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Comparison of Mammographic Changes Across Three Different Fractionation Schedules for Early-Stage Breast Cancer

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Abstract

Purpose—As the use of hypofractionated breast radiation therapy (RT) increases, so will the need for long-term data on post-RT mammographic changes. The purpose of the present study was to longitudinally compare the incidence of common mammographic sequelae seen after breast conserving surgery and RT in patients treated with accelerated partial breast irradiation (APBI), hypofractionated whole breast irradiation (HWBI), and conventionally fractionated whole breast irradiation (WBI).

Methods and Materials—Patients treated with either APBI or HWBI after breast conserving therapy and with 3 mammograms of the treated breast were identified. They were matched 1:1 by age ± 5 years to patients treated with WBI. The mammograms were evaluated for common post-RT breast findings by a mammographer who was unaware of the treatment. The outcomes were analyzed using a cumulative logistic regression model; $P < .05$ indicated statistical significance.

Results—Of 89 patients treated with RT from 2006 to 2011, 29 had received APBI, 30 had received HWBI, and 30 had received WBI. Their median age was 60 years (range 33–83). A total of 605 mammograms were evaluated, with a median follow-up of 48 months. The treatment technique did not affect the severity of architectural distortion when the groups were evaluated longitudinally. The likelihood of finding skin thickening decreased with increasing follow-up duration (odds ratio 0.6; $P < .001$) adjusted for fractionation schemes. No differences were seen with respect to changes in skin thickening, fluid collections, or calcifications among the treatment groups, after adjustment for the follow-up time. The clinical characteristics, including age, race, T stage, and chemotherapy use, were not linked to the likelihood of finding several mammographic phenomena over time.

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Conflict of interest: none.

Conclusions—Although specific post-treatment imaging findings evolved over time, RT fractionation did not alter the relative incidence or severity of architectural distortion, skin thickening, fluid collections, or calcifications. These findings will be useful to both radiologists and radiation oncologists when counseling patients regarding follow-up studies after RT.

Introduction

Breast cancer is the most commonly diagnosed non-cutaneous malignancy in women, with >230,000 estimated cases in 2015 in the United States (1). Patients with early-stage breast cancer commonly undergo breast conserving therapy (BCT), which entails lumpectomy followed by radiation therapy (RT). Large randomized trials with long-term follow-up have demonstrated equivalent overall survival in those treated with lumpectomy and radiation compared with those who underwent mastectomy (2, 3). Typically, whole breast irradiation (WBI) is given after lumpectomy in 1.8- to 2.0-Gy fractions to a total dose of 50 to 60 Gy over the course of 5 to 7 weeks. Hypofractionated treatment regimens, which deliver RT over 3 to 4 weeks, have been used and studied extensively; several large randomized control trials have revealed similar rates of local control and overall survival compared with conventional RT (4, 5).

Between 2008 and 2013, the use of hypofractionated RT for breast cancer patients increased threefold, and, in the United States, approximately 33% of patients meeting the criteria for the American Society for Radiation Oncology practice guidelines for hypofractionated WBI (HWBI) received this treatment (6). Thus, given the increased use of hypofractionated RT, the importance of understanding the potential long-term sequelae found with mammography is necessary. The mammographic changes that frequently occur after lumpectomy and RT are well known. The common imaging findings include architectural distortion, breast edema, skin thickening, fluid collections, and calcifications (7, 8). Because mammographic alterations after BCT can mimic or hide tumor recurrence, they become clinically relevant when unnecessary biopsies or delayed diagnoses occur. Studies have evaluated the mammographic findings after BCT with conventionally fractionated external beam radiation (9, 10) and brachytherapy-based APBI (11). However, to our knowledge, no studies have directly examined the effect of different hypofractionated RT schemes using external beam techniques on the mammographic findings after lumpectomy and RT.

The purpose of the present study was to longitudinally compare the incidence of common mammographic sequelae seen after breast conserving surgery and RT in patients treated with APBI, HWBI, and conventionally fractionated WBI treated at a single institution.

Methods and Materials

The medical records were reviewed for patients treated from May 2006 to November 2011 to identify those treated with either APBI or HWBI and with ≥ 2 years of mammographic follow-up data available. These patients were matched 1:1 to those who had received conventional WBI by reviewing the medical records of patients treated during the same period by age ±5 years. All patients included in the present study had had ≥ 3 mammograms of the treated breast, with the earliest mammogram performed ≥ 6 months after the end of

RT. The relevant patient information, including age at diagnosis, tumor characteristics, and total radiation dose, were maintained in a single database. The institutional review board approved the present study.

Each patient underwent computed tomography simulation to obtain 3-dimensional (3D) anatomy data for treatment planning purposes. During the simulation, each patient lay supine on a breast board with both arms above their head on the computed tomography couch, and the borders of the breast were determined by visual inspection and clinical palpation. Radiopaque wires were placed on the breast borders and the lumpectomy scar. After scan acquisition, the images were transferred to the Varian Eclipse Treatment Planning System, version 7.3.10 (Varian Medical Systems, Palo Alto, CA), where target delineation, isocenter placement, beam placement, and treatment planning were performed.

Patients receiving WBI were treated using opposed tangent beams. Patients treated with WBI received 1.8 to 2.0 Gy daily to a total median tangent dose of 50 to 50.4 Gy. Regional supraclavicular nodes were treated to 46 Gy; this third field was included at the discretion of the treating radiation oncologist ($n = 2$). A boost to the tumor bed of 10 Gy was typically delivered with electrons or photons to a total median dose of 60 Gy. Patients treated with HWBI received 11 daily fractions of 3.33 Gy using opposed tangent beams to a total median whole breast dose of 36.63 Gy. A boost to the tumor bed of 13.32 Gy over 4 fractions was delivered with electrons to a total dose of 49.95 Gy. Patients treated with APBI received 3.33 Gy daily fractions for 15 days of treatment with photons to a total median dose of 49.95 Gy (12), in accordance with the established partial breast guidelines set forth by the Radiation Therapy Oncology Group (RTOG). The biologic rationale for treatment using this dosing scheme has previously been published (13). In brief, assuming an α/β ratio of 4 Gy for tumor kill, 91.5 Gy₄ and 90 Gy₄ was estimated to be delivered using our fractionation scheme and standard WBI plus boost, respectively. Assuming an α/β ratio of 10 Gy for acute effects, 66.6 Gy₁₀ and 72 Gy₁₀ was estimated to be delivered using our fractionation scheme and standard WBI plus boost, respectively.

No patients in the present study received inverse- planned intensity modulated RT, although physical wedges, dynamic wedges, field-in-field technique, or electronic compensation could be used to improve dose homogeneity, keeping the maximum dose at <107% of the prescription dose for whole breast patients. A subset of patients treated with APBI was given a total dose of 38.5 Gy, with twice-daily 3.85 fractions, delivered over 5 days, using 3D conformal techniques, in accordance with the eligibility criteria and treatment schedule of RTOG study 0413.

Accelerated RT fractionation design

Patients receiving the APBI and HWBI accelerated regimens were treated using a novel fractionation scheme: 49.95 Gy in 15 single daily fractions. This was based on the hypofractionated whole breast dose fractionation scheme used by Owen et al (14): 42.9 Gy in 13 fractions delivered to the whole breast, followed by a 14-Gy boost in 7 fractions.

Each mammogram was reviewed by a radiologist with >15 years' experience in breast imaging, who was unaware of the treatment type and outcome. The mammograms were

evaluated for the presence of common postlumpectomy imaging sequelae. Architectural distortion was evaluated as none, mild, moderate, or severe. Post-treatment breast edema, which appears as an increased density with secondary trabecular thickening, was noted as either focal or diffuse (7). Edema severity was graded as <25%, 25% to 50%, or >50% of the breast volume. Skin thickening was described as either focal or diffuse, and its severity was quantified as <3, 3 to 5, or >5 mm. The presence of fluid collections and calcifications was recorded.

Associations among the categorical clinical characteristics at baseline were determined using Fisher exact test, as appropriate. Longitudinal variation in the incidence of imaging sequelae was determined, treating time as a continuous variable. Time was transformed to the square root of the number of months. For ordinal outcomes, including architectural distortion, breast edema, and skin thickening, comparisons over time and between groups were performed using a generalized linear mixed model with a cumulative logit link. The proportional odds assumption was tested using a χ^2 test. A comparison based on binomial outcomes, such as fluid collections and calcifications, was performed using a generalized linear mixed model with a logit link. The ratio of the odds ratio (rOR) and 95% confidence interval were recorded if the interaction term was significant; the OR was reported otherwise. P values were adjusted using the Hochberg method to control family-wise type I error at 5% over multiple tests. The tests were 2-sided, with $P < .05$ considered statistically significant. SAS, version 9.3 (SAS Institute, Cary, NC), was used for all statistical analyses.

Results

A total of 89 patients who had undergone treatment from June 2006 to June 2011 were included in the present analysis. Of the 89 patients, 29 were treated with APBI, 30 with HWBI, and 30 with WBI and were included in the present analysis. The median age for all patients was 60 years, with a median mammographic follow-up of 48 months. The median clinical follow-up was 62 months as of January 1, 2015. The clinical and pathologic variables of the patients are listed in Table 1. A single patient who had undergone APBI developed an invasive recurrence in the ipsilateral breast, 4.7 years after the initial diagnosis, and 1 patient treated with APBI developed metastatic disease 4.9 years after her initial diagnosis. A total of 5 cases of contralateral breast events occurred across the fractionation schemes: 2 cases of ductal carcinoma in situ in patients treated with once-daily APBI, 2 cases of invasive carcinoma in patients treated with HWBI, and 1 case of invasive cancer in a patient who had received conventional WBI.

A total of 605 mammograms were included in the present study. The mean number of mammograms reviewed per patient was 7.03 in the APBI group, 6.37 in the HWBI group, and 6.87 in the WBI group. The variation in the postconservation breast imaging findings over time within treatment groups and between treatment groups is summarized in Tables 2 and 3. Group effect testing was performed to evaluate the overall effect over 3 groups (HWBI, APBI, and WBI) with respect to each outcome. The only variable found to be significant was edema; specifically, we found that the volume of edema (focal vs diffuse) was different between the APBI and HWBI groups, but not in the WBI group. The extent of architectural distortion did not vary among the treatment arms with the follow-up time ($P = .$

627). The odds of moderate distortion (or moderate or mild) versus mild or no distortion (or none) decreased by 30% (OR 0.7; $P < .0001$) per unit of time adjusted for treatment groups. However, the odds regarding the severity of architectural distortion did not differ among the treatment arms after adjustment for time ($P = .27$). The extent of breast edema varied between fractionation schemes when evaluated longitudinally ($P = .02$). Patients treated with HWBI were less likely to develop diffuse (or focal/diffuse) versus focal/none (or none) edema than those treated with APBI per unit increase in time (rOR 0.44; $P = .007$). No difference was found in the same comparison between the WBI and HWBI versus APBI groups ($P = .55$; Fig. 1). Regardless of the treatment arm, the odds of developing diffuse skin thickening (or diffuse/focal) versus focal/none (or none) decreased 29% per unit of time (OR 0.71; $P < .001$), and the odds of developing calcifications increased by 131% per unit of time (OR 2.31; $P < .001$). The odds of developing skin thickening, fluid collections, and calcification severity was unaffected by treatment technique over time.

To quantitatively assess the rate of change in the development of mammographic findings, time was modeled as a categorical variable. The mammographic data were divided into 9 periods (6, 12, 18, 24, 30, 36, 48, 60, and 72 months), with 6 months after radiation as the reference period. The minimum follow-up time after RT completion demonstrating significance from baseline varied from 18 to 48 months (Table 3).

Age and race were particularly important clinical predictors of imaging sequelae over time. The ORs of outcome for 5 of the 6 imaging findings as follow-up time increased varied according to patient age or race (Table 4). Patient age affected the association of edema and skin thickening with time. Specifically, the OR of having diffuse (or diffuse/focal) versus focal/none (or none) edema per unit increment in time increased by 3% (rOR 1.03; $P = .012$) as patients became 1 year older. A similar effect of age on the OR per unit time was observed for skin thickening and skin thickening severity (rOR 1.02; $P = .009$ for skin thickening; rOR 1.01; $P = .02$ for skin thickening severity; Table 5). The association of edema severity or skin thickening severity or calcifications with time varied across race. Compared with Asians, the OR of more severe diffuse edema per unit of time increment in blacks was 0.35 (rOR 0.35; $P = .006$), and the OR of more severe skin thickening per unit time increment in Hispanics was more than two times greater (rOR 2.19; $P = .02$). With respect to calcifications, the OR of developing calcifications per unit time increment in blacks was lower (rOR 0.11; $P = .004$) compared with Asian patients. The OR of developing calcifications as time increased in patients diagnosed with T1 (or T2) disease was 83% (rOR 0.18; $P = .02$; or 92% with rOR 0.8; $P = .002$) lower than those who were treated for ductal carcinoma in situ. The OR of developing calcifications per unit increment in follow-up time decreased by one-half (rOR 0.5; $P = .026$) in those who were treated with adjuvant chemotherapy versus not.

Discussion

The expected radiologic phenomena originally established in the context of WBI (7) have been more recently evaluated in several populations treated with various APBI methods, including MammoSite brachytherapy (11, 15) and intraoperative RT (IORT) (16, 17). The mammographic findings after balloon-based brachytherapy were previously reported by

Ahmed et al (11), who reported the findings from a single cohort of 22 patients (total of 93 mammograms), with a median mammographic follow-up period of 46 months. They reported that 64% of patients had developed moderate architectural distortion by 22 months after treatment. The investigators noted that the rate of change was substantially faster than the previously reported rates of mammographic changes with conventional WBI, presumably owing to greater dose inhomogeneity and a higher dose-per-fraction with brachytherapy (7). In addition, the investigators reported that fat necrosis, seroma, and calcification frequently caused alterations in density and lucency at the lumpectomy site, making standardized assessment of mammographic distortion difficult (11).

In contrast, the architectural distortion in our study cohort who had undergone external beam RT techniques evolved over a longer period in the present study. Modeling time as a categorical variable, the profile of distortion severity consisting of all patients was significantly different at 36, 60, and 72 months compared with the baseline profile at 6 months after treatment. Additionally, no significant differences were seen across the treatment groups. The incidence of mild distortion continuously increased until the end of the follow-up period at 72 months, at which point it affected 58% to 70% of patients across the fractionation schedules. The incidence of moderate and severe distortion peaked early, at 12 months, and gradually decreased over the successive follow-up visits. Thus, the observed distortion pattern occurring after external beam APBI is distinctly different from that after brachytherapy APBI, most likely owing to the improved dose homogeneity seen with external beam techniques. In addition, no patients developed fat necrosis or symptomatic seromas, making the mammographic assessment less difficult than that for brachytherapy-based techniques. Monticciolo et al (15) compared the typical findings after balloon-based brachytherapy with a matched conventional external beam population. Notably, the prevalence of visible seroma formation was considerably greater in the APBI group (69% vs 7%; $P<.001$), a finding not reproduced in our study population. The question of whether APBI compromises mammographic follow-up data was assessed in a single-institution series of 54 patients treated with IORT (17). Wasser et al (17) found the mammographic evaluation of patients treated with IORT to be significantly more complicated after the first year (16%–21% vs 0%–8%). These results were corroborated by a similar analysis extended to the randomized setting (targeted intraoperative radiotherapy [TARGIT]) (18). Moreover, evidence has suggested that the differences in postoperative findings can be attributed to the IORT technique alone. In contrast, with the exception of less focal or no versus diffuse breast edema compared with HWBI, APBI does not appear to complicate mammographic follow-up evaluations.

The results should be interpreted with several important caveats. One major limitation was the heterogeneous composition of the APBI and hypofractionated patient populations. The inclusion of 11 patients treated according to the National Surgical Adjuvant Breast and Bowel Project B-39/RTOG 0413 protocol limited our ability to make conclusive statements regarding the once-daily APBI protocol. Similarly, 17% of patients were treated to 4256 cGy in the hypofractionated whole breast arm. Our sample size of approximately 30 patients per treatment arm is comparable with previous radiologic studies involving APBI techniques. Studies with larger sample sizes and experience with patients treated with the more

commonly used twice- daily fractionation scheme would serve to validate and extend the generality of the results found in the present study.

Interest and usage of shortened treatment designs have increased, especially in academic settings and when considering patient perspectives (19, 20). The adoption of hypofractionation continues to increase in Canada and the United States (19, 21). Several large randomized trials and smaller single-institution experiences have reported external beam APBI (12, 22–25). Although data continue to mature regarding the efficacy of partial breast irradiation, the interim data on cosmetic outcomes have been mixed, with inferior cosmetic outcomes observed after using 3D conformal and intensity modulated RT techniques (24, 26–28). Given that most women prefer once-daily treatments, despite doubling the total treatment days and a twice-daily schedule's potential effect on cosmesis, APBI structured with once-daily treatments might represent an attractive alternative to more common twice-daily APBI designs (29). The clinical efficacy of APBI consisting of 15 once-daily fractions of 3.33 Gy compares favorably to the more common reported twice-daily schedule (12).

Conclusions

Until such data matures, the present study is the only study to have evaluated follow-up mammograms from patients treated with APBI using external beam techniques. Additionally, no other studies to date have longitudinally compared common mammographic findings after breast conserving therapy or related the clinical characteristics to the changing prevalence of specific mammographic findings. We found that common mammographic phenomena in breast cancer patients, including breast edema, skin thickening, architectural distortion, and calcifications, continuously evolve during follow-up. APBI and hypofractionated treatments do not create significant deviations from the expected mammographic findings in the postconservation breast. Thus, the altered fractionations, as described in the present study, do not appear to complicate mammographic follow-up. Additionally, the clinical characteristics, including age, race, T stage at diagnosis, and the use of systemic agents are associated with the changing prevalence of specific mammographic findings over time. These findings will be useful to both radiologists and radiation oncologists when counseling patients regarding follow-up studies after RT.

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Summary

The purpose of the present study was to longitudinally compare the incidence of common mammographic sequelae seen after breast conserving surgery in patients treated with accelerated partial breast irradiation, hypofractionated whole breast irradiation, and conventionally fractionated whole breast irradiation. We found that radiation therapy fractionation and technique did not alter the relative incidence or severity of common mammographic sequelae.

Fig. 1.

Marginal probability of developing diffuse, focal, or no edema as a function of follow-up duration for each treatment arm. The accelerated partial breast irradiation patients were more likely to develop focal/none (or none) versus diffuse edema (or focal/diffuse) compared with those treated with hypofractionated whole breast irradiation (HWBI) (odds ratio 0.4; $P = .007$). *Abbreviations:* A = accelerated partial breast irradiation; H = hypofractionated whole breast irradiation; W = whole breast irradiation.

Table 1

Basic clinical characteristics of patients stratified by fractionation group

Characteristic	WBI (n = 30)	HWBI (n = 30)	APBI (n = 29)	P value
Age (y)	57.9 ± 10.1	58.4 ± 11.9	63.5 ± 9.6	
Median clinical follow-up (y)	6.3	5.0	4.8	
Median mammographic follow-up (y)	6.1	4.7	4.5	
T classification				.53
Tis	6 (20.0)	3 (10.0)	5 (17.2)	
T1	19 (63.3)	21 (70.0)	22 (75.9)	
T2	5 (16.7)	6 (20.0)	2 (6.9)	
N classification				.17
N0	26 (86.7)	24 (86.7)	28 (96.6)	
N1	4 (13.3)	6 (13.3)	1 (3.4)	
ER status				.43
Negative	4 (13.8)	3 (10.0)	1 (3.4)	
Positive	25 (86.2)	27 (90.0)	28 (96.6)	
PR status				.002
Negative	12 (40.0)	5 (16.7)	1 (3.4)	
Positive	18 (60.0)	25 (83.3)	28 (96.6)	
HER2 status				.45
Negative	20 (83.3)	23 (85.2)	20 (95.2)	
Positive	4 (16.7)	4 (14.8)	1 (4.8)	
Chemotherapy				.18
No	20 (66.7)	25 (83.3)	25 (86.2)	
Yes	10 (33.3)	5 (16.7)	4 (13.8)	
Hormonal therapy				.58
No	6 (20.0)	3 (10.0)	3 (10.3)	
Yes	24 (80.0)	27 (90.0)	26 (89.7)	
Total dose (cGy)				
3850	0	0	11 (37.9)	
4256	0	5 (16.7)	1 (3.4)	
4995	0	23 (76.7)	17 (58.6)	
5256	0	2 (6.7)	0	
6000	30 (100.0)	0	0	
Race				.30
White	17 (56.7)	22 (73.3)	22 (75.9)	
Black	4 (13.3)	6 (20.0)	2 (6.9)	
Asian	5 (16.7)	1 (3.3)	3 (10.3)	
Hispanic	4 (13.3)	1 (3.3)	2 (6.9)	
Smoking				.02
None	25 (83.3)	14 (56.0)	22 (81.5)	
Before RT	2 (6.7)	10 (40.0)	4 (14.8)	

Characteristic	WBI (n = 30)	HWBI (n = 30)	APBI (n = 29)	P value
During RT	3 (10.0)	1 (4.0)	1 (3.7)	

Abbreviations: APBI = accelerated partial breast irradiation; ER = estrogen receptor; HER2 = human epidermal growth factor receptor 2; HWBI = hypofractionated whole breast irradiation; PR = progesterone receptor; RT = radiation therapy; WBI = whole breast irradiation.

Data presented as mean $\pm$ standard deviation or n (%), unless otherwise noted.

Table 2

Variation in each mammographic finding with respect to time and among treatment groups

Imaging finding	OR	95% CI	P value
Distortion			
Time	0.70	0.59–0.83	<.0001 *
Group effect			.63
Edema			
Time			<.0001 *
Group effect			.02 *
HWBI vs APBI	0.44	0.24–0.80	.007 *
WBI vs APBI			.55
Edema severity			
Time			<.0001 *
Group effect			.12
Skin thickening			
Time			<.0001 *
Group effect			.73
Thickening severity			
Time	0.71	0.61–0.83	<.0001 *
Group effect			.41
Fluid collections			
Time			.17
Group effect			.15
Calcifications			
Time	2.31	1.72–3.1	<.0001 *
Group effect			.82

Abbreviations: APBI = accelerated partial breast irradiation; CI = confidence interval; HWBI = hypofractionated whole breast irradiation; OR = odds ratio; WBI = whole breast irradiation.

* Statistically significant.

Table 3

Minimum follow-up time after treatment completion for demonstrating significant change from baseline for each mammographic finding

Imaging finding	Follow-up after RT (mo)	<i>P</i> value
Architectural distortion	36	.05
Edema	18	.005
Edema severity	12	.012
Skin thickening	48	.002
Skin thickening severity	18	.012
Calcifications	24	.028

Abbreviation: RT = radiation therapy.

Table 4

Association between each mammographic finding and clinical variables with respect to time in an interaction model

Imaging findings	Clinical variable				
	Age	Race	Smoking	T stage	Chemotherapy
Distortion	0.650	0.111	0.200	0.068	0.729
Edema	0.012 *	0.056	0.611	0.694	0.105
Edema severity	0.861	0.028 *	0.264	0.140	0.401
Skin thickening	0.009 *	0.224	0.878	0.838	0.131
Skin thickening severity	0.021 *	0.001 *	0.326	0.576	0.300
Calcifications	0.420	0.0005 *	0.521	0.005 *	0.026 *

^{*} Statistically significant.

Table 5

Relationship between developing various mammographic findings over time and selected clinical variables with significant associations

Clinical association	OR	95% CI	Estimate (SE)	P value
Edema				
Age	1.03	1.01–1.05	0.030 (0.01)	.012 *
Edema severity				
Race				
White vs Asian			–0.33 (0.27)	.223
Black vs Asian	0.35	0.17–0.74	–1.048 (0.38)	.006 *
Hispanic vs Asian			0.117 (0.45)	.795
Skin thickening				
Age	1.02	1.01–1.04	0.021 (0.008)	.009
Skin thickening severity				
Age	1.01	1.01–1.02	0.016 (0.001)	.021 *
Race				
White vs all others			0.428 (0.23)	.066
Black vs all others			–0.294 (0.29)	.312
Hispanic vs all others	2.19	1.13–4.27	0.785 (0.34)	.021 *
Calcifications				
Race				
White vs Asian			–0.426 (0.65)	.512
Black vs Asian	0.11	0.09–0.12	–2.246 (0.76)	.004 *
Hispanic vs Asian			–0.346 (0.83)	.677
T classification				
T1 vs Tis	0.18	0.04–0.75	–1.725 (0.73)	.018 *
T2 vs Tis	0.80	0.20–0.33	–2.535 (0.81)	.002 *
Adjuvant chemotherapy				
Chemotherapy use vs none	0.50	0.27–0.93	–0.685 (0.31)	.026 *

Abbreviations: CI = confidence interval; OR = odds ratio; SE = standard error.

* Statistically significant.