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Delay in Radiation Therapy Is Associated with Increased Risk of Recurrence in Women with Ductal Carcinoma in Situ

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Abstract

BACKGROUND—To examine the association between ipsilateral breast tumor recurrence (IBTR) and timing of radiation therapy (RT) in women with ductal carcinoma in situ (DCIS) undergoing breast-conserving surgery (BCS).

METHODS—Women with DCIS treated with BCS and RT from 1980–2010 were identified from a prospectively-maintained database. IBTR rates, measured from RT completion, were compared between those who began RT 8 weeks, >8–12 weeks, and >12 weeks after completion of surgery. Association between RT timing and IBTR was evaluated by Kaplan-Meier and log-rank analysis; Cox modeling was used for multivariable analysis.

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Conflict of interest information

The authors have no conflict of interest disclosures to report, and this manuscript is not under consideration elsewhere.

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RESULTS—1323 women met inclusion criteria. Median follow-up was 6.6 years, with 311 patients followed for 10 years. 129 IBTR events occurred. Patients were categorized by RT timing: 806 (61%) ≤8 weeks, 386 (29%) >8–12 weeks, and 131 (10%) >12 weeks. 5- and 10-year IBTR rates were: 5.8% and 13.0% RT starting ≤8 weeks, 3.8% and 7.6% RT >8–12 weeks, and 8.8% and 23.0% with RT delayed >12 weeks after surgery, respectively (p=0.004). On multivariable analysis, menopause (HR 0.54, p=0.0009) and endocrine therapy (HR 0.45, p=0.002) were IBTR-protective, whereas delay in RT >12 weeks compared to ≤8 weeks was associated with higher risk of IBTR (HR 1.92, p=0.014). There was no difference in IBTR between RT initiation ≤8 weeks and >8–12 weeks (p=0.3).

CONCLUSIONS—Delay in RT >12 weeks is associated with a significantly higher risk of IBTR in women undergoing BCS for DCIS. Efforts should be made to avoid delay in starting RT to minimize risk of recurrence.

Keywords

ductal carcinoma in situ; radiotherapy; recurrence; breast cancer

INTRODUCTION

Ductal carcinoma in situ (DCIS), or stage 0 breast cancer, is a noninvasive breast lesion that comprises approximately 20% of all breast cancer diagnoses. In 2017 it is estimated that nearly 53,000 women will be diagnosed with DCIS in the United States.^{1, 2} The majority (60–77%) of these women will undergo breast-conserving surgery (BCS), with or without adjuvant therapy.^{3–6} Survival is excellent following BCS for DCIS, with 10-year breast cancer-specific mortality rates of 1–4%.^{7–10} However, rates of ipsilateral breast tumor recurrence (IBTR) are not insignificant, with risk of IBTR reported as 1–3% per year,^{5, 8} with long-term recurrence rates ranging from 25% to 35% following BCS alone in four large, prospective, randomized controlled trials.^{9, 11–13}

A marked decrease in risk of IBTR in DCIS patients has been seen with the utilization of adjuvant radiation therapy (RT) after BCS. The Early Breast Cancer Trialists' Collaborative Group meta-analysis of 3729 women with DCIS from four randomized controlled trials revealed a 10-year relative risk reduction of 54% and 10-year absolute risk reduction of 15% for IBTR with the addition of RT.⁸ Despite the demonstration of clear benefit for the use of RT in DCIS patients, evidence regarding optimal timing of adjuvant RT is lacking. Of the four mature randomized controlled trials, only two specified timing of RT therapy in the protocol: patients enrolled in National Surgical Adjuvant Breast and Bowel Project (NSABP) B-17 and European Organisation for Research and Treatment of Cancer (EORTC) 10853 initiated RT within 8 and 12 weeks, respectively.^{14, 15} However, it is well documented that in patients with invasive breast cancer, RT delay of more than 8 to 12 weeks leads to an increased risk of IBTR.^{16–18} The aim of this study was to examine the association between timing of adjuvant RT and risk of IBTR in women with DCIS undergoing BCS.

METHODS

Women were identified from a prospectively maintained database of patients with DCIS undergoing BCS at Memorial Sloan Kettering Cancer Center (MSK). Patients were included if they were female, had undergone surgery between 1980 and 2010, and received adjuvant RT. Patients excluded were those with a previous breast cancer diagnosis, those with synchronous invasive breast cancer, those unknown RT total dose or with total RT dose less than 4240 cGy, and those missing both RT initiation and completion date. If the start or end date of RT was not known, it was inferred from the known corresponding end or start date of RT, respectively, using the median duration of RT therapy in the cohort (6 weeks). Of 1323 patients, 53 start dates were inferred from known RT completion dates, and one RT end time was inferred from a known start date. Four patients had non-synchronous bilateral DCIS and were included in the dataset as separate entries. The use of these data was approved by the MSK Institutional Review Board.

Time to RT was defined as the interval between final definitive surgery, defined as date of surgery if only one excision was required, or date of final re-excision if multiple procedures were required, and the date of RT initiation. Patients were grouped and analyzed according to timing of RT initiation (< 8 weeks, > 8 to 12 weeks, > 12 weeks). Other factors included were age, menopausal status, family history of breast cancer (defined as one or more first- or second-degree family members with breast cancer), presentation (radiological or clinical), nuclear grade (low, intermediate, or high), presence of tumor necrosis, number of excisions required (< 2 or ≥ 3), margin status [positive/close (< 2 mm) or negative (> 2 mm)], endocrine therapy, total RT dose, and treatment time period (< 2000 or ≥ 2001). Number of surgical excisions was included as a surrogate for size/extent of DCIS.

The primary endpoint was time interval to first IBTR, calculated from the date of completion of RT to the date of histologically proven recurrence. Both biopsy-proven DCIS and invasive breast carcinoma in the ipsilateral treated breast were included as IBTR.

Whole breast radiation was used on all patients, generally prescribed with either the standard schedule of 5000cGy in 25 treatments, or the “hypofractionated” schedule of 4240 cGy in 16 treatments. The additional use of a boost was based on clinical judgment and the final margin status. A sequential boost to the lumpectomy cavity, ranging from 360cGy to 2160cGy, was delivered to 81% of patients (n = 1072). For the patients who received RT at an outside institution, treatment summaries documenting the dose and fraction size were obtained and reviewed. Follow-up consisted of annual mammograms, routine interval history, and physical examinations.

Differences in patient characteristics by time to RT initiation were assessed using the χ^2 square test. The Kaplan-Meier method was used to estimate 5- and 10-year recurrence rates in the entire population as well as in each of the time-to-RT cohorts. Hazard ratios (HRs) and Wald test p-values for each variable were estimated from univariate and multivariable Cox regressions. A multivariable Cox regression model was used to assess the relationship between delay in RT initiation and IBTR while adjusting for patient clinicopathological factors that were associated with IBTR on univariate Cox regression analysis, or that varied

between RT timing groups. RT dose was modeled as a continuous variable and was rescaled so that the hazard ratio (HR) corresponded to the effect of a 100 cGy increase in RT dose on the outcome. A sensitivity analysis was performed to ensure that the main finding on the relationship between RT timing and IBTR was robust with the inclusion of 54 patients with inferred start or end dates. All analyses were performed using SAS v9.4 and R 3.1.1. All statistical tests were two-sided, and $P < 0.05$ was considered statistically significant.

RESULTS

Of 3001 cases of DCIS treated with BCS, 1596 patients underwent RT and 1323 patients had known RT initiation or completion dates with RT dose 4240 cGy (See Figure 1). Median patient age was 56 years (range 27–86 years). Median follow-up was 6.6 years (range 0–30.7 years), with 311 women followed for at least 10 years. Of the 126 IBTR events, 56% were DCIS recurrences and 44% were invasive carcinoma. The overall cumulative incidence of IBTR at 5 and 10 years was 5.5% and 12.5%, respectively (Figure 2A).

Differences in Patient, Tumor, and Treatment Characteristics by RT Cohort

Radiation therapy was initiated within 8 weeks of surgery in 806 patients (61%), while 386 patients (29%) began RT between 8 and 12 weeks after surgery, and 131 patients (10%) experienced delay in RT more than 12 weeks after surgery. The median delay in the group that initiated RT more than 12 weeks after definitive surgery was 14.1 weeks, with a range of 12.1 to 62.4 weeks. Patient, tumor, and treatment characteristics are listed in Table 1. As compared to the longer time to RT cohorts, women starting RT within 8 weeks had a non-significantly higher proportion of pre/perimenopausal women (40% vs 35% and 33%, respectively, $P = 0.10$) and nonsignificant difference in the use of endocrine therapy between groups, with less frequent usage in women who experienced a delay in RT therapy (28% vs 25% and 19%, $P = 0.07$). DCIS with necrosis significantly varied between groups (78% vs 73% and 71%, respectively, $P = 0.05$). RT dose varied by time to RT ($P < 0.0001$), with mean (median) RT doses of 5778 cGy (6000 cGy), 5665cGy (6000 cGy), and 5595cGy (5980 cGy) in patients who initiated RT within 8 weeks, between 8 and 12 weeks after surgery, and more than 12 weeks after surgery, respectively. Patient age, family history of breast cancer, presentation, nuclear grade, number of surgical excisions, margin status, and year of surgery did not vary significantly between RT timing cohorts.

Differences in IBTR Rates by Clinical, Pathologic, and Treatment Characteristics

Incidence of IBTR varied significantly by time to initiation of RT ($P < 0.005$, Figure 2B). Five-year IBTR rates for patients initiating RT within 8 weeks, between 8 to 12 weeks, and beyond 12 weeks were 5.8%, 3.8%, and 8.8%, respectively. Ten-year IBTR rates for patients starting RT within 8 weeks, between 8 to 12 weeks, and beyond 12 weeks were 13.0%, 7.6%, and 23.0%, respectively (Table 2).

On univariate regression analysis, delay in RT initiation more than 12 weeks was associated with a higher risk of IBTR (HR 1.82, 95% confidence interval [CI] 1.12–2.94, $P = 0.015$), whereas postmenopausal status (HR 0.50, 95% CI 0.35–0.71, $P < 0.0001$), radiologic

presentation (HR 0.63, 95% CI 0.40–0.99, $P=0.048$), and usage of endocrine therapy (HR 0.43, 95% CI 0.26–0.70, $P=0.0007$) were associated with a lower risk of IBTR (Table 3). Of the patients taking hormonal therapy ($n=348$), 329 (94.5%) did not experience a recurrence, 19 patients (5.5%) experienced a recurrence. This is in contrast to patients who did not take endocrine therapy ($n=970$), where 863 (89.0%) did not experience a recurrence, whereas 107 (11.0%) had a documented recurrence. Family history of breast cancer, nuclear grade, necrosis, number of surgical excisions, margin status, total RT dose, and year of surgery were not significantly associated with IBTR in this cohort of women who received RT. As a sensitivity analysis, we performed the analysis excluding 54 patients with inferred RT start ($n=53$) or end ($n=1$) date to ensure that the main finding on the relationship between RT timing and IBTR was robust. The results from the sensitivity analyses were similar to those based on the full sample of 1323 patients. The logrank test for the full sample comparing IBTR by RT timing groups was 0.0042, and the logrank test for the sample without the 54 patients with inferred dates was $P=0.0015$.

Multivariable Model for IBTR

On multivariable analysis, after adjustment for clinicopathologic and treatment factors significantly associated with IBTR on univariate analysis (menopausal status, clinical versus radiologic presentation, use of endocrine therapy), as well as factors that varied between RT timing groups (menopausal status, necrosis, endocrine therapy, RT dose), delay in RT initiation remained a significant risk factor for IBTR (Table 4, overall $P<0.02$). Patients who received RT more than 12 weeks after surgery had an increased risk of IBTR compared to patients initiating RT within 8 weeks after surgery (HR 1.92, 95% CI 1.14–3.24, $P=0.014$). There was no significant difference in IBTR between patients who initiated RT within 8 weeks compared to those who initiated RT between 8 to 12 weeks after surgery (HR 0.80, 95% CI 0.51–1.27, $P=0.35$). Lower risk of IBTR was observed in patients who were postmenopausal (HR 0.54, 95% CI 0.37–0.78, $P=0.0009$) and in those who received endocrine therapy (HR 0.45, 95% CI 0.27–0.74, $P=0.0018$). Radiologic presentation, presence of necrosis, and total RT dose were not statistically significant predictors of IBTR on multivariable analysis.

DISCUSSION

In this population of patients with DCIS undergoing BCS with adjuvant RT, we observed higher IBTR rates among those who experienced a delay in initiation of RT following surgical excision, with a 1.9 times increased risk of IBTR in women who initiated RT more than 12 weeks after surgery as compared to patients who started RT within 8 weeks of surgery. This relationship persisted after adjusting for other variables correlated with time to RT or associated with IBTR in this population.

The overall 10-year IBTR rates for patients receiving RT within 8 weeks and between 8 to 12 weeks after surgery were 13.0% and 7.6%, respectively, which align with previous studies delineating an IBTR rate of approximately 1% per year in patients with DCIS undergoing BCS and RT.^{5, 8, 10, 19} Conversely, 10-year recurrence rates for patients in whom RT was delayed more than 12 weeks was 23.0%—nearly double than expected based on

previous studies. Interestingly, IBTR rates in the cohort of patients starting RT more than 12 weeks from definitive surgery mirrors that seen in DCIS patients treated at our institution with BCS without adjuvant treatment.²⁰ This suggests a smaller benefit from initiation of RT beyond 12 weeks after surgery.

While the literature shows that positive margins are associated with a higher risk of IBTR^{12, 21–23}, we have previously demonstrated that positive or close margins were not associated with IBTR in this population of women undergoing adjuvant RT after BCS for DCIS ($P = 0.95$).¹⁹ Our current study reiterates these findings with the addition of RT timing in the analysis. It is likely that the observed lack of effect of positive/close margins on IBTR in this population is due to the fact that few women had positive margins. Furthermore, most “positive” or close margins were only focally positive rather than across a broad front, and most were positive or close at the fascia or the dermis rather than at a radial margin. Therefore, our patients with positive/close margins probably had a lower residual disease burden than some other studied populations.

In addition to the known clinicopathologic and treatment factors associated with increased risk of IBTR among women with DCIS, such as premenopausal status and lack of adjuvant endocrine therapy, delay in RT initiation of more than 12 weeks appears to be associated with worse outcomes. Our findings are similar to those of numerous studies demonstrating increased IBTR with RT delay more than 8 to 12 weeks after surgery for invasive breast cancer.^{16–18} In a meta-analysis by Huang et al examining 7401 breast cancer patients, patients who initiated RT between 9 to 16 weeks after BCS had a 62% increased risk of local recurrence at 5 years compared to patients who initiated RT within 8 weeks; however, the analysis is limited, as use of chemotherapy was not analyzed as a possible confounding variable.¹⁶ Similarly, using the Quebec Tumor Registry, Hébert-Croteau et al studied 1062 patients with stage I–II breast cancer with negative lymph nodes undergoing BCS with RT. With a mean follow-up of 7.1 years and while controlling for multiple clinicopathologic factors, such as age, comorbidity, adjuvant systemic therapies, and margins, this study found a 75% increased risk of local recurrence in women who initiated RT more than 12 weeks after surgery compared to those who initiated RT within 8 weeks.¹⁸ Delay in RT also has been shown to be associated with breast cancer-specific survival among patients with invasive breast cancer. In a SEER-based study of 13,907 women older than 65 years of age with stage I–II invasive breast cancer undergoing BCS with RT, Hershman et al found close to a four-fold increased risk of disease-specific mortality for women who initiated RT more than 12 weeks after surgery compared to patients who received RT within 12 weeks.²⁴

The reason for an association between RT delay and IBTR is likely complex and multifactorial. Retrospective series highlight a number of variables associated with a delay in RT that may also impact IBTR risk. Madubata and colleagues examined the relationship between time to RT initiation and race among 9138 women diagnosed with DCIS between 1996 and 2011 in the Missouri Cancer Registry. While there was no difference in rates of RT usage by race, Black women experienced significant delay in initiation of RT after BCS (8.1 weeks versus 6.3 weeks in White women; odds ratio 1.9, $P < 0.0001$).²⁵ In addition to a delay in RT, Black women also experienced an increased risk of IBTR, though a causal relationship could not be determined.²⁵

Race may also affect risk of disease-specific mortality in women with DCIS. In a SEER-based review of 108,196 women, Narod et al examined breast cancer-specific mortality in patients with first primary DCIS. With a median follow-up of 7.5 years, this study revealed that Black women had a 2.4-fold increased risk of death following a diagnosis of stage 0 breast cancer when compared to White non-Hispanic women ($P < 0.001$), whereas other patient ethnicities included in the analysis (White Hispanic, Asian, other) did not show significantly increased risk.⁷ However, this retrospective study did not examine the association of race with use of or delay in adjuvant therapies.

Other factors may also affect both outcomes and timing to RT. In a study of nearly 25,000 women with invasive breast cancer, of whom more than 13,000 underwent BCS with adjuvant RT, longer time to RT initiation was associated with older age, advanced stage, being unmarried, and increased comorbidities, in addition to Black race.²⁴ Warren et al used a two-year SEER sample of 1103 women with DCIS, of whom 7% had a Charlson comorbidity index of one or more, and found a 62% increased risk of IBTR with the presence of patient comorbidities compared to patients without comorbidities.²⁶ In a study of 1026 women with DCIS by Gold et al, patients with higher comorbidity burden experienced 1.8 times increased odds of experiencing RT delay more than 8 weeks compared to those without the presence of comorbidities.²⁷ Lack of data on race and comorbidities in our study cohort is a limitation, as these factors may influence timely receipt of RT and IBTR.

Another possibility is that the association between delay in RT initiation and increased IBTR risk may be related to a biologic difference in effectiveness of RT at different time points. If the effect of RT after surgery is time-dependent secondary to the inflammatory state and acute changes in the tissue microenvironment postoperatively, then one would expect a difference in therapeutic effectiveness with RT delay.

The major strengths of this study are the large study population and prospectively recorded data with long-term follow-up. Although the follow-up for this cohort ranged up to 30 years, with 311 patients being followed for at least 10 years, additional long-term follow-up is indicated for a disease process with a long-term risk of recurrence. These findings should be generalizable to other populations given that previous MSK studies²⁰ using the same database reveal prognoses and outcomes that closely match those of other American, European, and Asian populations.^{28–32} Furthermore, these data have the advantage of robust clinical data as compared to population-based databases that use coded data. However, this work is subject to the same limitations of all retrospective analyses, including the inability to determine causality versus association.

CONCLUSIONS

Delay in initiation of RT more than 12 weeks following BCS for women with DCIS is associated with a significantly higher risk of IBTR. Future research should aim to understand the reasons for RT delay and to explore whether the relationship between RT delay and IBTR is causal or simply associative. While confounding factors may underlie this

relationship, until a causal relationship can be excluded, efforts should be made to avoid delay in starting RT to minimize risk of recurrence.

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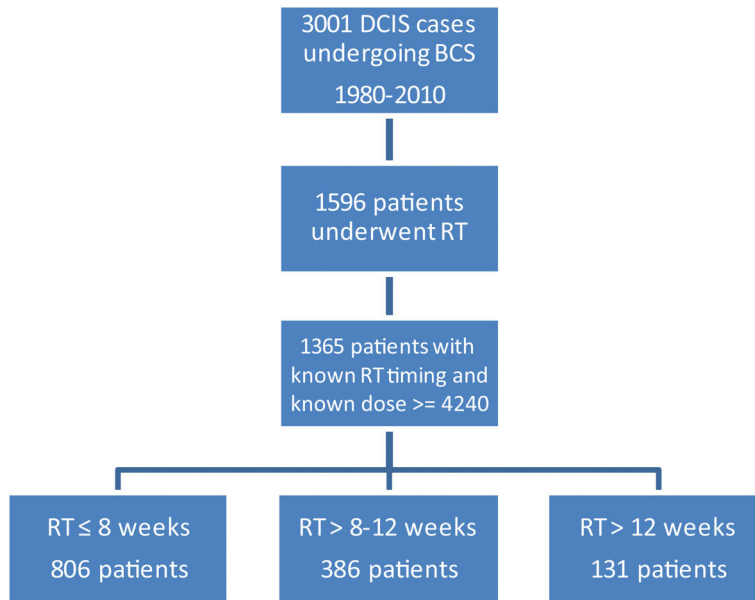


Figure 1. CONSORT Diagram. DCIS, ductal carcinoma in situ; BCS, breast-conserving surgery; RT, radiation therapy

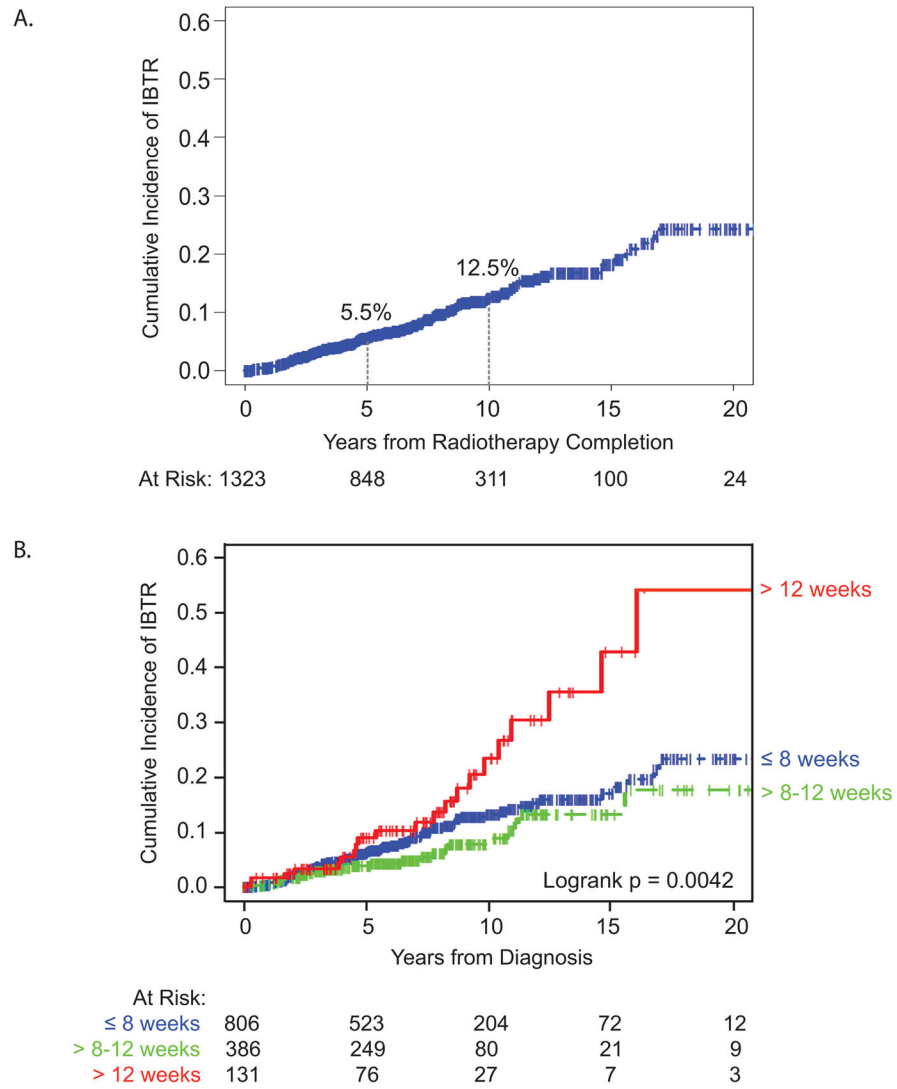


Figure 2. Cumulative incidence of ipsilateral breast tumor recurrence in (A) the overall patient cohort and patient cohort stratified by (B) timing of radiation therapy initiation.

TABLE 1
Clinical Characteristics of Entire Patient Cohort, and Stratified by Radiation Therapy Timing

Characteristic	Entire Population n = 1323		RT 8 weeks n = 806		RT > 8–12 weeks n = 386		RT > 12 weeks n = 131		P value*
	n	%	n	%	n	%	n	%	
Age (years)									<i>P</i> = 0.33
< 50	411	31%	260	32%	117	30%	34	26%	
50	912	69%	546	68%	269	70%	97	74%	
Unknown	0	0%	0	0%	0	0%	0	0%	
Menopausal Status									<i>P</i> = 0.10
Pre/peri	504	38%	325	40%	136	35%	43	33%	
Post	818	62%	480	60%	250	65%	88	67%	
Unknown	1	<1%	1	<1%	0	0%	0	0%	
Family History									<i>P</i> = 0.34
No	808	61%	481	60%	246	64%	81	62%	
Yes	509	39%	323	40%	137	36%	49	38%	
Unknown	6	<1%	2	<1%	3	<1%	1	<1%	
Presentation									<i>P</i> = 0.69
Clinical	140	11%	87	11%	42	11%	11	8%	
Radiologic	1182	89%	718	89%	344	89%	120	92%	
Unknown	1	<1%	1	<1%	0	0%	0	0%	
Nuclear Grade									<i>P</i> = 0.16
Low	106	8%	55	7%	38	10%	13	10%	
Intermediate	570	43%	340	42%	173	45%	57	43%	
High	609	46%	390	48%	164	42%	55	42%	
Unknown	38	3%	21	3%	11	3%	6	5%	
Necrosis									<i>P</i> = 0.05
Absent	295	22%	162	20%	101	26%	32	24%	
Present	1005	76%	632	78%	280	73%	93	71%	
Unknown	23	2%	12	2%	5	<1%	6	5%	

Characteristic	Entire Population n = 1323		RT 8 weeks n = 806		RT > 8–12 weeks n = 386		RT > 12 weeks n = 131		P-value*
	n	%	n	%	n	%	n	%	
Number of Excisions									<i>P</i> = 0.48
2	1182	89%	716	89%	345	89%	121	92%	
3	141	11%	90	11%	41	11%	10	8%	
Unknown	0	0%	0	0%	0	0%	0	0%	
Margins									<i>P</i> = 0.28
Positive/close	276	21%	160	20%	91	24%	25	19%	
Negative	995	75%	616	76%	279	72%	100	76%	
Unknown	52	4%	30	4%	16	4%	6	5%	
Endocrine Therapy									<i>P</i> = 0.07
No	970	73%	576	72%	289	75%	105	80%	
Yes	348	26%	227	28%	96	25%	25	19%	
Unknown	5	<1%	3	<1%	1	<1%	1	1%	
Year of Surgery									<i>P</i> = 0.23
1980–2000	342	26%	216	27%	88	23%	38	29%	
2001–2010	981	74%	590	73%	298	77%	93	71%	
Unknown	0	0%	0	0%	0	0%	0	0%	

Abbreviation: RT, radiation therapy

* Chi-squared analysis based on complete data

Five- and 10-Year Ipsilateral Breast Tumor Recurrence Rate in Entire Population and by Time to Receipt of Radiation

TABLE 2

	Total IBTR events	5-year IBTR rate	95% CI	10-year IBTR rate	95% CI
Entire Population (n = 1365)	126	5.5%	4.3–7.0%	12.5%	10.2–15.2%
RT < 8 weeks (n = 833)	80	5.8%	4.3–7.9%	13.0%	10.2–16.4%
RT > 8–12 weeks (n = 399)	25	3.8%	2.2–6.5%	7.6%	4.7–12.1%
RT > 12 weeks (n = 133)	21	8.8%	4.6–16.4%	23.0%	14.0–36.5%

Abbreviations: IBTR, ipsilateral breast tumor recurrence; CI, confidence interval; RT, radiation therapy

TABLE 3
Univariate Cox Regression Analysis of Time to Ipsilateral Breast Tumor Recurrence

Variable	n	Events (IBTR)	HR	95% CI	P value
Time to Initiation of RT					
8 weeks	806	80	1.00		
> 8 weeks–12 weeks	386	25	0.70	0.45–1.10	0.12
> 12 weeks	131	21	1.82	1.12–2.94	0.015
Menopausal Status					
Pre/peri	504	69	1.00		
Post	818	57	0.50	0.35–0.71	< 0.0001
Family History					
No	808	74	1.00		
Yes	509	51	1.13	0.79–1.62	0.49
Presentation					
Clinical	140	23	1.00		
Radiologic	1182	103	0.63	0.40–0.99	0.048
Nuclear Grade					
Low	106	6	1.00		
Intermediate	570	48	1.61	0.68–3.76	0.27
High	609	62	1.62	0.70–3.74	0.26
Necrosis					
Absent	295	23	1.00		
Present	1005	95	1.25	0.79–1.97	0.34
Number of Excisions					
2	1182	109	1.00		
3	141	17	1.27	0.76–2.11	0.37
Margins					
Positive/close	276	28	1.00		
Negative	995	89	1.08	0.71–0.66	0.71

Variable	n	Events (IBTR)	HR	95% CI	P value
RT dose					
per 100 cGy increase in RT dose			1.00*	1.00–1.00	0.55
Endocrine Therapy					
No	970	107	1.00		
Yes	348	19	0.43	0.26–0.70	0.0007
Year of Surgery					
1980–2000	342	62	1.00		
2001–2010	981	64	0.82	0.56–1.21	0.31

Abbreviations: IBTR, ipsilateral breast tumor recurrence; HR, hazard ratio; CI, confidence interval; RT, radiation therapy

* HR is expressed per 100cGy increase in RT dose

Multivariate Cox Regression Analysis of Time to Ipsilateral Breast Tumor Recurrence*

TABLE 4

Variable	n	Events (IBTR)	HR	95% CI	P value
Time to Initiation of RT					0.015 [†]
8 weeks	790	75	1.00		
> 8 weeks–12 weeks	380	25	0.80	0.51–1.27	0.35
> 12 weeks	124	18	1.92	1.14–3.24	0.014
Menopausal Status					
Pre/peri	494	64	1.00		
Post	800	54	0.54	0.37–0.77	0.0009
Presentation					
Clinical	134	20	1.00		
Radiologic	1160	98	0.68	0.42–1.10	0.12
Necrosis					
Absent	293	23	1.00		
Present	1001	95	1.23	0.77–1.94	0.39
RT dose					
Per 100 cGy			1.01	0.97–104	0.77
Endocrine Therapy					
No	949	100	1.00		
Yes	345	18	0.45	0.27–0.74	0.0018

Abbreviations: IBTR, ipsilateral breast tumor recurrence; HR, hazard ratio; CI, confidence interval; RT, radiation therapy

* The multivariable model included 1294 patients with complete data and 118 IBTR events.

[†]Type III Wald test for overall difference in IBTR event rate across the three RT timing groups.