Is Boost Therapy Necessary in the Treatment of DCIS with Breast-Conserving Therapy?

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ABSTRACT

Background: Whole-breast irradiation (WBI) therapy following lumpectomy for invasive breast cancer (IBC) and noninvasive breast cancer (DCIS) significantly reduces the risk of local recurrence. Boost radiotherapy (RT) to the tumor bed has been proven to additionally lower the risk of recurrence for IBC. The benefit of boost RT in patients with DCIS is less certain. Because of concerns regarding the optimal treatment of DCIS, we undertook a review of the results of NSABP trial B-24 to assess the benefit of boost therapy.

Methods: Following lumpectomy and RT, 1,804 women with DCIS were randomly assigned in NSABP B-24 to placebo (902) or tamoxifen (902). WBI (50 Gy) was mandatory. Boost RT was optional. 1,392 patients (86.97%) were identified as having all data sufficient for analysis. Of these, 613 received boost RT ranging from 1 Gy to 20 Gy, with 81.5% receiving 10 Gy. Mean time of follow-up was 161 months.

Results: Patients who underwent boost RT were more likely to be younger ($p=0.04$), to have positive margins ($p=0.007$), and to have comedo necrosis ($p=0.03$). Treatment (HR=0.74, $p=0.03$), age (HR=0.47, $p<0.0001$), and margin status (HR: 1.79, $p<0.001$) were significant predictors for ipsilateral breast tumor recurrence (IBTR). Boost had no significant effect on IBTR (HR=0.87, $p=0.33$). The lack of boost effect was true for both invasive (HR=0.86, $p=0.44$) and noninvasive IBTR (HR=0.89, $p=0.56$).

Conclusions: In NSABP B-24, the addition of boost RT was not found to be of value in reducing IBTR of invasive or noninvasive breast cancers for patients with DCIS.

INTRODUCTION

The incidence of clinically occult ductal carcinoma in situ (DCIS) has increased over the past decades, now representing nearly 25% of all new breast cancers. (1) Traditionally, mastectomy was employed as the standard of care, providing excellent local control and survival rates. For various reasons, the adoption of breast-conserving therapy (BCT) for DCIS lagged behind its use in invasive breast cancer (IBC). However, in the mid-1980's, data from single institution nonrandomized prospective studies emerged indicating that local control was satisfactory after BCT for DCIS and that breast cancer-specific mortality was equivalent to treatment by mastectomy.(2)

In 1985, the NSABP initiated a groundbreaking prospective randomized trial - - NSABP B-17 (3) - - comparing lumpectomy to lumpectomy plus breast irradiation in patients with DCIS, the results of which reported that women treated by breast irradiation after lumpectomy had 60% (RR 0.40) lower in-breast failures than those treated by lumpectomy alone. Subsequent updates continue to demonstrate benefit for lumpectomy with radiotherapy verses lumpectomy alone. Following the B-17 trial, a second trial - - NSABP B-24 - - investigated the addition of tamoxifen to radiotherapy (4). Both initial results and long term data on B-24 showed that women treated by tamoxifen in addition to radiotherapy experienced 23% fewer ipsilateral breast tumor recurrence (IBTR)s, as well as statistically fewer contralateral breast tumors. (4,5)

In those analyses, IBTRs were the most common failure events, representing >90% of breast cancer recurrence events.

Both trials identified a number of variables associated with increased risk for IBTR, which have been helpful in refining and optimizing the use of BCT in these patients. Several variables analyzed included margin status, patient age, method of detection, and use of tamoxifen (5,6). With earlier detection and improved surgical disease clearance through contemporary radiographic, surgical, and pathologic practices, questions about post-lumpectomy radiotherapy reduction (both target size and/or length of treatment), and elimination of radiotherapy in selected patients have emerged. Consistent with this, the value of a boost dose to the surgical bed following whole-breast irradiation (WBI) for DCIS has been questioned. Despite phase III data demonstrating that boost radiotherapy to the tumor bed with BCT lowers risk of IBTR for IBC, the benefit of a boost in patients with DCIS is less certain (7). Recent research has focused on the identification of clinical factors and biological markers to define the optimal treatment of DCIS, particularly because of concerns for the over-diagnosis and over-treatment of this entity (8). The benefit of boost therapy in protocol B-24 was reviewed to help address the latter issues.

METHODS

NSABP B-24 Randomized Clinical Trial for DCIS

Descriptions of the B-24 study design, patient eligibility, and treatment are detailed in the literature (4). All patients signed informed consent before random assignment, and the trial was approved by Institutional Review Boards. B-24 opened 5-9-91, and closed 4-13-94 after 1,804 patients were enrolled. Patients underwent lumpectomy plus breast radiotherapy and were randomly assigned (double-blind) to receive either five years of tamoxifen or placebo. Axillary dissections were excluded. Radiotherapy had to begin within 8 weeks of definitive surgery and encompassed the whole breast to a dose of 50 Gy given at 10 Gy per week, excluding nodal basins. A boost to the lumpectomy site was allowed and recorded in 38.5%.

Of the 1,804 patients, follow-up information was available for 1,799. Boost status was determined for 1,569, 177 of whom had missing values for margin status and/or comedo necrosis, leaving 1,392 with adequate data for multivariate analyses of recurrences (613 with boost and 779 without boost). These patients constitute the study population.

Follow-up exams were conducted semi-annually, with mammography performed annually. Local or regional tumor recurrences were defined as events when proven by biopsy. Distant failure events were confirmed by clinical, radiographic, or pathologic findings. Second primary cancers were also verified by central medical review, as were deaths without evidence of recurrence or second primary cancer.

Statistical Methods

Primary endpoint was event-free survival, defined as time from surgery free of recurrence at any site (IBTR, other local, regional, distant), second primary cancer (including contralateral breast tumors), or death. Although these endpoints were the focus of earlier reports, IBTR is the primary event of interest for this report. All analyses are based on time to IBTR as a first failure event.

Cox proportional hazards regression models were used to analyze the effect of boost on three outcomes including IBTR, noninvasive IBTR, and invasive IBTR. These analyses were performed to determine any benefit of boost while controlling for treatment, age, margin status, comedo necrosis, and possible interactions among these parameters and boost. Hazard ratios (HR) and 95% confidence intervals (CI) were obtained comparing those who got boosts to those who did not get boosts. Chi-square tests compared patient characteristics between those who received or did not receive a boost. Cumulative incidence curves adjusted for competing risks assessed the effect of boost while controlling for treatment, age, and margin status via stratified estimates (9,10).

Findings reflect information reported to the NSABP Biostatistical Center through 5-1-07, at which time follow-up was discontinued. The median time from random assignment to last follow-up for patients included in this report was 161 months.

RESULTS

Distribution of Patient and Disease Characteristics

Patient and tumor characteristics based on boost use are detailed in **Table 1**. Overall, two-thirds of the women were ≥50 years and ~86% were white. Cancers were detected by mammogram in >80%. Most cancers measured ≤1cm (84%). Approximately 25% of lumpectomy margins were reported as either involved or of unknown status, and ~47% of tumors showed presence of comedo necrosis. Boost status was unknown for 230 patients. These patients were comparable on most characteristics to those for whom boost status was known. There were no statistically significant differences in the distribution by treatment, age, margin status, or comedo necrosis (data not shown). There were more blacks in the unknown boost status group (10.4% versus 6.4%, p=0.01) and fewer with unknown status had tumors ≤1 cm (79.1% versus 84.5%, p=0.005).

When comparing patients who did receive a boost to those who did not, there were no statistically significant differences in the distribution of patients by treatment group, race, or tumor size. However, there were statistically significant differences among boost status groups by age, margin status, and comedo necrosis.

Of patients <50 years, 36.4% received a boost and 31.5% received no boost (p=0.04). Those who received a boost more frequently had involved margins (18.9 versus 13.2%, p=0.007) and comedo necrosis (51.0 versus 44.4%, p=0.03).

Table 2 shows the distribution of 1,392 patients with known values for all variables noted in the table, and provides the number at risk and the number of events for all IBTR, invasive IBTR, and noninvasive IBTRs for each category. Overall, there were 208 IBTRs, with 117 occurring in those who did not receive a boost and 91 in those who did; 108 were invasive disease and 100 were noninvasive disease. Of the invasive IBTR cases, 46 with recurrence had received a boost and 62 had not. Of the 100 patients who did develop non-invasive disease, 45 had received a boost, and 55 had not received boost.

Events and Impact of Boost Therapy

Table 3 provides results from multivariable proportional hazards regression modeling, assessing effect of boost on time to all IBTR, and time to invasive and noninvasive IBTRs separately. When adjusting for treatment group (tamoxifen or placebo) and for the three variables showing statistical significance in **Table 1** (age, margin status, and comedo necrosis), the use of boost had no statistically significant effect on any of these IBTR endpoints. The adjusted HRs comparing boost to no boost were 0.87 (p=0.33, CI=0.87-0.66) for overall IBTR, 0.86 (p=0.44, CI=0.58-1.27) for invasive IBTR, and 0.89 (p=0.56, CI=0.60-1.33) for noninvasive IBTR. We also assessed for statistical interactions among boost, treatment, age, margin status, and comedo necrosis (data not shown). None of the interactions showed statistically significant evidence that boost had an effect on risk of IBTR for any subset of patients based on these variables. Factors that were statistically associated with overall IBTR included treatment (HR=0.74, p=0.034, CI=0.57-0.98), age (HR=0.47, p<0.0001, CI=0.36-0.61), and margin status (HR= 1.79, p<0.001, CI=1.31-2.43). When assessing invasive and noninvasive IBTRs separately, age (HR=0.53, p=0.001, CI=0.36-0.78) and margin status (HR=2.36, p<0.0001, CI=1.56-3.57) were factors associated with invasive IBTR, and age (HR=0.40, p<0.0001, CI=0.27-0.59) and comedo necrosis (HR=2.26, p<0.001, CI=1.47-3.47) were associated with noninvasive IBTR.

To further illustrate the absence of boost effect, **Figures 1, 2, and 3** provide a comparison of cumulative incidence curves for IBTR (invasive and noninvasive combined) while controlling for treatment group, margin status, and age. Despite small numbers of events in some of the subsets, there is no suggestion of a boost effect.

DISCUSSION

WBI therapy following lumpectomy for IBC and DCIS has been shown to significantly reduce risk of IBTR in multiple, prospective randomized trials (11-14) and in a recent meta-analysis (7). Boost radiotherapy has also been shown to additionally lower risk of recurrence for IBC, but its benefit in patients with DCIS is less certain (15). In our analysis, we reviewed NSABP B-24 to assess the benefit of boost radiotherapy. Boost had no statistically significant effect on risk of overall IBTR (HR=0.87, p=0.33). When assessed separately, boost also had no statistically significant effect on risk of invasive IBTR (HR=0.86, p=0.44) or noninvasive IBTR (HR=0.89, p=0.56). Factors that were statistically significant association with overall IBTR included tamoxifen treatment (HR=0.74, p=0.034), age (HR=0.47, p<0.0001), and margin status (HR=1.79, p<0.001). Comedo necrosis resulted in a borderline statistical significance (HR=1.29, p=0.07). The effects of these factors have been noted as significant in previous analyses (1,10). Although tamoxifen treatment showed a statistically significant association for overall IBTR, treatment was not significant in the separate analyses of invasive or noninvasive IBTRs. Of note, the point estimates of HRs for treatment effect of 0.70 and 0.79 are similar to that for overall IBTR (HR=0.74) and the analyses based on subsets by type of IBTR would provide reduced statistical power for detecting effects as statistically significant.

Factors Associated with IBTR with BCT

Four prospective randomized trials have demonstrated the importance of WBI after lumpectomy in patients with DCIS. These include NSABP B-17 (3); the European Organization for Research and Treatment of Cancer (EORTC) 10853 (14); the United Kingdom Coordinating Committee on Cancer Research (UKCCCR) DCIS (13,14); and the Swedish multi-center (SweDCIS) (15). All four studies found that RT substantially reduced risk of local recurrence (LR). A recent meta-analysis of these trials showed that RT reduced risk of IBTR by ~60% (7). More recently, the RTOG 9804, a randomized trial of RT in low-risk DCIS patients, identified benefit from radiotherapy without boost as well (16). Although the RTOG phase III trial did not complete accrual, interesting findings have been reported. The 9804 trial compares postoperative radiotherapy to observation following lumpectomy for mammographically-detected DCIS of low or intermediate nuclear grade, <2.5cm size, and surgical margins of ≥3mm. Of the planned 1,790 patients, 636 were randomly assigned to one of two groups. The 5-year in-breast failure was 0.4% in the radiotherapy arm and was 3.2% in the observation arm (p=0.0023). These data suggest that a subgroup of patients diagnosed with low-risk DCIS can be identified who would be managed appropriately without boost with it being unlikely that a boost would improve upon the recurrence rate of 0.4%; although longer follow-up will be helpful, the reported outcomes should begin to influence treatment recommendations.

In addition to radiotherapy use after lumpectomy, multiple prospective studies (17,18) and numerous retrospective analyses (19-22) have attempted to identify other patient, tumor, and treatment-related factors associated with IBTR in patients with invasive or noninvasive disease. Results from those studies have provided useful information, suggesting that patient age, method of detection, lumpectomy margin status (e.g., adequacy of excision), tumor grade, presence of necrosis, and use of tamoxifen may be related to optimal tumor control rates with BCT. The total radiotherapy dose has also been shown to improve outcomes in patients with IBC, particularly in younger patients or in those with close/involved margins (17).

Lumpectomy-Only for DCIS

With improvements in early detection of DCIS, and with improved surgical techniques coupled with complete pathologic evaluations, we again face the question of the benefit of post-lumpectomy irradiation and whether it could be avoided in selected women with DCIS.

A recent report suggests that in older women with small, grade 1-2 DCIS, resected with a negative pathologic margin of >2-3mm, post-op radiotherapy may be avoided. The ECOG study E5194 (23), latest results of which were published in 2009, allowed registration of selected patients with DCIS to be followed prospectively following lumpectomy with a negative margin of ≥3mm. Breast radiotherapy was not delivered, and tamoxifen was optional. Eligible patients had G1-G2 DCIS of tumor sizes up to 2.5cm or G3 DCIS with tumor sizes up to 1.0cm. Grade was found to be an important factor regarding in-breast failure. The in-breast rate of failure for patients with G1-G2 DCIS treated with lumpectomy only was reported as 10.8% at 7 years. The 7-year rate for G3 disease was 18.0%.

Data on the Use of Boost with BCT

Despite evidence suggesting postoperative radiotherapy can be omitted in a select group, (23) there continues to be a large group for whom postoperative radiotherapy is recommended to obtain optimal in-breast control. In this group, the amount of radiotherapy needed to be successful (i.e., whether or not to include a boost), has not been clearly determined. Although three separate prospective randomized trials (24,25,26) have demonstrated the importance of a boost (e.g., increased dose) to improve local control in patients with IBC treated with BCT, there have been no completed phase III trials exploring use of boost with DCIS. As a result, the efficacy of this supplemental dose of radiotherapy directed to the tumor bed has been estimated from numerous small and uncontrolled trials from multiple institutions (**Table 4**) (18-21, 27-30) or extrapolated from results of treatment in patients with IBC.

Meattini et al. (31) reviewed their experience in DCIS treatment, focusing on prognostic factors and the impact of boost on LR. After a follow-up of 7.7 years, in a multivariate analysis, they showed a negative prognostic effect of surgical margins <1mm and the protective role of radiotherapy boost on LR. Side effects of boost radiotherapy were not assessed. In 2009 Poortmans et al. (32) reported cosmetic results after boost radiotherapy and showed that the development of fibrosis was significantly dependent on boost dose, with a 10-year rate for severe fibrosis of 1.6% after 0 Gy, 3.3% after 10 Gy, 4.4% after 16 Gy, and 14.4% after 26 Gy. Of note, the majority of patients (77.9%) were >50 years. As demonstrated in a previous study (13), one predictive factor for LR is age, with younger patients having a higher risk of IBTR with DCIS or invasive cancer.

The largest retrospective study addressing this issue was reported by Omlin et al., (27) but only in younger patients. The authors studied 373 patients from 18 institutions by the Rare Cancer Network. All patients were <45 years (median, 41) and were treated with BCT (57 no radiotherapy, 166 with radiotherapy but no boost, and 150 with radiotherapy and a boost [median dose, 60 Gy]). With a median follow-up of 72 months, the 10-year rate of IBTR was 54% without radiotherapy, 28% with radiotherapy (no boost), and 14% with radiotherapy and a boost ($p<0.0001$). Age, margin status, and dose were significant predictors of IBTR. However, there were statistically significant differences in the baseline characteristics of boost versus no boost patients, including method of detection, tumor size, grade, margin status, and receptor status, and in many patients, these characteristics were simply unknown. These differences were especially high for the boost group, 49% of whom had absent tumor size; 35%, no grade assessment; and

35%, no details on margin status. Finally, in a proportional hazards analysis, a statistically significant difference in HRs of 0.33 for radiotherapy without a boost versus 0.15 for radiotherapy with a boost was shown. Unfortunately, the authors did not state in what form the unknown data were included in the proportional hazards analysis, or whether testing variables for proportionality before using "unknown" as a value for every variable analyzed.

Rakovitch et al, (33) recently report that the cumulative 10-year rate of LR was 13% for women who underwent boost radiotherapy and 12% for those who had not (P=.3). For these two groups, the 10-year LR-free survival (LRFS) rates were 88% and 87%, respectively (P=.27); 94% and 93% for invasive LRFS (P=.58); and 95% and 93% for DCIS LRFS (P=.31). Multivariable analyses showed that boost radiotherapy was not associated with lower risk of LR (HR=0.82).

Other uncontrolled, retrospective studies investigating usage of boost in patients with DCIS treated with BCT have reported very inconsistent results (**Table 4**). Limitations to those studies include: (1) small patient numbers and few IBTRs (e.g., limited statistical power); (2) uncontrolled, unknown, or variable competing risk factors for IBTR between boost versus no-boost patients; (3) limited follow-up; (4) no centralized pathologic analysis; and (5) substantial differences in management techniques utilized over extended periods of time (e.g., duration of each trial). As discussed, the rationale for this additional dose of radiotherapy is the potential reduction in risk of IBTR. In patients with IBC, a recent meta-analysis (34) has suggested that there is also a potential survival advantage with the addition of radiotherapy after lumpectomy. Late tissue toxicities (breast fibrosis) are clearly increased with additional dose of radiotherapy, partially offsetting the small improvements in survival gained for the patient. Breast cancer mortality rates after DCIS are extremely low (even with salvage surgery after invasive IBTR), suggesting that additional tissue toxicities that occur with a boost dose to the tumor bed may not be justified. (35) Of note, tissue toxicity data was not collected in this study and therefore we cannot meaningfully comment on these long-term effects.

Objective Review of the Current Analysis

To our knowledge, NSABP B-24 the largest controlled study in patients with DCIS treated with BCT (with the longest follow-up) where a nearly equal percentage of patients with similar pre-treatment characteristics did or did not receive boost therapy. Despite the fact that boost treatment was not used as a stratification factor, we believe these results are meaningful. Analyses were performed while controlling for known risk factors for IBTR in patients with DCIS treated with BCT (e.g., age, margin status, comedo necrosis, and treatment), and interactions among all of these variables were investigated. We were unable to demonstrate that use of boost lowerd IBTR rates. There were also no statistically significant interactions among boost, treatment, age, or margin status, indicating that the boost did not impact IBTR for subsets of patients based on any combination of these variables.

The ongoing TROG 07.01 phase III trial (36) is assessing radiotherapy doses and fractionation schedules with or without boost in medium/high risk DCIS. Its primary endpoint is to evaluate time to LR in women with DCIS treated with BCT followed by WBI alone versus WBI plus boost, as well as differences in the standard fractionation schedule versus the shorter schedule. Cosmetic results and quality of life are also being evaluated. That study, as well as the ongoing BONBIS trial (37) may provide additional information, helping to confirm or negate our findings from the NSABP B-24 trial. Additionally, the results of NSABP B-39 may shed further light on local toxicities and local recurrence rates using accelerated partial breast irradiation.

Currently, the need for personalizing the treatment of DCIS for each individual patient is at hand. To better identify subtypes of DCIS requiring radiotherapy with or without boost or without radiotherapy is necessary. This has, in part, led to the development of the Onco*type* DCIS Score (38). Although the information the score provides may be useful, it is not a definitive guide for the treatment of DCIS and further validation is warranted before it can be incorporated into clinical practice. Boost in the treatment of DCIS is still an evolving idea, which may prove useful in the management of DCIS subtypes yet to be defined.

CONCLUSIONS

The addition of radiotherapy in the management of DCIS treated with BCT provides significant reduction in risk of recurrence of invasive and noninvasive disease, particularly in younger patients with an initial diagnosis of DCIS. However, in NSABP B-24, the addition of boost radiotherapy was not found to be valuable in reducing IBTR overall, nor for reducing invasive or noninvasive IBTR for any subset of patients initially diagnosed with DCIS. Until phase III data addressing the impact of a boost in patients with DCIS are available, we advise selective use of any supplemental dose of radiotherapy to the tumor bed.

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Table 1. Distribution of patients by treatment, age, race, tumor characteristics, margin status, comedo necrosis, and use of boost: NSABP B-24

Characteristics	All Patients w/follow-up	Boost	No boost	Chi-Square *P***
Number of Patients	1799*	692	877	
Treatment				
Placebo	900 (50.0%)	342 (49.4%)	434 (49.5%)	0.98
Tamoxifen	899 (50.0%)	350 (50.6%)	443 (50.5%)	
Age				
≤49	601 (33.4%)	252 (36.4%)	276 (31.5%)	0.04
≥50	1198 (66.6%)	440 (63.6%)	601 (68.5%)	
Race				
White	1541 (85.7%)	607 (87.7%)	752 (85.8%)	0.19
Black	125 (7.0%)	46 (6.7%)	55 (6.3%)	
Other/Unknown	133 (7.4%)	39 (5.6%)	70 (8.0%)	
Tumor size				
≤1.0cm	1508 (83.8%)	586 (84.7%)	740 (84.4%)	0.54
1.0-2.0cm	187 (10.4%)	65 (9.4%)	96 (11.0%)	
≥2.1cm	78 (4.3%)	33 (4.8%)	32 (3.7%)	
Unknown	26 (1.4%)	8 (1.2%)	9 (1.0%)	
Margin status				
Free	1346 (74.8%)	494 (71.4%)	678 (77.3%)	0.007
Involved	284 (15.8%)	131 (18.9%)	116 (13.2%)	
Unknown	169 (9.4%)	67 (9.7%)	83 (9.5%)	
Comedo necrosis				
Absent	916 (50.9%)	324 (46.8%)	470 (53.6%)	0.03
Present	847 (47.1%)	353 (51.0%)	389 (44.4%)	
Unknown	36 (2.0%)	15 (2.2%)	18 (2.1%)	

*Boost status was unknown for 230 patients.
**P-value for comparing difference between the distribution for those with and without boost.

Table 2. Number of events by cross-classification of treatment, age, margin status, comedo necrosis, and boost for patients included in multivariate modeling: NSABP B-24

Variable Categories	Number at Risk	Number of Events		
		IBTR	Invasive IBTR	Non-Invasive IBTR
Treatment				
Placebo	695	116	61	55
Tamoxifen	697	92	47	45
Age				
≤49	463	107	51	56
≥50	929	101	57	44
Boost				
No-Boost	779	117	62	55
Boost	613	91	46	45
Margin status				
Free	1151	150	74	76
Involved	241	58	34	24
Comedo necrosis				
Absent	717	90	59	31
Present	675	118	49	69
Age, Margin Status, Comedo Necrosis, Boost				
≤49, Free: Absent, No Boost	111	18	8	10
Boost	77	12	9	3
Present, No Boost	89	24	8	16
Boost	90	25	8	17
≤49, Involved: Absent, No Boost	13	3	3	0
Boost	16	4	2	2
Present, No Boost	24	11	7	4
Boost	43	10	6	4
≥50, Free: Absent, No Boost	258	24	18	6
Boost	171	11	7	4
Present, No Boost	208	21	10	11
Boost	147	15	6	9
≥50, Involved: Absent: No Boost	42	7	5	2
Boost	29	11	7	4
Present, No Boost	34	9	3	6
Boost	40	3	1	2
Total	1392	208	108	100

Table 3.
Results of multivariable proportional hazards regression modeling to assess the effect of boost on IBTR when adjusting for treatment, age, margin status, and comedo necrosis: NSABP B-24

	Hazard Ratio (95% CI)			***P* Value**		
	IBTR	**Invasive IBTR**	**Non-invasive IBTR**	**IBTR**	**Invasive IBTR**	**Non-invasive IBTR**
Boost (Boost versus No Boost)	0.87 (0.66-1.15)	0.86 (0.58-1.27)	0.89 (0.60-1.33)	0.33	0.44	0.56
Treatment (Tamoxifen versus Placebo)	0.74 (0.57-0.98)	0.70 (0.48-1.03	0.79 (0.53-1.17)	0.034	0.07	0.23
Age (≥50 versus ≤49)	0.47 (0.36-0.61)	0.53 (0.36-0.78)	0.40 (0.27-0.59)	<0.0001	0.001	<0.0001
Margin status (Involved versus Free)	1.79 (1.31-2.43)	2.36 (1.56-3.57)	1.30 (0.82-2.08)	<0.001	<0.0001	0.27
Comedo Necrosis (Present versus Absent)	1.29 (0.98-1.71)	0.80 (0.54-1.17)	2.26 (1.47-3.47)	0.07	0.25	<0.001

Table 4. Published data on the use of a boost with DCIS

Series	Total pts	Median age (yrs)	Boost pts	Follow-up (Months)	Impact of boost
Current Analysis (NSABP B-24)	1799	NA	692	169.8	No effect
Israel (19)	104	NA	NA	52	No effect
British Columbia (20)	957	57	144 (yes) 338 (no)	111	No effect
Israel (21)	75	58	26 (yes) 49 (no)	81.5	No effect
Rare Cancer Network (27)	373 (Only <45 yrs)	41	150 (yes) 166 (no)	72	Yes (□ IBTR)
William Beaumont Hospital (28)	313	63	298 (yes) 15 (no)	84	No effect
UCLA (29)	38	55	20 (yes) 18 (no)	100	No effect
Hungary (18)	235 Phase III	NA	High-risk pts n= boosted	36	NA
Hong Kong (30)	75	47.5	50 (yes) 25 (no)	62	No effect

IBTR=Ipsilateral breast tumor recurrence.

Figure Legends

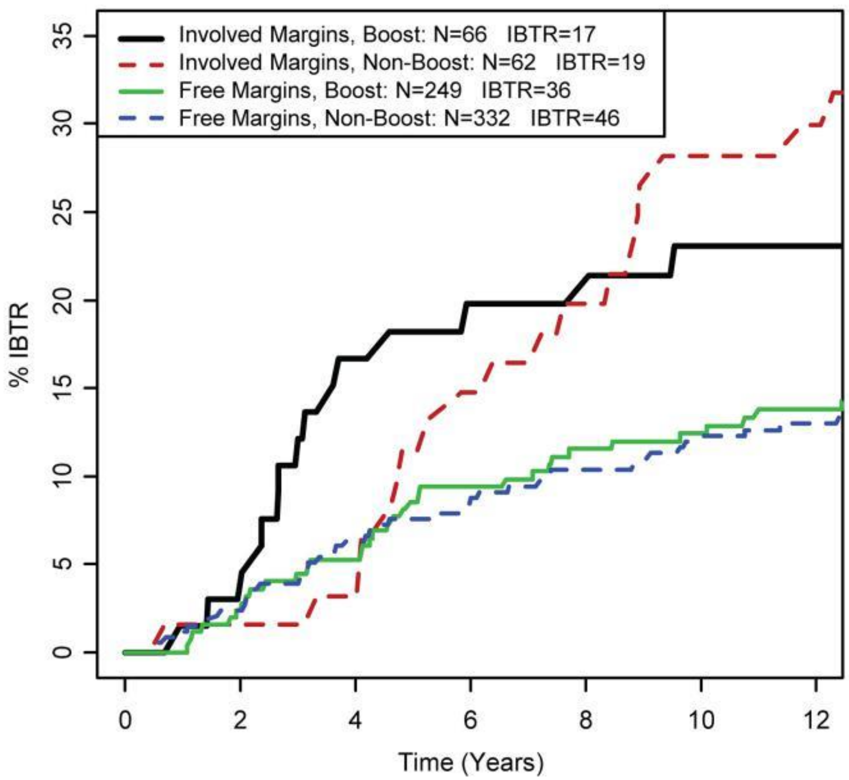
Figure 1. NSABP Protocol B-24: Cumulative incidence of IBTR over time, all patients
Panel A. Placebo Patients **Panel B.** Tamoxifen Patients

Figure 2. NSABP Protocol B-24: Cumulative incidence of IBTR over time for patients ≤49 years
Panel A. Placebo Patients **Panel B.** Tamoxifen Patients

Figure 3. NSABP Protocol B-24: Cumulative incidence of IBTR over time for patients ≥50 years
Panel A. Placebo Patients **Panel B.** Tamoxifen Patients

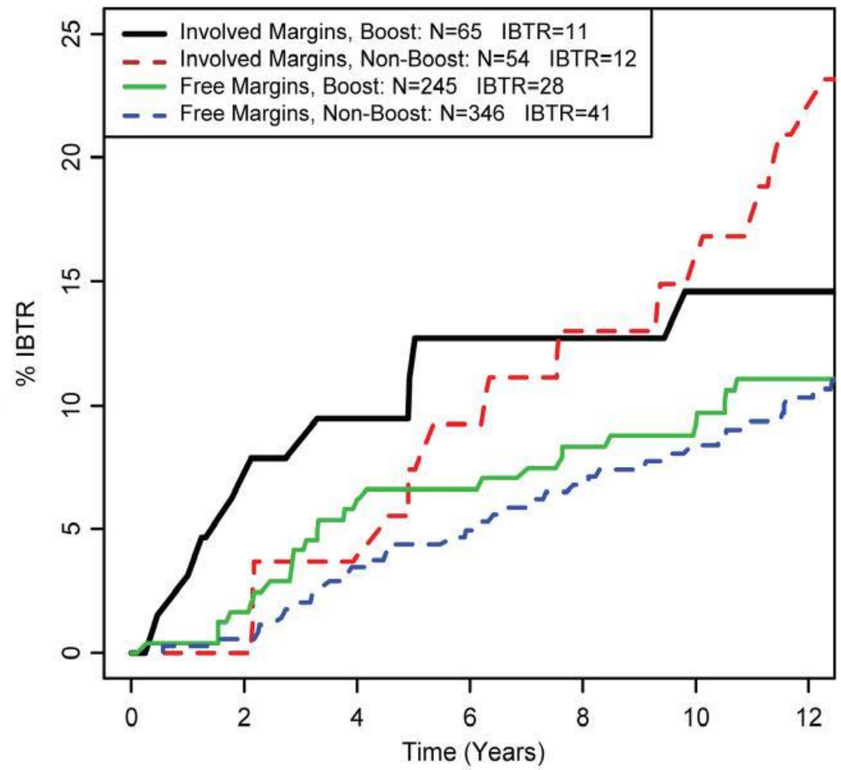
Figure 1. NSABP Protocol B-24: Cumulative incidence of IBTR over time, all patients

Panel A. Placebo Patients



Comparison	*P*
Comparing Boost for Margin Status= Involved	0.93
Comparing Boost for Margin Status= Free	0.81

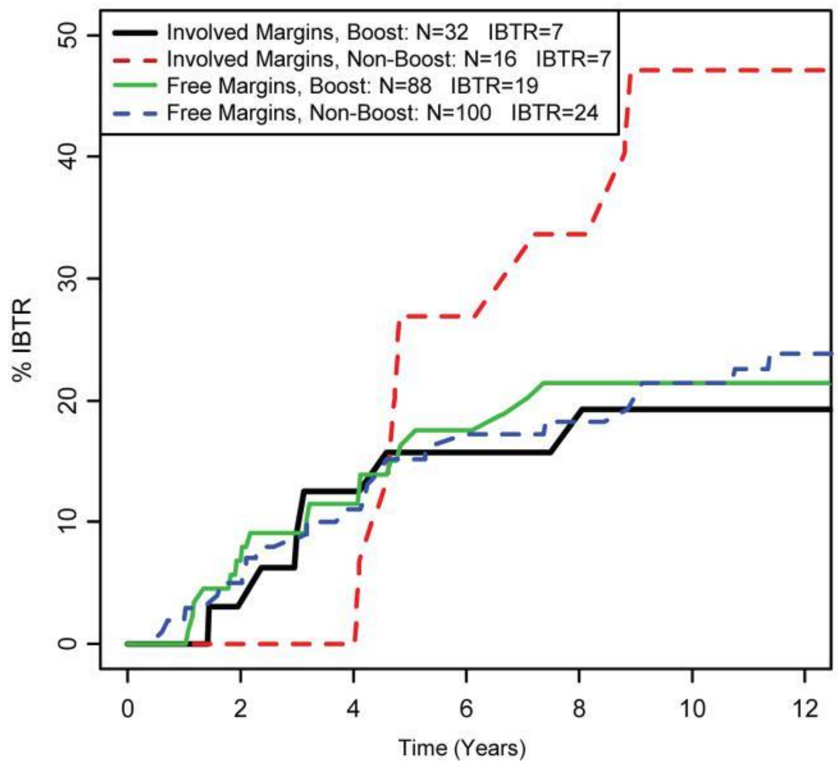
Panel B. Tamoxifen Patients



Comparison	*P*
Comparing Boost for Margin Status= Involved	0.86
Comparing Boost for Margin Status= Free	0.66

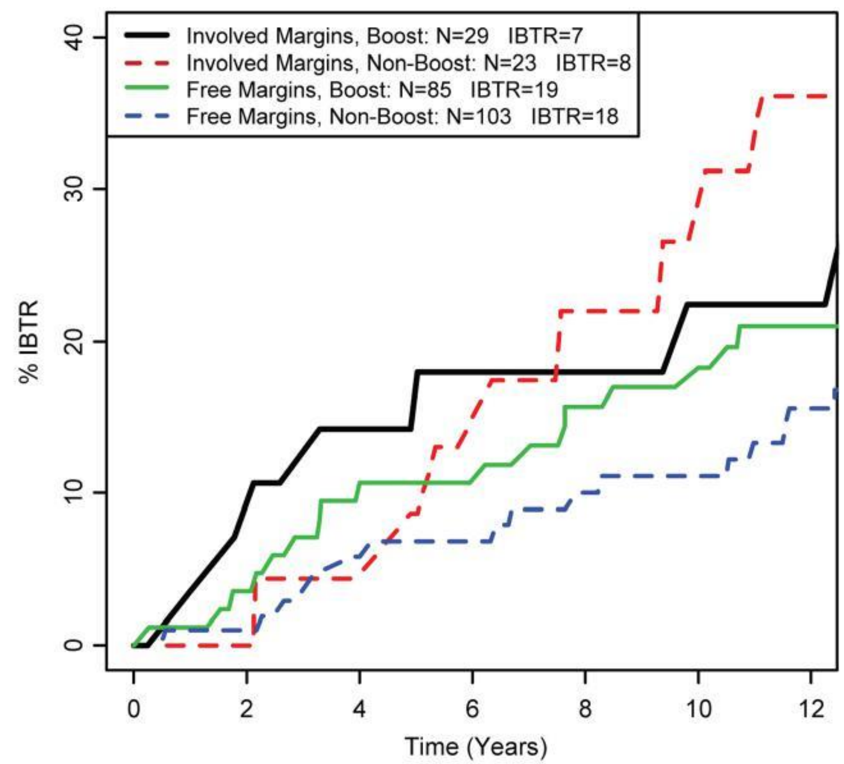
Figure 2. NSABP Protocol B-24: Cumulative incidence of IBTR over time for patients ≤49 years

Panel A. Placebo Patients



Comparison	*P*
Comparing Boost for Margin Status= Involved	0.24
Comparing Boost for Margin Status= Free	0.97

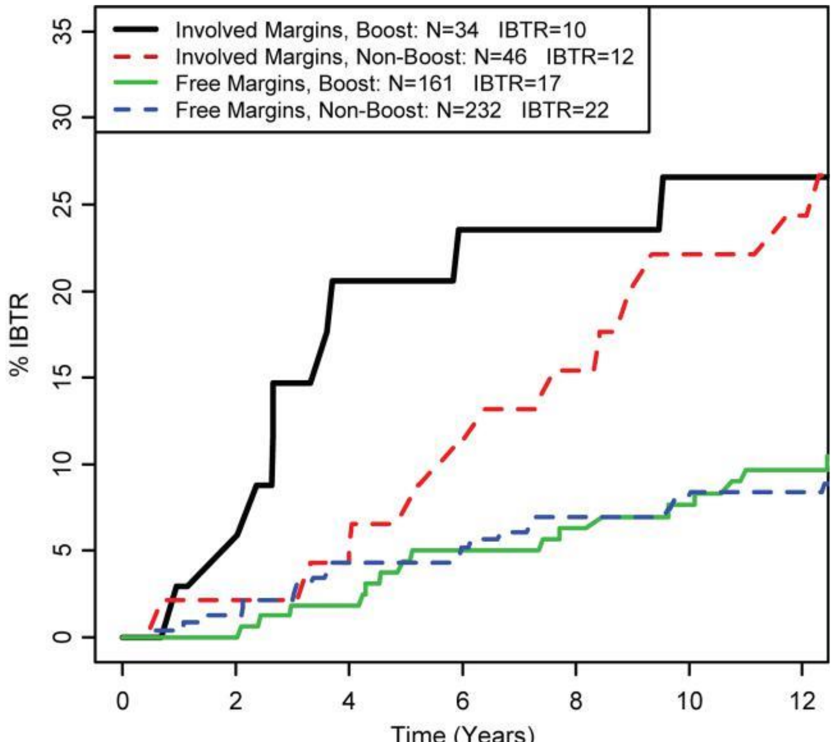
Panel B. Tamoxifen Patients



Comparison	*P*
Comparing Boost for Margin Status= Involved	0.83
Comparing Boost for Margin Status= Free	0.27

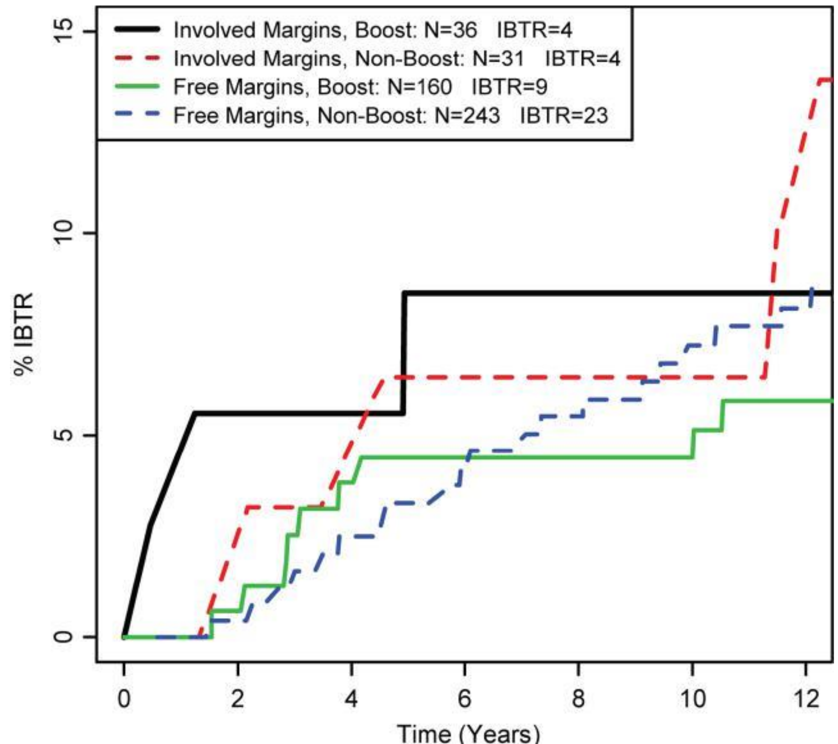
Figure 3. NSABP Protocol B-24: Cumulative incidence of IBTR over time for patients ≥50 years

Panel A. Placebo Patients



Comparison	*P*
Comparing Boost for Margin Status= Involved	0.51
Comparing Boost for Margin Status= Free	0.97

Panel B. Tamoxifen Patients



Comparison	*P*
Comparing Boost for Margin Status= Involved	0.97
Comparing Boost for Margin Status= Free	0.41