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Timing of radiotherapy and outcome in patients receiving adjuvant endocrine therapy

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Abstract

Purpose—To evaluate the association between time from breast-conserving surgery (BCS) to radiotherapy and clinical outcome among patients treated with adjuvant endocrine therapy.

Methods—Patient information was obtained from three International Breast Cancer Study Group trials. Analysis was restricted to 964 patients treated with BCS and adjuvant endocrine therapy. Patients were divided into two groups based on the median number of days between BCS and radiotherapy and into 4 groups based on the quartile of time between BCS and radiotherapy. Endpoints were time to local recurrence (TLR), disease-free survival (DFS) and overall survival (OS). Proportional hazards regression analysis was used to perform comparisons after adjustment for baseline factors.

Results—The median time between BCS and radiotherapy was 77 days. Radiotherapy timing was significantly associated with age, menopausal status, and estrogen receptor status. After adjustment for these factors no significant effect of radiotherapy delay of up to 20 weeks was found. Adjusted hazard ratios (HRs) (radiotherapy within 77 days vs. after 77 days) were 0.94 (95% CI 0.47–1.87) for TLR, 1.05 (95% CI 0.82–1.34) for DFS and 1.07 (95% CI 0.77–1.49) for OS. For TLR the adjusted HRs for ≤ 48 days, 49–77 days, and 78–112 days were 0.90 (95% CI 0.34–2.37), 0.89 (95% CI, 0.33–2.25), and 0.89 (95% CI, 0.33–2.41), respectively relative to ≥ 113 days.

Conclusions—Radiotherapy delay of up to 20 weeks was significantly associated with baseline factors such as age, menopausal status, and estrogen-receptor status. After adjustment for these factors, timing of radiotherapy was not significantly associated with TLR, DFS, or OS.

Keywords

breast cancer; radiotherapy; radiotherapy timing; breast-conserving surgery; endocrine therapy

Introduction

Radiotherapy to the breast after breast-conserving surgery reduces the risk for local recurrence and improves breast cancer specific survival [1]. The optimal time between surgery and the start of radiotherapy is not known. Theoretically, the risk of recurrence is related to the density of clonogenic cells in the surgical bed. Therefore, a delay between surgery and the start of radiotherapy may increase the likelihood of tumor cell growth and development of radioresistance [2]. Several retrospective studies have yielded variable results [3–8]. Generally, in univariate analysis, an increased risk for local recurrence was observed with longer delay between surgery and the start of radiotherapy. However, in multivariate analysis, this effect was not observed. Two systematic reviews showed an increase in the risk of local recurrence with radiotherapy delay of longer than 8 weeks [9,10]. However, these reviews included all subtypes of breast cancer and a variety of study designs rendering interpretation of the results difficult. The risk of local recurrence in relation to radiotherapy delay may vary by breast cancer subtype and systemic treatment. An International Breast Cancer Study Group (IBCSG) study has shown that delaying radiotherapy until the completion of chemotherapy does not adversely affect treatment outcome [11]. There has been no study that examines the effect of radiotherapy delay on local recurrence in breast cancer exclusively in patients receiving endocrine therapy. The aim of the present study is to investigate the impact of delay from breast-conserving surgery

(BCS) to the start of radiotherapy in patients treated with endocrine therapy in three IBCSG trials.

Patients and Methods

Patient information was obtained from 1,108 patients who had BCS and were randomized to selected treatment arms from IBCSG trials VII, VIII and IX. Of the 1,108 patients identified, 135 did not receive radiotherapy and an additional nine did not have a record of radiotherapy commencement dates, leaving 964 patients in the analyzed cohort.

Trial VII compared adjuvant tamoxifen alone vs. chemoendocrine treatments of tamoxifen with concurrent classical cyclophosphamide, methotrexate, and 5-fluorouracil (CMF) in postmenopausal patients with node-positive breast cancer. [12]. Trial VIII studied adjuvant ovarian function suppression with LH-RH analogue for two years vs. six courses of CMF vs. six courses of CMF followed by 18 months of ovarian function suppression in premenopausal patients with node-negative disease [13]. Trial IX compared adjuvant tamoxifen vs. 3 courses of CMF followed by tamoxifen in postmenopausal patients with node-negative disease [14]. The present study was restricted to the following treatment groups receiving adjuvant endocrine therapy: trial VII Arm A (tamoxifen for 5 years) (n=69), trial VIII Arm B (LH-RH analogue for two years) (n=173), trial IX Arm A (tamoxifen for 5 years) (n=374), and trial IX Arm B (CMFx3 followed by tamoxifen for 57 months) (n=370). Trial VII specified that radiotherapy was required for all patients who had BCS. Although trials VIII and IX did not mandate radiotherapy to the conserved breast, 88% of the patients who had BCS were treated with radiotherapy. In all three trials, patients who had BCS and radiotherapy and were randomized to receive endocrine therapy alone were required to begin radiotherapy within three months of randomization, and those randomized to receive CMF prior to tamoxifen in trial IX were to begin radiotherapy two weeks after the end of the last cycle of chemotherapy. For the present study, patients were divided into two groups based on the median number of days from surgery to commencement of radiotherapy. Kaplan-Meier survival curves were plotted for the two groups, and the log-rank test was used to compare them. The endpoints were time to local recurrence, disease-free survival (DFS) and overall survival (OS), measured from start of radiotherapy. This approach accounts for the fact that the time to an event must exceed the number of days between surgery and the start of radiotherapy. In addition, patients were divided into four groups based on the quartiles of days from surgery until start of radiotherapy. Proportional hazards regression was used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for the 2-group and 4-group analyses. Wald tests were used to evaluate heterogeneity among the HRs based on the 4-group analysis. Of the 964 patients in the analytic cohort, 715 had estrogen receptor (ER)-positive disease. All analyses were repeated for the ER-positive cohort.

Results

The median number of days from surgery to the start of radiotherapy was 77 days (mean 84 days, standard deviation 45 days, range 14 to 436 days). 409 patients (42%) received radiotherapy more than 90 days following surgery. Table 1 shows the baseline characteristics of the two groups of patients who started radiotherapy within or after 77 days (median number of days) from surgery. Age, pre-menopausal status, and hormone receptor status were significantly associated with radiotherapy timing. However it should be noted that some of these differences may be due to the CMF-tamoxifen arm of Trial IX in which patients had radiotherapy after chemotherapy.

The median follow-up was 10.5 years. The total numbers of events were 37 local recurrences, 271 disease-free survival events and 161 deaths. Adjusting for the differences in baseline characteristics the HR for starting radiotherapy within 77 days relative to after 77 days was 0.94 (95% CI 0.47–1.87) for local recurrence, 1.05 (95% CI 0.82–1.34) for DFS and 1.07 (95% CI 0.77–1.49) for OS (Table 2). When patients were divided into quartiles according to surgery-to-radiotherapy interval the adjusted HRs were not significantly different (Table 3). The Kaplan-Meier curves for time to local recurrence, DFS and OS with time to event from the start of radiotherapy for the two-group analysis and for the four-group analysis are shown in Figure 1 and Figure 2 respectively. Kaplan-Meier analysis with time to event measured from day 77 after surgery gave similar results (data not shown). The analyses were repeated for the ER-positive cohort (n = 715) with similar results (Table 2B and Table 3B), and there were no significant interactions between RT timing and ER-positivity (data not shown).

The mean time from surgery to the start of endocrine therapy was 33 days in the group that started radiotherapy within 77 days and 81 days in the group that started radiotherapy after 77 days. Among the 841 patients (89%) who began endocrine therapy prior to radiotherapy, the mean time from start of endocrine therapy to start of radiotherapy was 26 days in the group that started radiotherapy within 77 days and 48 days in the group that started radiotherapy after 77 days.

Discussion

After adjustment for differences in the baseline characteristics, radiotherapy timing was not significantly associated with time to local recurrence, DFS or OS in patients receiving adjuvant endocrine therapy for radiotherapy delay of up to about 20 weeks. Postoperative radiotherapy after breast conserving surgery reduces local failure rates substantially and is therefore well accepted [1], but the optimal time interval between surgery and start of irradiation is still controversial. A recent meta-analysis by Chen et al indicated an increasing relative risk of 1.11 per month of irradiation delay for local recurrence in so-called 'high quality' series, irrespective of whether chemotherapy was given or not [9], but there was no significant impact on distant metastasis or overall survival. This meta-analysis confirmed a previous systematic review [10], in which the 5-year local relapse rate was significantly higher in breast cancer patients starting adjuvant radiotherapy more than 8 weeks after surgery compared to patients treated within 8 weeks (odds ratio: 1.62; 95% CI 1.21–2.16). However, these meta-analyses included patients with a variety of breast cancer subtypes and in whom the use of systemic therapy was inconsistent. Both of these factors may have an impact on the local recurrence rate. Only a few studies have evaluated the time interval of radiotherapy after surgery in the absence of chemotherapy. The more recent meta-analysis [9] identified only four studies [3,5,15,16], all of them observational, but with an adequate description of the distribution of relevant prognostic factors, which were either well balanced between the comparison groups or appropriately adjusted for in the analyses. Among the individual studies, the largest by far [5] examined the impact of radiotherapy delay of <6 weeks, 6–8 weeks, 9–12 weeks and ≥13 weeks on 1,962 patients who had BCS. Of the 1,962 patients, 677 received tamoxifen and no patients had chemotherapy. Twenty-three patients had a radiotherapy delay of longer than 20 weeks. At a median follow-up was 71 months, the local recurrence rate was significantly associated with the omission of tamoxifen and high histologic grade of the tumors. The interval between BCS and radiotherapy was not significantly associated with local recurrence in a model incorporating tamoxifen use and histologic grade, which was in contrast to the overall finding of the meta-analysis, but consistent with our results.

A more recent publication from the British Columbia Cancer Agency examined different time intervals between surgery and radiotherapy in early-stage breast cancer patients in the absence of chemotherapy [8]: The study yielded similar results as the present study for radiotherapy delay of up to 20 weeks. However, radiotherapy delay of more than 20 weeks resulted in an inferior outcome. Patients who were not given endocrine therapy were separately analyzed and findings were similar as for the entire cohort, but there was no separate subgroup analysis for patients who were given endocrine therapy [8]. In a recent study from Florence [4] the risk of developing breast failure for patients without any systemic adjuvant treatment (n=1935) was inversely proportional to the interval between surgery and radiotherapy in univariate analysis, but timing of radiotherapy was not statistically significant in a multivariate analysis. Similar results were obtained in the treatment groups of radiotherapy/endocrine therapy (n=1684) and radiotherapy/endocrine therapy/chemotherapy (n=529). Radiotherapy timing was statistically significant in multivariate analysis only in the group of patients with radiotherapy and chemotherapy (n=672) (hazard ratio: 1.69; p=0.045) [4]. This paper also did not provide separate analyses for patients with radiotherapy and endocrine therapy. In a previous publication of our group we analyzed the impact of radiotherapy delay due to chemotherapy in IBCSG trials VI and VII [11]. The current analysis was undertaken as studies investigating radiotherapy timing in patients with endocrine therapy are rare. Similar to others [4], we could not find any impact of the time interval from surgery to radiotherapy on local control or other endpoints. However, the present study has too few events to provide an accurate estimate of the effect of radiotherapy delay of over 20 weeks. In addition, a limitation of the present study is the insufficient power to reject an association between radiotherapy delay of shorter intervals and a small increase in the local recurrence risk. Nevertheless, and despite its retrospective design, the current study deals with patients treated in a randomized study with defined inclusion/exclusion criteria, uniform adjuvant therapy/-ies and rigid follow-up control, which is in contrast to most observational series available in the literature.

The question of the effect of sequential or concurrent use of endocrine treatment and radiotherapy on tumor control could not be addressed in the present study. In IBCSG Trials VII–IX, most patients started endocrine therapy within two days after randomization, except for those assigned to receive CMF first, and radiotherapy was administered concurrently with endocrine therapy.

A study of IBCSG Trials VI and VII showed that a delay of radiotherapy from BCS of up to 6.6 months (28 weeks), during which chemotherapy was given, did not adversely influence treatment outcome [11]. The present IBCSG study indicates that an interval of up to about 20 weeks between breast conserving surgery and radiotherapy does not increase the risk of local recurrence in a cohort of patients receiving standard adjuvant endocrine treatment.

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Figure 1.

Kaplan-Meier curves for time to local recurrence (A), disease-free survival (B) and overall survival (C) with time to event from start of radiotherapy for patients with radiotherapy within or after 77 days from surgery.

Figure 2.

Kaplan-Meier curves for time to local recurrence (A), disease-free survival (B) and overall survival (C) with time to event from start of radiotherapy as in quartiles (≤ 48 days, 49–77 days, 78–112 days and ≥ 113 days).

Table 1

Baseline Characteristics

Characteristic	RT within 77 Days (N = 492)	RT after 77 Days (N = 472)	P-value *
<i>Mean ± SD</i>			
Age, years	55.6 ± 8.9	58.8 ± 7.3	<0.0001
<i>Number (%)</i>			
Menopausal status			
Pre	128 (26)	45 (10)	<0.0001
Post	364 (74)	427 (90)	
ER Status			
Negative	123 (25)	89 (19)	0.042
Positive	357 (73)	358 (76)	
Unknown	12 (2)	25 (5)	
Tumor Grade			
1	89 (18)	86 (18)	0.94
2	237 (48)	221 (47)	
3	165 (34)	162 (34)	
Unknown	1 (0)	3 (1)	
Number of Positive Lymph Nodes			
0	454 (92)	441 (93)	0.62
1–3	25 (5)	23 (5)	
4+	13 (3)	8 (2)	
Tumor Size			
≤ 2 cm	371 (75)	366 (78)	0.35
>2 cm	118 (24)	100 (21)	
Unknown	3 (1)	6 (1)	
Vessel Invasion			
No	378 (77)	364 (77)	0.098
Yes	94 (19)	67 (14)	
Unknown	20 (4)	41 (9)	

* Unknowns for a given category are excluded from calculation of p-values.

Table 2

Adjusted Proportional Hazards Regression Results Dividing at the Median

RT Timing (from Surgery)	Hazard Ratio	95% CI	P-Value
Local Recurrence			
≤ 77 Days	0.94	0.47 to 1.87	0.86
≥ 78 Days	1.00		
Disease-Free Survival			
≤ 77 Days	1.05	0.82 to 1.34	0.73
≥ 78 Days	1.00		
Overall Survival			
≤ 77 Days	1.07	0.77 to 1.49	0.67
≥ 78 Days	1.00		

Table 2B. ER-positive cohort: Adjusted Proportional Hazards Regression Results Dividing at the Median

RT Timing (from Surgery)	Hazard Ratio	95% CI	P-Value
Local Recurrence			
≤ 77 Days	0.84	0.38 to 1.89	0.68
≥ 78 Days	1.00		
Disease-Free Survival			
≤ 77 Days	0.95	0.71 to 1.28	0.73
≥ 78 Days	1.00		
Overall Survival			
≤ 77 Days	1.16	0.77 to 1.74	0.48
≥ 78 Days	1.00		

Table 3A

Adjusted Proportional Hazards Regression Results Based on Quartiles

RT Timing (Days from Surgery)	Hazard Ratio	95% CI	P-Value
Local Recurrence		<i>Overall Wald P = 0.99</i>	
≤ 48	0.90	0.34 to 2.37	0.83
49 to 77	0.86	0.33 to 2.25	0.76
78 to 112	0.89	0.33 to 2.41	0.81
≥ 113	1.00		
Disease-Free Survival		<i>Overall Wald P = 0.12</i>	
≤ 48	0.78	0.55 to 1.10	0.16
49 to 77	0.95	0.68 to 1.32	0.75
78 to 112	0.68	0.47 to 0.97	0.03
≥ 113	1.00		
Overall Survival		<i>Overall Wald P = 0.03</i>	
≤ 48	0.70	0.45 to 1.11	0.13
49 to 77	0.86	0.56 to 1.31	0.47
78 to 112	0.50	0.31 to 0.81	0.005
≥ 113	1.00		

Table 3B. ER-positive cohort: Adjusted Proportional Hazards Regression Results Based on Quartiles

RT Timing (Days from Surgery)	Hazard Ratio	95% CI	P-Value
Local Recurrence		<i>Overall Wald P = 0.85</i>	
≤ 48	1.03	0.34 to 3.14	0.96
49 to 77	0.67	0.21 to 2.17	0.50
78 to 112	0.99	0.31 to 3.17	0.99
≥ 113	1.00		
Disease-Free Survival		<i>Overall Wald P = 0.20</i>	
≤ 48	0.72	0.48 to 1.09	0.12
49 to 77	0.82	0.55 to 1.22	0.32
78 to 112	0.65	0.42 to 0.99	0.04
≥ 113	1.00		
Overall Survival		<i>Overall Wald P = 0.05</i>	
≤ 48	0.76	0.44 to 1.32	0.33
49 to 77	0.80	0.47 to 1.38	0.42
78 to 112	0.42	0.23 to 0.78	0.005
≥ 113	1.00		