative RT at the University of

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Florence. In the present analysis, we included patients without clinical and radiographic evidence of local or distant recurrence after conservative surgery at presentation. The median age of the patient population was 55.5 years (range, 26.6–85.2).

All patients were followed at the Radiotherapy Unit of the University of Florence until the end of the follow-up period or death, and all treatment details and outcomes, including local, regional, and distant recurrences, were recorded prospectively. All patients were followed for a mean of 9.1 years (range, 1–25).

We divided the patients into subgroups: first, according to the interval between surgery and RT; and second, according to the treatment received. The number of patients in each subgroup and the most important prognostic factors are listed in Table 1. Wide excision was performed in 1,294 patients (26.8%), and 3,505 patients (72.8%) underwent quandrantectomy. Axillary dissection was performed in 4,036 patients (83.7%), with a median number of 16 nodes removed. Sentinel lymph node biopsy was performed on 441 patients (9.1%), and axillary dissection was not performed in 343 patients (7.2%).

All patients received RT only to whole breast. All patients were treated with external beam RT to the whole breast using tangential fields with 6-MV photons. The mean dose delivered was 50 Gy (range, 46–52) in 2-Gy daily fractions. The tumor bed boost was administrated by electrons. At the discretion of the radiation oncologist, the total boost dose (2-Gy daily fractions) was 6–10 Gy for patients with negative surgical margins and 14–16 Gy for patients with positive margins.

Chemotherapy (CHT) was recommended for 1,201 patients (24.9%). Of those, 20% received anthracycline-based CHT: 70% of these received 4 courses of epidoxorubicin (100 mg/m^2) followed by 4 courses of intravenous CMF (cyclophosphamide, 600 mg/m^2; methotrexate, 40 mg/m^2; and 5-fluorouracil, 600 mg/m^2), and 30% were treated with 6 courses of 5-fluorouracil (500 mg/m^2), epidoxorubicin (75 mg/m^2), and cyclophosphamide (500 mg/m^2). Of the patients receiving CHT, 65% received 6 courses of intravenous CMF and 15%, other types of CHT. A total of 180 patients (3.7%) were treated with CHT at other institutions.

Statistical analysis

The clinicopathologic data collected for each patient were linked to the vital status information. For the survival analysis, the date of surgery was used as the start of observation. The survival time was

Table 1. Distribution of 4,820 breast cancer patients who underwent radiotherapy stratified by selected clinicopathologic features

Feature	RT	RT+CHT	RT+HT	RT+CHT+HT	Total
Age group (y)					
≤50	671 (34.7)	392 (58.3)	231 (13.7)	218 (41.2)	1,512 (31.4)
51–60	618 (31.9)	167 (24.9)	566 (33.6)	182 (34.4)	1,533 (31.8)
61–70	487 (25.2)	98 (14.6)	616 (36.6)	113 (21.4)	1,314 (27.3)
>70	159 (8.2)	15 (2.2)	271 (16.1)	16 (3)	461 (9.5)
pT category*					
1	1,311 (67.9)	420 (63)	1,301 (77.7)	370 (71.3)	3,402 (71.0)
2	467 (24.2)	230 (34.5)	309 (18.5)	136 (26.2)	1,142 (23.8)
3	124 (6.4)	7 (1)	26 (1.6)	3 (0.6)	160 (3.4)
4	28 (1.5)	10 (1.5)	38 (2.3)	10 (1.9)	86 (1.8)
Positive nodes *(n)*					
None	1,868 (96.5)	268 (39.9)	1,184 (70.3)	197 (37.2)	3,517 (73.0)
1–3	53 (2.7)	272 (40.5)	362 (21.5)	235 (44.4)	922 (19.1)
>3	14 (0.7)	132 (19.6)	138 (8.2)	97 (18.3)	381 (7.9)
Histotype					
Ductal	987 (51)	426 (63.4)	905 (53.7)	317(59.9)	2,635 (54.7)
Lobular	174 (9)	68 (10.1)	206 (12.2)	83 (15.7)	665 (13.8)
Ductal+lobular	240 (12.4)	82 (12.2)	275 (16.3)	68 (12.9)	531 (11.0)
Other	534 (27.6)	96 (14.3)	298 (17.7)	61 (11.5)	989 (20.5)
Multifocal*					
No	1,765 (93.4)	563 (88.7)	1142 (90.8)	392 (85)	4,132 (91.0)
Yes	124 (6.6)	72 (1.3)	143 (9.2)	69 (15)	408 (9.0)
Margins					
Negative	1,184 (93.7)	609 (90.6)	1,590 (94.4)	491 (92.8)	4,504 (93.4)
Positive	121 (6.3)	63 (9.4)	94 (5.6)	38 (7.2)	316 (6.6)
Estrogen receptor*					
Negative	475 (40.6)	348 (62.8)	228 (16.7)	81 (16.8)	1,132 (31.7)
Positive	696 (59.4)	206 (37.2)	1136 (83.3)	401 (83.2)	2,439 (68.3)
Progesterone receptor*					
Negative	574 (50.2)	357 (65.3)	477 (35.3)	163 (33.9)	1,571 (44.6)
Positive	569 (49.8)	190 (34.7)	874 (64.7)	318 (66.1)	1,951 (55.4)
Timing (d)					
<60	367 (19)	101 (15)	207 (12.3)	46 (8.7)	721 (15.0)
61–120	1,063 (54.9)	331 (49.3)	881 (52.3)	229 (43.3)	2,504 (52.0)
121–180	459 (23.7)	197 (29.3)	521 (30.9)	193 (36.5)	1,370 (28.3)
>180	46 (2.4)	43 (6.4)	75 (4.5)	61 (1.5)	225 (4.7)
Total	1935	672	1684	529	4820

Abbreviations: RT = radiotherapy; CHT = chemotherapy; HT = hormonal therapy.
Data presented as number of patients, with percentages in parentheses.
* Some data not available.

calculated from the date of surgery to the date of the last follow-up or date of death. The disease-free survival time was defined as survival without local recurrence and was calculated from the date of surgery to the date of local recurrence.

Timing was defined as the interval from surgery to the start of RT. The patients were categorized into four groups according to the interval between surgery and RT (T1, <60 days; T2, 61–120 days; T3, 121–180 days; and T4, >180 days).

The crude probability of local recurrence was estimated using the Kaplan-Meier method, and differences between patient groups were assessed using the log-rank test. Incidence comparisons were performed using Cox proportional hazard regression models. The estimated relative risks of local recurrence are expressed as hazard ratios (HRs) and corresponding 95% confidence intervals (CIs). Univariate models were used to evaluate the effect of each parameter. Multivariate regression models, also with stepwise selection, were used to test the independent effect of timing after adjusting for known prognostic factors.

The statistical results were considered significant at $p < 0.05$. All statistical tests were performed using the Statistical Analysis Systems (SAS Institute, Cary, NC) software.

RESULTS

To evaluate the effect of the timing in delivering RT, we divided our series into four groups according to treatment (Table 1): those who received postoperative RT only (40.1%), those who received RT and CHT (13.9%), those who received RT and hormonal therapy (HT) (34.9%), and those who received RT, CHT, and HT (11.1%).

On univariate regression analysis, the risk of developing breast relapse (BR) for patients treated with postoperative RT only ($n = 1,935$) was inversely proportional to the interval between surgery and RT, although the statistical significance was reached only for T3 (T2: HR, 0.94; 95% CI, 0.66–1.35; T3: HR, 0.54; 95% CI, 0.32–0.89; T4: HR, 0.24; 95% CI, 0.03–1.70). Analyzing the prognostic factors in the T3 and T4 groups, we noted that most patients had a tumor size of <2 cm, negative axillary lymph nodes, age at presentation of >50 years, negative surgical margins, and had received a boost to the tumor bed.

On multivariate analysis, adjusted for the known prognostic factors, the timing of RT lost any statistical significance; however, age at presentation, surgical margin status, and boost to the tumor bed were independent prognostic factors for BR (Table 2).

Similar results were obtained in the groups of patients who received RT and HT ($n = 1,684$) or RT, CHT, and HT ($n = 529$). In both groups, on multivariate-adjusted analysis, the timing of RT did not achieve any statistical significance. In the RT and HT group, age at presentation and RT boost emerged as independent prognostic factors for BR ($p = 0.006$ and $p = 0.049$, respectively). In the RT, CHT, and HT group, only multifocality was an independent BR predictor ($p = 0.01$).

Only in the group of patients treated with RT and CHT ($n = 672$) did multivariate analysis with stepwise selection show timing as independent prognostic factor (HR, 1.59; 95% CI, 1.01–2.52; $p = 0.045$). The major effect was confined to the T4 group (HR, 4.79; 95% CI, 0.93–24.72; $p = 0.06$). Analyzing the prognostic factors of the patients in this group, we noted that most had a tumor size >2 cm, positive axillary lymph nodes, age at presentation <50 years, had undergone CMF at other institutes before starting RT, and were referred to our institution for RT only after CHT completion.

Table 2. Multivariate regression analysis to identify the major predictor factors of local breast relapse in series of 1,935 patients treated with radiotherapy without other systemic treatment

Parameter	Parameter estimate	p	HR	95% CI
Age*	−0.32128	0.0012†	0.725	0.597–0.880
pT*	−0.03172	0.7886	0.969	0.768–1.222
Positive nodes*	−0.46712	0.4736	0.627	0.175–2.249
Multifocal (yes)	0.10016	0.7472	1.105	0.601–2.032
Margins (positive)	0.89610	0.0004†	2.450	1.490–4.029
Boost (yes)	−0.52408	0.0017†	0.592	0.427–0.821
Timing*	0.13272	0.2561	0.876	0.696–1.101

Abbreviations: HR = hazard ratio; CI = confidence interval.
* Category at risk according to ordinal scale (Table 1).
† Statistically significant.

DISCUSSION

Earlier studies that considered the effect of adjuvant therapy for patients with breast cancer showed that systemic treatment alone does not prevent BR properly (10, 11). Because it is still unclear how the interval between surgery and adjuvant RT affects BR, we analyzed our series, categorizing patients into four groups according to the adjuvant treatment received.

Although the sample size of our population was adequate, the major bias of our study was the lack of a randomized design; therefore, it should be interpreted only as a retrospective analysis. We included no inclusion or exclusion criteria at presentation, but the subgroups were identified from a database compiled at the University of Florence.

In our study, we considered 1,935 patients who had undergone postoperative RT only without any systemic treatment. Only a few studies have examined the effect of the surgery–RT interval on local recurrence in the absence of systemic therapy in breast cancer patients. Clarke *et al.* (12) suggested a surgery–RT interval of ≥7 weeks was associated with increased local recurrence; however, this result was not significant on multivariate analysis. In agreement, our study showed that the timing of RT was not an independent prognostic factor for BR on multivariate analysis. Similar results have been published by other investigators (13, 14).

Whelan *et al.* (15), for the Ontario Clinical Oncology Group, stated that the 12.4% local recurrence rate for patients ($n = 185$) treated >8–12 weeks from surgery was not significantly different from the 8.4% rate for patients ($n = 215$) treated within 8 weeks of surgery. In the Joint Center for Radiation Therapy series of 653 patients, an interval of ≤8 weeks was not found to be detrimental to the risk of

recurrence (16). Moreover, Vujovic *et al.* (17) reported that a delay in the start of breast RT of ≤16 weeks from definitive breast surgery was not associated with an increased recurrence rate for patients with good prognostic features.

Jobsen *et al.* (3) analyzed 1,473 breast-conserving therapy cases in 1,446 breast cancer patients from their prospective cohort, with Stage I or II, node-negative disease, who had not received adjuvant systemic therapy. The patients were categorized into 3 timing tertiles: 1–36 days, 37–53 days, and 54–112 days. The 10-year local relapse-free survival rates did not show significant differences among the 3 groups. The 10-year distant metastasis-free survival rate was 78.9% for the first tertile, 86.1% (HR, 0.6; $p = 0.009$) for the second, and 90.7% (HR, 0.3; $p < 0.001$) for the third tertile. The 10-year disease-specific survival rate was 83.8% for the first tertile, 90.6% (HR, 0.5; $p = 0.007$) for the second, and 97.2% (HR, 0.2; $p < 0.001$) for the third tertile. Also, on multivariate Cox regression analysis, the second (HR, 0.6; $p = 0.053$) and third (HR, 0.3; $p = 0.002$) tertiles had significantly better disease-specific survival. They concluded that a longer delay showed a positive effect on distant metastasis-free survival and disease-specific survival (3).

Froud *et al.* (18) in a series of 1,962 breast cancer patients with a median follow-up of 71 months showed that the crude incidence of BR for the entire sample was 3.9%. The cumulative incidence of BR in the 6–8-, 9–12-, and >13-week groups between surgery and RT was not significantly different statistically from the cumulative incidence of BR in the 0–5-week group. Multivariate analyses demonstrated that patients not using tamoxifen ($p = 0.027$) and those with Grade 3 histologic features ($p = 0.003$) were more likely to develop recurrence in the breast. The interval between surgery and RT was not a statistically significant predictor of BR when entered into a model incorporating tamoxifen use and tumor grade (0–5 vs. 6–8 weeks, $p = 0.872$; 0–5 vs. 9–12 weeks, $p = 0.665$; and 0–5 vs. >13 weeks, $p = 0.573$).

In our analysis, we found that a boost to the tumor bed was an independent prognostic factor for BR, consistent with the report by Bartelink *et al.* (19), in which the cumulative incidence of local recurrence at 10 years was 10.2% vs. 6.2% for the no-boost and boost group, respectively.

Our study showed that the timing of RT after surgery did not reach statistical significance on multivariate analysis in the group of patients treated with HT or those treated with CHT and HT. Only for the group treated with CHT and RT was timing an independent prognostic factor on multivariate analysis. This finding might have been related to the worse prognostic factors in patients treated with CHT. CHT, in fact, has been shown to not affect BR, in contrast to HT (20, 21). Moreover, in most patients treated with CHT and RT who developed BR, RT was delayed because they had undergone CMF at other institutions.

Toledano *et al.* (22) in the Irradiation et chimiothérapie concomitantes après chirurgie pour cancer du sein: étude Arcosein study reported that in the node-positive subgroup, the 5-year disease-free survival was significantly better in the concurrent arm (CHT and RT) than in the sequential treatment arm (RT after full courses of CHT): 97% vs. 91%, respectively ($p = 0.02$). The CHT regimen consisted of mitoxantrone (12 mg/m^2), 5-fluorouracil (500 mg/m^2), and cyclophosphamide (500 mg/m^2).

Four randomized controlled studies have been conducted to address the sequencing of CHT and RT for localized breast cancer. The first trial involved 80 patients randomized to RT first before 6 cycles of CMF, or CHT first (6 cycles of CMF) before RT, or a sandwich technique in which RT was given after 3 cycles of CMF followed by 3 more cycles of CMF. They concluded the sandwich technique was superior (23).

Wallgren *et al.* (24) evaluated the outcomes of patients who received breast RT after completing CHT within the context of 2 concurrent randomized clinical trials. In the first, they randomly assigned 1,554 pre/perimenopausal node-positive breast cancer patients to receive CMF for either 3 consecutive courses on Months 1–3 or 6 consecutive courses on Months 1–6. In the second trial, they randomly assigned 1,266 postmenopausal node-positive breast cancer patients to receive tamoxifen for 5 years or tamoxifen for 5 years with 3 early cycles of CMF, both with or without 3 courses of delayed CMF. They found no compromise in local control for increasing the delay to RT to allow for CHT. The estimates of the 4-year crude percentage of local failures was 8% and 9% for the pre/perimenopausal patients who underwent RT at 4 or 7 months after surgery and 3% and 6% for the postmenopausal patients who underwent RT at 2 months or 4 months after surgery (24).

The ''Up-Front Out-Back'' study (25) randomized breast cancer patients to receive either CHT before RT or RT before CHT. It established that patients with early-stage breast cancer who had an increased risk of systemic metastases should receive CHT before RT in the context of breast conservation therapy. The benefit was most pronounced in patients with four or more positive nodes. Although a statistically significant benefit was found, by decreasing the rate of distant metastasis at 5 years (25% vs. 36% for CHT first vs. RT first, respectively), the local failure rates were worse (14% vs. 5% for CHT first vs. RT first).

The French Adjuvant Study Group trials investigated 1,831 patients, including 475 patients who received RT directly after breast-conserving surgery (95 patients received no adjuvant therapy, and 380 patients received HT), 567 patients who received RT after the third CHT cycle (250 patients received 1 to 3 courses, and 317 patients received 4 to 6 courses), and 789 patients who received RT after the sixth CHT cycle. An improvement in local control for patients who received 4 to 6 courses of CHT, irrespective of the interval before starting RT ($p = 0.02$), was reported. Interestingly, the regimens were all anthracycline-based CHT.

Our findings suggest that the radiotherapist should pay most attention to the prognostic factors and that the waiting list should be renamed the programming list. This would mean that the radiotherapist would program the beginning of RT according to the prognostic factors and not the time of surgery.

On multivariate analysis of the entire population, patient age, margin status, and the type of adjuvant treatment emerged as statistically significant factors, but not the timing of RT. However, evaluating the subgroups, we noted that the timing of RT was an independent prognostic factor for patients treated with RT plus CHT. This could further suggest that timing becomes an important factor in those patients who have high-risk disease.

New studies are needed to better establish the best interval between RT and CHT, especially in patients with high-risk factors, because newly available anticancer drugs and biologic agents seem to produce better survival and local control (26, 27).

CONCLUSION

Although our results must be interpreted cautiously, because they were from a nonrandomized study, they seem to suggest that the timing of RT itself does not affect local recurrence, which is mainly related to the prognostic factors. Thus, we believe that the ''waiting list'' should be thought of as a ''programming list'' and determined by the prognostic factors.

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