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Research Letter

Locoregional Control Benefit of a Tumor Bed Boost for Ductal Carcinoma In Situ

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Purpose: Radiation therapy (RT) after breast-conserving surgery (BCS) for ductal carcinoma in situ (DCIS) reduces invasive and in situ recurrences. Whereas landmark studies suggest that a tumor bed boost improves local control for invasive breast cancer, the benefit in DCIS remains less certain. We evaluated outcomes of patients with DCIS treated with or without a boost.

Methods and Materials: The study cohort comprised patients with DCIS who underwent BCS at our institution from 2004 to 2018. Clinicopathologic features, treatment parameters, and outcomes were ascertained from medical records. Patient and tumor characteristics were evaluated relative to outcomes using univariable and multivariable Cox models. Recurrence-free survival (RFS) estimates were generated using the Kaplan-Meier method.

Results: We identified 1675 patients who underwent BCS for DCIS (median age, 56 years; interquartile range, 49-64 years). Boost RT was used in 1146 cases (68%) and hormone therapy in 536 (32%). At a median follow-up of 4.2 years (interquartile range, 1.4-7.0 years), we observed 61 locoregional recurrence events (56 local, 5 regional) and 21 deaths. Univariable logistic regression demonstrated that boost RT was more common among younger patients ($P < .001$) with positive or close margins ($P < .001$) and with larger tumors ($P < .001$) of higher grade ($P = .025$). The 10-year RFS rate was 88.8% among those receiving a boost and 84.3% among those without a boost ($P = .3$), and neither univariable nor multivariable analyses revealed an association between boost RT and locoregional recurrence.

Conclusions: Among patients with DCIS who underwent BCS, use of a tumor bed boost was not associated with locoregional recurrence or RFS. Despite a preponderance of adverse features among the boost cohort, outcomes were similar to those of patients not receiving a boost, suggesting that a boost may mitigate risk of recurrence among patients with high-risk features. Ongoing studies will elucidate the extent to which a tumor bed boost influences disease control rates.

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Introduction

The incidence of ductal carcinoma in situ (DCIS) has risen from 5.8 per 100,000 women in the 1970s to approximately 30 per 100,000 in the current era, partly owing to

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improvements in screening.[1,2] Breast conservation has long been a suitable treatment for DCIS, with the benefit of adjuvant radiation therapy (RT) exceeding a 50% to 60% relative improvement in local control across several landmark trials.[3-6] Building upon these studies, several investigators have questioned the more nuanced technical consideration of whether a tumor bed boost should be routinely administered in addition to whole-breast RT.

Boost RT is a common technique across an array of malignancies and typically involves administering additional RT dose to a limited portion of the overall treatment volume, thereby increasing the total dose to higher-risk targets (ie, the resected tumor bed). This can be done either sequentially or concurrently with the primary RT treatment course. The differential dosing between high-risk, or boost, regions and baseline-risk, or nonboost, regions is designed to improve tumor cell eradication in areas most likely to harbor a higher burden of disease while sparing the anticipated toxicity of high-dose treatment to the remainder of the at-risk target (ie, breast tissue distal to the tumor bed in the case of adjuvant breast RT).

The use of boost RT in breast cancer was cemented by a major study randomizing patients with early-stage invasive disease to boost versus no boost after breast-conserving surgery (BCS) and whole-breast RT, ultimately demonstrating a 4% reduction in local recurrence with boost at 20 years of follow-up (albeit with increased rates of fibrosis).[7] For years, these landmark results have been extrapolated to support the use of a tumor bed boost in patients with DCIS as well. However, several groups have since analyzed the long-term influence of boost on local recurrence and survival for patients with DCIS, with varying results.[8-18] Most recently, the BIG 3-07/TROG 07.01 trial reported that at 5 years, boost significantly improved local control, but as seen previously, at the cost of increased toxicity for some.[19] Therefore, to further optimize patient selection for boost RT, we evaluated local control outcomes across a heterogeneous cohort of patients with DCIS, all of whom underwent BCS and whole-breast RT, with or without a tumor bed boost.

Methods and Materials

Study population

Patients who had undergone BCS for DCIS from 2004 to 2018 were identified from a prospectively maintained institutional database according to an institutional review board–approved protocol. From this database, we conducted a retrospective cohort study including only those patients with evaluable clinicopathologic parameters regarding age at presentation, estrogen receptor status, DCIS nuclear grade, resection margin status, use of hormone therapy, and RT parameters, including use of a boost. Patients were excluded if any invasive component or nodal disease was identified. There were no preplanned analyses for this subcohort of patients. The collection, storage, and retrieval of data for this study were performed in compliance with the institutional review board at our center and the Health Insurance Portability and Accountability Act.

Statistical analysis

Locoregional recurrence rate was defined as the time from surgery to first recurrence in the ipsilateral breast or lymph nodes. Recurrence-free survival (RFS) was defined as the time from surgery to recurrence in the ipsilateral breast or lymph nodes or to death. Patient and treatment parameters were characterized using medians and interquartile ranges (IQRs), and groups were stratified by receipt of a tumor bed boost (boost vs no boost). Parameters were compared using the Pearson χ^2 test for categorical variables and the Wilcoxon rank sum test for continuous variables. Univariable Cox regression models were then constructed to evaluate age, estrogen receptor status, DCIS grade, resection margin status, use of hormone therapy, tumor size, and RT boost. Logistic regression was implemented to evaluate factors associated with the receipt or omission of an RT boost in the cohort. All variables included in multivariable models were selected a priori. Analyses were conducted in R, version 4.0.5 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Study population

The study cohort consisted of 1675 patients with DCIS who underwent BCS followed by adjuvant whole-breast RT (Table 1). Of these, 1146 (68%) received a tumor bed boost to a median dose of 1000 cGy in 4 or 5 fractions. Median age for the overall cohort was 56 years (IQR, 49-64 years), whereas median age among those receiving a boost was 54 years (IQR, 48-63 years) versus 60 years (IQR, 51-67 years) among those not receiving a boost ($P < .001$). Those with close or positive margins were more likely to receive a boost (86%) than those with negative margins (67%) ($P < .001$). Boost was similarly more likely among those with larger tumor size ($P = .042$).

Outcomes

At a median follow-up of 4.2 years, we observed 61 recurrence events (56 local recurrences and 5 regional

Table 1 Patient and disease characteristics

Characteristic	Overall (N = 1675)	No boost (n = 529)	Boost (n = 1146)	*P* value*
Age, median (IQR), y	56 (49-64)	60 (51-67)	54 (48-63)	<.001
Estrogen receptor status, no. (%)				
Negative	102 (9.0)	27 (7.8)	75 (9.6)	.4
Positive	1026 (91)	317 (92)	709 (90)	
Unknown, no.	547	185	362	
Margins, no. (%)				
Negative	1539 (93)	505 (97)	1034 (91)	<.001
Positive/<2 mm	120 (7.2)	17 (3.3)	103 (9.1)	
Unknown, no.	16	7	9	
Hormone therapy, no. (%)	536 (32)	166 (31)	370 (32)	.7
Tumor grade, no. (%)				
Low or intermediate	992 (60)	329 (63)	663 (58)	.11
High	670 (40)	197 (37)	473 (42)	
Unknown, no.	13	3	10	
Size, median (IQR), cm	1.27 (0.81-2.10)	1.20 (0.62-2.00)	1.40 (0.90-2.40)	.042
Unknown, no.	997	323	674	

* Wilcoxon rank sum test; Pearson χ^2 test.

nodal recurrences) and 21 deaths. The 5-year locoregional recurrence-free rate was 96.5% (95% CI, 95.3%-97.8%) among those receiving a boost and 94.7% (95% CI, 92.1%-97.5%) among those not receiving a boost (P = .30); the 10-year locoregional recurrence rate was 91.2% (95% CI, 87.6%-95.0%) versus 90.0% (95% CI, 85.3%-94.9%), respectively (Fig. 1). Of note, multivariable analysis did not reveal significant associations between boost RT and locoregional recurrence (hazard ratio [HR], 0.74; 95% CI, 0.43-1.28; P = .3), or significant associations between any of the additional variables and locoregional recurrence listed in Table 2.

The 5-year RFS was 95.8% (95% CI, 94.4%-97.2%) among those receiving boost RT and 94.3% (95% CI, 91.5%-97.2%) without boost RT (P = .3), consistent with longer-term findings suggesting a 10-year RFS of 88.8% (85%-92.7%) after boost versus 84.3% (78.4%-90.8%) without a boost (Fig. 2). There was no significant difference in RFS between patients with low-intermediate grade and high-grade DCIS (P = .5). Multivariable analysis revealed no significant associations between boost RT and RFS (HR, 0.87; 95% CI, 0.54-1.39; P = .6). The only variable found to trend with RFS was patient age (HR, 1.02; 95% CI, 1.00-1.04; P = .09) (Table 3).

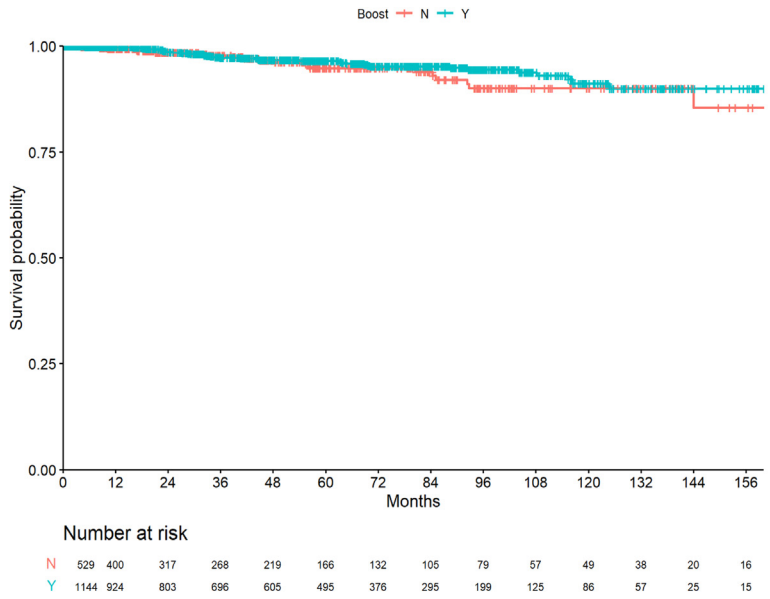
Analysis of factors associated with receipt of a tumor bed boost revealed, on logistic regression multivariable analysis, that younger patients (odds ratio [OR], 0.96; P < .001) with close or positive margins (OR, 3.36; P < .001) were more likely to receive an RT boost (Table 4).

Discussion

In this article, we report on a large cohort of 1675 patients with DCIS treated with BCS and adjuvant RT, with or without a tumor bed boost. Our analysis revealed that 68% of patients received a boost, and despite more adverse features among those receiving a boost (younger age, larger tumors, <2-mm resections margins), we observed no differences in locoregional recurrence or RFS with or without the use of a tumor bed boost.

The role of adjuvant RT after BCS for DCIS is well established, with 4 large randomized trials demonstrating a greater than 50% reduction in local recurrence rates with the use of RT.[3,5,20,21] Treatment with a tumor bed boost, however, was not studied on these trials, and its role in DCIS has been largely extrapolated from studies of invasive breast cancer. Given the better prognosis of DCIS compared with invasive breast cancer and the increased toxicity that may be introduced with higher RT doses, investigators have questioned whether the addition of an RT boost is appropriate for DCIS.

In 2 of the earliest such studies, Yerushalmi et al[8] and Jiveliouk et al[9] evaluated independent small cohorts and



Characteristic	3 year	5 year	10 year
Boost			
No	97.8% (96.3%, 99.4%)	94.7% (92.1%, 97.5%)	90.0% (85.3%, 94.9%)
Yes	97.3% (96.2%, 98.4%)	96.5% (95.3%, 97.8%)	91.2% (87.6%, 95.0%)

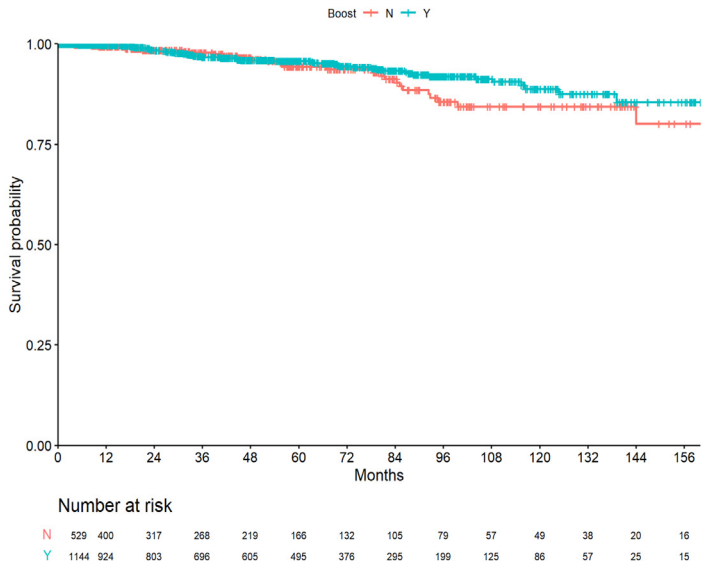
Log-rank p-value: 0.30

Figure 1 Locoregional recurrence-free patients with ductal carcinoma in situ treated with and without boost radiation therapy.

Table 2 Univariate and multivariate analysis for association with locoregional recurrence

Characteristic	UVA		MVA	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age	0.99 (0.97-1.02)	.5	0.99 (0.96-1.02)	.5
Estrogen receptor status				
Negative	-	.2	-	-
Positive	0.56 (0.25-1.23)		-	
Margins				
Negative	-	.5	-	-
Positive/close	0.90 (0.36-2.25)		-	
Hormone therapy				
No	-	.13	-	.2
Yes	1.48 (0.89-2.46)		1.44 (0.86-2.40)	
Boost				
No	-	.3	-	.3
Yes	0.76 (0.45-1.29)		0.74 (0.43-1.28)	
Tumor grade				
Low or intermediate	-	.4	-	.5
High	0.81 (0.48-1.36)		0.84 (0.49-1.41)	
Size, cm	1.09 (0.78-1.51)	.6	-	-

Abbreviations: CI = confidence interval; HR = hazard ratio; MVA = multivariate analysis; UVA = univariate analysis.



Characteristic	3 year	5 year	10 year
Boost			
No	97.8% (96.3%, 99.4%)	94.3% (91.5%, 97.2%)	84.3% (78.4%, 90.8%)
Yes	96.7% (95.5%, 97.9%)	95.8% (94.4%, 97.2%)	88.8 (85%, 92.7%)

Log-rank p-value: 0.30

Figure 2 Recurrence-free survival of patients with ductal carcinoma in situ treated with and without boost radiation therapy.

found no difference in local recurrence rates with or without a boost at a median of 6.8 and 4 years, respectively. Several subsequent larger analyses corroborated these findings, also failing to demonstrate an association between a tumor bed boost and locoregional recurrence.[10-12] The largest negative study conducted to date was similar to ours, reporting local recurrence rates of 12% with a boost and 13% without at a median follow-up of 10 years (HR, 0.77; $P = .2$).[13] Although our median follow-up period was shorter at 4.2 years and our cohort was more homogeneous as single-institutional versus population-based, we nevertheless observed similar local recurrence rates and RFS. Both study findings are also concordant with those reported in an unplanned subcohort analysis of the National Surgical Adjuvant Breast and Bowel Project B-24 trial, which identified 1569 patients with DCIS with complete data for analysis who received BCS and RT, with or without tamoxifen. Among these patients, 692 patients (44%) received a tumor bed boost, but no effect on ipsilateral breast tumor recurrence was observed (13.8% vs 14.3%; $P = .27$; HR, 1.12; $P = .69$).[22] In contrast to these studies, several series have reported improvements in local recurrence rates with a boost, one of which included 389 patients with a median follow-up of 7.7 years (HR, 0.17; 95% CI, 0.04-0.7; $P = .014$).[14-17]

Among the most compelling analyses to support use of a boost for DCIS was a 2017 study of 4000 patients demonstrating an absolute RFS benefit of 3.6% at 15 years (92% versus 88%), similar to what was found in the EORTC22881 boost RT trial for invasive cancer.[18] Although retrospective, this study highlighted several possible etiologies for the mixed results observed in the existing DCIS boost literature. For one, an a priori power analysis was used to determine both the total cohort size and the proportion of patients treated with a boost required to detect a 3% difference in local recurrence rates. Indeed, it is noteworthy that the previously mentioned studies demonstrating better outcomes with a boost involved a greater percentage of patients treated with a boost than those studies reporting no difference in outcomes (36%-71% versus 25%-48%). Although a comparatively high percentage (68%) of the patients in our cohort did in fact receive a boost, it is possible that we did not observe any boost effect due to our overall cohort size being underpowered. It is also notable that among randomized studies of DCIS, most recurrences arise >5 years after treatment, such that our follow-up may have been too short to observe a true therapeutic effect.[23,24] Long-term follow-up may be of particular importance for studies investigating the effect of a tumor bed boost in DCIS.

Table 3 Univariate and multivariate analysis for association with recurrence-free survival

Characteristic	UVA		MVA	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age	1.02 (1.00-1.04)	.068	1.02 (1.00-1.04)	.090
Estrogen receptor status				
Negative	-	.2	-	-
Positive	0.59 (0.28-1.23)		-	
Margins				
Negative	-	.8	-	-
Positive/close	0.90 (0.36-2.23)		-	
Hormone therapy				
No	-	>.9	-	.8
Yes	1.03 (0.65- 1.63)		1.07 (0.68-1.70)	
Boost				
No	-	.3	-	.6
Yes	0.78 (0.49-1.24)		0.87 (0.54-1.39)	
Grade				
Low or intermediate	-	.5	-	.5
High	0.87 (0.55-1.35)		0.86 (0.55-1.35)	
Size, cm	1.01 (0.72-1.43)	>.9	-	-

Abbreviations: CI = confidence interval; HR = hazard ratio; MVA = multivariate analysis; UVA = univariate analysis.

To that end, the recently reported BIG 3-07/TROG 07.01 trial randomized 1608 patients in a 2 × 2 factorial design to receive conventional versus hypofractionated whole-breast RT and to boost versus no-boost RT.[19] At a median follow-up of 6.6 years, the 5-year free-from-local-recurrence rates were 92.7% in the no-boost arm versus 97.1% in the boost arm (HR, 0.47; $P < .001$). Notably, the boost group had higher rates of breast pain and induration. Consistent with our findings, univariate analysis revealed that time-to-local-recurrence favored boost RT in younger patients, those with larger tumors, and those with suboptimal margins. Thus, it is entirely plausible that most patients harboring these features in our non-randomized cohort underwent boost RT, which ultimately mitigated their local recurrence risk. Indeed, we observed no increase in local recurrence among the boost group, which harbored a constellation of adverse features. Still, it is worth mentioning that although older patients were significantly less likely to receive an RT boost, age was the only variable that trended with better RFS, despite the higher likelihood of older patients to die of any cause. Nevertheless, were boost RT ineffective at mitigating risk, one would expect our boost arm to exhibit inferior outcomes to the much more favorable no-boost arm in our analysis (comprising older patients with smaller tumors that were more optimally resected). In addition to the BIG 3-07 / TROG 07.01 trial, the multicenter phase III BONBIS French trial is estimated to near completion in 2029 and will further illuminate the effect of boost on DCIS.[25,26]

Table 4 Logistic regression multivariate analysis for receipt of an RT boost

Characteristic	OR (95% CI)	*P* value
Age	0.96 (0.95-0.97)	<.001
Estrogen receptor status		
Negative	-	.3
Positive	0.75 (0.44-1.25)	
Margins		
Negative	-	<.001
Positive/close	3.36 (1.86-6.64))	
Hormone therapy		
No	-	.9
Yes	0.98 (0.75-1.28)	
Tumor grade		
Low or intermediate	-	.090
High	1.27 (0.96-1.69)	

Abbreviations: CI = confidence interval; OR = odds ratio.

Our findings must be interpreted in the context of the study design. Although our cohort of 1675 patients is among the largest investigating use of a tumor bed boost

in DCIS, the retrospective nature of our analyses is limited by loss to follow-up and several patients with missing clinicopathologic and treatment parameters. The lack of toxicity data available for these patients also limits our ability to report on potential differences in adverse outcomes with or without a tumor bed boost. Additionally, most of our cohort was treated with hypofractionated whole-breast RT and boost doses of 1000 cGy in 4 to 5 fractions, in contrast to the conventional fractionation and boost doses of 1600 cGy in 8 fractions most commonly reported in previous studies. However, numerous studies have established the equivalence in outcomes with conventional and hypofractionated RT regimens, including the latest BIG/TROG trial, and we expect the toxicity results from studies of a tumor bed boost in invasive cancer to be directly translatable to patients with DCIS. Despite these limitations, our findings represent an important contribution to the literature for a pertinent and persistent clinical question.

Conclusion

In summary, we did not find an association between tumor bed boost and locoregional recurrence or RFS after adjuvant whole-breast RT for DCIS. However, because we did observe a higher frequency of boost RT among patients with higher-risk features, namely younger age, larger tumor size, and <2-mm margins, boost RT may be warranted to mitigate the adverse implications of these unfavorable features. Ongoing randomized trials will elucidate the role of boost RT in DCIS.

Disclosures

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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