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Accelerated Partial Breast Irradiation through Brachytherapy for Ductal Carcinoma in situ: Factors Influencing Utilization and Risks of Second Breast Tumors

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Abstract

Purpose—To examine influencing factors and outcomes of accelerated partial breast irradiation through brachytherapy (APBIB) versus whole breast irradiation (WBI) for ductal carcinoma in situ (DCIS).

Patients and Methods—From the Surveillance Epidemiology and End Results program, we identified 40749 women who were diagnosed with first primary DCIS between 2002 and 2011 and treated with breast conserving surgery (BCS) and radiotherapy. A multi-level logistic regression analysis was performed to estimate odds ratios of APBIB use. Hazard ratios (HRs) of developing ipsilateral breast tumors (IBTs) and contralateral breast tumors (CBTs) were analyzed in 1962 patients with APBIB and 7203 propensity score-matched patients with WBI, using Cox proportional hazards regression.

Results—Overall, 2212 (4.5%) of 40749 women (the whole cohort) received APBIB. Factors associated with the increased use of APBIB included older age, non-Hispanic white race/ethnicity, smaller tumor size, hormone receptor positivity, comedo subtypes and urban residence. During the 46-month follow-up, 74 (0.8%) and 131 (1.4%) of 9165 propensity score-matched patients developed IBTs and CBTs, respectively. Compared with WBI, APBIB was associated with a

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Acquisition of data: Liu.

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significantly increased risk of IBTs (HR, 1.74; 95% CI, 1.06 to 2.85) but not CBTs (OR, 0.91; 95% CI, 0.59 to 1.41).

Conclusion—This population-based study suggests that APBIb use for DCIS was influenced by patient and tumor characteristics as well as urbanization of residence. We observed a moderately increased IBT risk associated with APBIb versus WBI, suggesting that APBIb should be used with caution for DCIS before data from randomized controlled trials with long-term followups are available.

INTRODUCTION

Breast-conserving surgery (BCS) followed by external beam radiation to the whole breast (WBI), is considered the standard of care for early-stage breast cancer [1–3]. Accelerated partial breast irradiation through brachytherapy (APBIb) is a new technique that delivers radiation to the tissue immediately surrounding the lumpectomy cavity, which is at the highest risk of recurrence. Compared with WBI, APBIb typically requires shorter treatment times and, due to the targeted nature of delivering radiotherapy from inside the body, allows less radiation to unaffected breast and other tissues [4]. However, APBIb could not irradiate cancer cells in the untargeted part of the breast and may result in increased local recurrence risk. In the absence of evidence from randomized controlled trials demonstrating equivalent benefit in local control with WBI, APBIb has been increasingly used from 2% in 2002 to 10% in 2006 for invasive breast cancer [5–8].

Little is known about clinical outcomes after APBIb for ductal carcinoma in situ (DCIS), a precancerous breast lesion with treatment options similar to early invasive breast cancer. APBIb is not considered suitable for DCIS according to the American Society for Radiation Oncology (ASTRO) guidelines [9]. However, 6.5% of DCIS patients from the Commission on Cancer (CoC)-accredited hospitals received APBIb following BCS. APBIb use was associated with characteristics of patients and facilities where patients received treatment [10]. Limited data are available regarding influencing factors of APBIb use for DCIS in population-based cancer registries. A pooled analysis of a single-arm clinical trial and a series from William Beaumont Hospital documented favorable outcomes in 300 DCIS patients treated with APBIb (nine ipsilateral breast recurrences at five years) [11]. However, this did not allow for direct comparison of APBIb to WBI.

In a population-based cohort of women with DCIS who received BCS and radiotherapy, we examined influencing factors of APBIb utilization and the association of APBIb versus WBI with the risks for developing second breast tumors in the ipsilateral and contralateral breasts.

METHODS

Study Sample

We used data from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program, which captures approximately 97% of incident cancers from population-based cancer registries and covers nearly 28% of the US population [12]. De-identified SEER data were used, exempting the study from review by our Institutional Review Board.

Given the clearance of the balloon-based breast brachytherapy device in 2002 by the US Food and Drug Administration (FDA), we selected women with first primary, unilateral DCIS diagnosed from 2002 to 2011 who received BCS and radiation therapy (n=41300). We excluded patients who had incomplete treatment information, a cancer history, a diagnosis through death certificate or autopsy, or no information on age at diagnosis or county where they lived (n=551). This study included 40749 patients.

APBib and WBI

Patients who received external beam radiation with or without a brachytherapy boost were assigned to the WBI group. Patients who received radioactive implants or radioisotopes alone were assigned to the APBib group [6].

Covariates

Patient-level covariates included age (<50, 50–59, 60–69, 70–79, or 80 years), race and ethnicity (non-Hispanic white (hereafter called white), non-Hispanic black (black), non-Hispanic Asian (Asian), Hispanic, or others), marital status (married, unmarried, divorced, widowed, or unknown), and registry. Tumor characteristics included tumor size (<10 mm, 11–20 mm, 21–30 mm, >30 mm, or unknown), nuclear grade (well differentiated, moderately differentiated, poorly differentiated, or unknown), histological subtype (not otherwise specified, comedo, papillary, cribriform, or solid), and estrogen receptor (ER) and progesterone receptor (PR) status (ER+/PR+, ER+/PR–, ER–/PR+, ER–/PR–, and unknown).

County-level covariates included socioeconomic deprivation, urbanization (urban, near metropolis, or rural), and number of radiation oncologists per 10000 cancer patients. Using the principal-components common factor analysis as described previously [13], we identified six county-level variables from the 2000 US Census that had substantially higher factor loading on the first common factor and a high internal consistency (Cronbach's $\alpha=0.93$). They were percentage of the total adult population with less than high school education, percentage of unemployed adults, percentage of households without phones, percentage of households on public assistance, percentage of population below federal poverty line, and percentage of households in poverty. A county socioeconomic deprivation index was computed by summing the six county variables weighted by their standardized scoring coefficients. We used the 2003 rural-urban continuum codes (ranging from 1 to 9) developed by the US Department of Agriculture to define urban regions as counties coded as 1, near metro regions as counties coded as 2 to 5, and rural regions as counties coded as 6 to 9 [14]. We obtained the physical addresses of radiation oncologists from the US National Plan and Provider Enumeration System database and the total number of incident cancer cases during the study period from the SEER. The number of radiation oncologists per 10000 cancer patients was computed for each county.

Disease Outcomes

The diagnosis of a second primary breast tumor was determined according to SEER rules for defining multiple primary cancers [15]. A breast tumor following DCIS diagnosis was registered as a second primary breast tumor if it was histologically different, occurred more

than five years after the first DCIS, or was identified in the contralateral breast. An invasive breast cancer in the ipsilateral breast following DCIS was also registered as a second primary breast tumor if it was identified more than 60 days after diagnosis. For this analysis, ipsilateral breast tumors (IBTs) and contralateral breast tumors (CBTs) were defined as second primary breast tumors occurring in the ipsilateral and contralateral breasts, respectively. We excluded IBTs and CBTs identified within the first six months of followup to increase the likelihood that they represented true second primaries rather than residual disease or synchronous bilateral primaries. Person-years were calculated from six months after the first DCIS until the date of the second primary breast tumor, death, or December 31, 2011, whichever occurred first.

Statistical Analysis

Baseline characteristics were compared between groups with Wilcoxon rank sum tests and χ^2 tests. We performed a two-level multivariable logistic regression analysis to estimate odds ratios (ORs) and 95% confidence intervals (95% CIs) of APBIb use for patient-level and county-level factors. This model accounted for the non-independence of treatment selection among patients from the same county.

To minimize any imbalances in covariates between the radiation therapy groups, we estimated the association of APBIb versus WBI with the risks for IBTs and CBTs in a propensity score-matched cohort. Evidence suggests that variables that are related to the disease outcome should be included in a propensity score model [16, 17]. All aforementioned patient-level and county-level factors, with the exception of marital status and radiation oncologists per 10000 cancer patients, have been associated with DCIS or breast cancer outcomes [18–20] and thus were used to estimate propensity scores. Considering a low rate of IBTs and a relatively short followup, we matched no more than four patients who received WBI to each patient who received APBIb on the logit of propensity scores by using calipers of width equal to 0.2 of the standard deviation of the logit of propensity score [21]. Nearest-neighbor matching without replacement was used. We computed standardized differences for covariates before and after propensity score matching, with a standardized difference of 10% or more considered indicative of imbalance [22].

The stratified log-rank test was conducted to compare the two Kaplan-Meier curves derived from the propensity score-matched sample [23]. Marginal hazard ratios (HR) of IBTs and CBTs were estimated using Cox proportional hazards regression with a robust variance estimator that accounts for matching [23, 24]. IBT and CBT were analyzed as competing risks. The proportional hazard assumption for APBIb versus WBI, which was assessed by using an interaction with log-time, was appropriate. Finally, we assessed the sensitivity of the result to unmeasured confounding using an array approach [25]. All tests were performed two sided at the 5% significance level using SAS (version 9.3; SAS Institute, Cary, NC).

RESULTS

Among 40749 women receiving BCS and radiation therapy, 2212 (4.5%) received APBIb between 2002 and 2011. The median age at diagnosis was 58 years (range 18 to 100). Racial and ethnic minority patients comprised 22.1% of the patient population, and 12.1% were unmarried. The patient population was further characterized by 5.3% with tumors >30mm, 41.5% with poorly differentiated tumors, and 10.6% with comedocarcinoma. ER status was available for 74.3% of patients, of which 85.0% were positive. PR status was available for 70.1% of patients, of which 74.9% were positive. Compared with patients who received WBI, patients who received APBIb were significantly older at the diagnosis of their first DCIS and were more likely to be white or black, be diagnosed more recently, and have small, well or moderately differentiated, ER+/PR+, and comedo tumors (each $P<0.05$). APBIb use varied substantially across SEER registries; APBIb was used more frequently in patients living in urban areas and counties with the least socioeconomic deprivation (each $P<0.0001$) (Table 1).

Influencing Factors (Table 1)

Patients diagnosed from 2005 to 2007 (OR, 4.79; 95% CI, 3.89 to 5.89) and from 2008 to 2011 (OR, 8.65; 95% CI, 7.07 to 10.57) were more likely to receive APBIb than those diagnosed from 2002 to 2004. Older women were more likely to receive APBIb; the odds of APBIb use increased by greater than two fold in women older than 70 years compared with those younger than 50 years (For ages 70–79: OR, 2.09; 95% CI, 1.77 to 2.46; for ages 80: OR, 2.10; 95% CI, 1.60 to 2.75). Black (OR, 0.77; 95% CI, 0.66 to 0.91), Asian (OR, 0.58; 95% CI, 0.47 to 0.72) and Hispanic (OR, 0.69; 95% CI, 0.57 to 0.83) women were less likely than white women to receive APBIb. Marital status was not related to APBIb use.

In addition, patients with tumors >30 mm in size (OR, 0.39; 95%CI, 0.30 to 0.51) were less likely to receive APBIb than those with tumors ≤10 mm. ER–/PR– tumors (OR, 0.83; 95%CI, 0.71 to 0.97) and comedo tumors (OR, 1.26; 95%CI, 1.09 to 1.46) were associated with reduced odds and increased odds of APBIb use, respectively. Nuclear grade was not associated with APBIb use.

Urbanization was the only county-level factor associated with APBIb use. Patients residing in non-urban areas near a metropolis (OR, 0.59; 95%CI, 0.42 to 0.81) or in a rural location (OR, 0.53; 95%CI, 0.36 to 0.79) were less likely to receive APBIb than those residing in urban areas. Degree of socioeconomic deprivation and number of radiation oncologists per 10000 cancer patients were not associated with APBIb use.

Matching

Women who were free from second breast tumors for at least six months after the first DCIS were eligible for the analysis of disease outcomes ($n=38514$). Among them, 2043 (5.3%) received APBIb and 36471 (94.7%) received WBI. We successfully matched 1962 patients receiving APBIb with 7203 patients receiving WBI, consisting of 1650 1:4 matches, 84 1:3 matches, 123 1:2 matches and 105 1:1 matches. After matching, the absolute standardized differences were less than 0.1 for variables included in the propensity score model (Table 2).

Disease Outcomes

Among 9165 propensity score-matched patients, 74 (0.8%) developed IBTs and 131 (1.4%) developed CBTs during a median follow-up of 46 months. A statistically significant difference in the cumulative incidence of IBTs was observed between APBIb and WBI groups, with a 5-year rate of 2.0% in the APBIb group and 1.0% in the WBI group (Figure 1A, $p=0.03$). However, the cumulative incidence of CBTs was similar between APBIb and WBI groups (Figure 1B, 1.5% versus 2.0%, $p=0.91$).

Compared with women receiving WBI, women receiving APBIb had significantly higher IBT risk (HR, 1.74; 95% CI, 1.06 to 2.85) and no difference for CBT risk (HR, 0.91; 95% CI, 0.59 to 1.41) in the propensity score-matched sample. We also estimated the HRs using the propensity score adjustment method among all eligible women, with an HR of 1.68 (95% CI, 1.13 to 2.49) for IBTs and an HR of 0.87 (95% CI, 0.65 to 1.15) for CBTs (Table 3).

The array-approach sensitivity analysis showed that an unmeasured confounder would have to be moderately imbalanced in the prevalence between the APBIb and WBI groups and moderately associated with IBT risk to account for the observed HR for APBIb (Supplementary Tables). For example, if there was a 10% absolute difference in prevalence of an unmeasured confounder between two groups of radiation therapy, an HR of at least 1.7 was required for an unmeasured confounder to attenuate the observed HR for APBIb to nonsignificance.

DISCUSSION

In a nationally representative cohort of women with DCIS who received both BCS and radiation therapy, APBIb was more likely to be used in older patients, white patients, patients with small tumors, comedo subtypes, ER+/PR+ tumors, patients living in urban areas, and patients diagnosed more recently. Compared with WBI, APBIb was associated with a significantly higher risk of IBTs and a similar risk of CBTs during a median 46-month followup.

APBIb may be inappropriate for DCIS according to the ASTRO guidelines. However, 4.5% of our sample received APBIb between 2002 and 2011, which was lower than that in DCIS patients from the CoC-accredited hospitals (6.5%) [10]. APBIb use for DCIS and invasive breast cancer increased significantly from 2005 through 2008 and stabilized afterwards, possibly reflecting the beginning of Medicare reimbursement for APBIb in 2004 [26], and then decreased reimbursement for APBIb by Centers for Medicare and Medicaid Services in 2008 and the ASTRO guidelines published in 2009 [9].

Multiple patient and tumor characteristics have been related to APBIb use. An analysis of the National Cancer Database showed that being older, being white, having private insurance, and having small tumors were associated with increased odds of APBIb use for DCIS [10]. Although poorly differentiated DCIS and comedo DCIS are associated with increased IBT risk [27], we found that APBIb use was comparable between women with poorly differentiated tumors and those with well differentiated tumors, and that women with

comedo DCIS were more likely to use APBib. We analyzed the influence of ER and PR status on APBib use for DCIS as women with ER-/PR- DCIS may have higher IBT risk [27]. We found that patients with ER-/PR- DCIS were less likely than those with ER+/PR+ DCIS to receive APBib, which was consistent with the result reported in women with early invasive breast cancer [7].

APBib use for breast tumors was reported to vary substantially across large geographic areas [6, 7, 10, 28]. We found a higher prevalence of APBib for DCIS in urban regions, which was consistent with previous reports of increased APBib use for DCIS or invasive breast cancer among women residing in urban areas [6, 10, 29]. We did not find an association of county-level socioeconomic deprivation or number of radiation oncologists per 10000 cancer cases with APBib use. Yao et al. [10] reported an increased use of APBib for DCIS in women residing further from radiation treatment facilities.

There are limited data from prospective clinical trials evaluating APBib for DCIS. The American Society of Breast Surgeons MammoSite breast brachytherapy registry trial has the longest follow-up (70.6 months) and largest number of DCIS patients (n=192) to date. Seven local recurrences were reported and the five-year actuarial IBT rate was 4.1% [30]. The MammoSite DCIS phase II clinical trial used intracavitary balloon APBib and reported two IBTs in 100 patients but had a short follow-up of 9.5 months [31]. Another prospective trial evaluated intracavitary balloon APBib and included 41 patients, with four IBTs reported at a follow-up of 5.3 years [32].

Data comparing APBib and WBI with regards to DCIS outcomes are lacking. In the Hungarian phase III trial for invasive breast cancer (n=258), there was no difference in risks of local recurrence, overall survival, cancer-specific survival, or disease-free survival at a 10-year follow-up between the accelerated partial breast irradiation (APBI) and the WBI groups [33]. However, APBI was delivered through an electron beam in addition to brachytherapy for APBI in this trial. Several randomized controlled trials are ongoing to compare local control effects of partial breast irradiation and WBI [34–41].

We observed a 74% increased IBT risk in women receiving APBib versus WBI. However, the absolute difference in the 5-year rate was only one per 100 patients. The moderately increased IBT risk might be acceptable to some patients after considering the benefits of APBib. Due to a small number of DCIS patients receiving APBib and few IBT events, our results need to be validated in randomized phase III trials with longer followups.

This study had limitations. Some potential confounders were unavailable, including surgical margins, multifocality, endocrine therapy and comorbidities. Women with positive margins, due to a higher IBT risk [42], are not recommended for APBib [9]. APBib was more likely to be used in women with hormone receptor-positive DCIS, who typically received endocrine therapy. Thus, lack of the information on surgical margins and endocrine therapy may result in the underestimation of DCIS outcomes in APBib patients. Comorbidity was not related to APBib use for breast cancer [7]. Data from William Beaumont Hospital showed comparable IBT rates between APBib-treated breast cancer patients with and without multifocality [43]. In addition, the classification of external beam radiation as WBI

might include APBI using external beam techniques such as three-dimensional conformal radiotherapy or intensity-modulated radiotherapy. APBI delivered through external beam technologies was reported to account for 3.3% of all external beam radiation delivered between 2003 and 2010 [7]. There was a potential for misclassification of residual disease as second primaries. We attempted to reduce this misclassification by restricting second primary cases to those that were diagnosed at least six months after the first primary DCIS. Additional limitations included the short follow-up and the incomplete capture of second breast tumors, especially second DCIS occurring in the first five years, by the SEER program.

In summary, APBIb was associated with a moderately increased IBT risk in DCIS patients during a median 46-month followup compared with WBI, while the absolute difference in the 5-year IBT rate was small. APBIb use for DCIS was influenced by patient and tumor characteristics and residential location. Given the long natural history of breast cancer, future work should focus on long-term local control outcomes of APBIb versus WBI. APBIb has been associated with worse breast preservation and increased complications in older women with invasive breast cancer compared with WBI [44]. Radiation therapy may represent overtreatment for DCIS patients at low IBT risk [45, 46]. Therefore, a patient's risk of IBT derived from histopathological factors and molecular subtypes, benefit, harms and costs of APBIb should be incorporated to define DCIS patients most appropriate for APBIb.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Cumulative incidence of second breast tumors in the ipsilateral breast (A; stratified log-rank $P = 0.03$) and in the contralateral breast (B; stratified log-rank $P = 0.91$) in women with DCIS by type of radiation therapy.

Table 1

Characteristics of DCIS patients who underwent breast-conserving surgery by the type of radiation therapy and the adjusted odds ratios (ORs) of accelerated partial breast irradiation through brachytherapy use associated with these characteristics (n=40749)

	WBI (n=38537) No. (%)	APBIB (n=2212) No. (%)	P value	OR [†] (95% CI)	P value
Age, years			<.0001		<.0001
Median (range)	58 (18–100)	60 (33–93)		1.00 (reference)	
<50	9535 (24.7)	345 (15.6)		1.69 (1.48, 1.94)	
50–59	12116 (31.4)	719 (32.5)		1.90 (1.65, 2.18)	
60–69	10145 (26.3)	694 (31.4)		2.09 (1.77, 2.46)	
70–79	5491 (14.2)	372 (16.8)		2.10 (1.60, 2.75)	
80	1250 (3.2)	82 (3.7)			
Race and ethnicity			<.0001		<.0001
Non-Hispanic white	27281 (70.8)	1717 (77.6)		1.00 (reference)	
Non-Hispanic black	3882 (10.1)	236 (10.7)		0.77 (0.66, 0.91)	
Non-Hispanic Asian	3487 (9.0)	101 (4.6)		0.58 (0.47, 0.72)	
Hispanic	3375 (8.8)	138 (6.2)		0.68 (0.57, 0.83)	
Others	512 (1.3)	20 (0.9)		0.82 (0.52, 1.31)	
Marital status			0.03		0.31
Married	24827 (64.4)	1440 (65.1)		1.00 (reference)	
Unmarried	4691 (12.2)	221 (10.0)		0.85 (0.73, 0.99)	
Divorced	3944 (10.2)	235 (10.6)		0.96 (0.83, 1.11)	
Widowed	3838 (10.0)	235 (10.6)		0.93 (0.79, 1.09)	
Missing	1237 (3.2)	81 (3.7)		1.00 (0.79, 1.28)	
Year of diagnosis			<.0001		<.0001
2002–2004	10465 (27.2)	116 (5.2)		1.00 (reference)	
2005–2007	11663 (30.3)	601 (27.2)		4.79 (3.89, 5.89)	
2008–2011	16409 (42.6)	1495 (67.6)		8.65(7.07,10.57)	
Tumor size			<.0001		<.0001
10 mm	15831 (41.1)	1048 (47.4)		1.00 (reference)	
11–20 mm	7792 (20.2)	415 (18.8)		0.83 (0.73, 0.93)	

	WBI (n=38537) No. (%)	APBIB (n=2212) No. (%)	P value	OR [†] (95% CI)	P value
21–30 mm	2544 (6.6)	115 (5.2)		0.69 (0.57, 0.85)	
>30 mm	2092 (5.4)	57 (2.6)		0.39 (0.30, 0.51)	
Unknown	10278 (26.7)	577 (26.1)		0.94 (0.84, 1.05)	
Nuclear grade			0.003		0.84
Well differentiated	4186 (10.9)	247 (11.1)		1.00 (reference)	
Moderately differentiated	13385 (34.7)	841 (38.0)		1.05 (0.90, 1.23)	
Poorly differentiated	16032 (41.6)	882 (39.9)		1.01 (0.86, 1.19)	
Unknown	4934 (12.8)	242 (10.9)		1.03 (0.85, 1.25)	
Histological subtype			0.002		0.02
Not otherwise specified	26182 (67.9)	1454 (65.7)		1.00 (reference)	
Comedo	4047 (10.5)	260 (11.8)		1.26 (1.09, 1.46)	
Papillary	1666 (4.3)	73 (3.3)		0.89 (0.69, 1.14)	
Cribiform	3874 (10.1)	232 (10.5)		1.03 (0.89, 1.20)	
Solid	2768 (7.2)	193 (8.7)		1.12 (0.95, 1.32)	
Hormone receptor status			<.0001		0.05
ER+/PR+	19711 (51.1)	1405 (63.5)		1.00 (reference)	
ER+/PR–	2905 (7.5)	189 (8.5)		0.88 (0.75, 1.04)	
ER–/PR+	247 (0.6)	13 (0.6)		0.77 (0.43, 1.37)	
ER–/PR–	3838 (10.0)	224 (10.1)		0.83 (0.71, 0.97)	
Unknown	11836 (30.7)	381 (17.2)		0.88 (0.77, 1.00)	
Quartiles of county-level socioeconomic deprivation			<.0001		0.43
Q1 (Least deprived)	14872 (38.6)	969 (43.8)		1.00 (reference)	
Q2	11822 (30.7)	721 (32.6)		1.31 (0.93, 1.85)	
Q3	6787 (17.6)	250 (11.3)		1.13 (0.77, 1.65)	
Q4 (Most deprived)	5056 (13.1)	272 (12.3)		1.30 (0.84, 2.00)	
Urban/rural residence			<.0001		<0.01
Urban	24731 (64.2)	1553 (70.2)		1.00 (reference)	
Near metropolis	11885 (30.8)	568 (25.7)		0.59 (0.42, 0.81)	
Rural	1921 (5.0)	91 (4.1)		0.53 (0.36, 0.79)	
No. of radiation oncologists per 10000 cancer patients at the county level, median (range)	5.43 (0–38.91)	5.57 (0–24.75)	0.15	0.75 (0.52, 1.09)	0.13

	WBI (n=38537) No. (%)	APBIb (n=2212) No. (%)	P value	OR [‡] (95% CI)	P value
SEER registry [‡]			<.0001		-
Hawaii	1103 (2.9)	3 (0.1)			-
San Francisco-Oakland	2289 (5.9)	67 (3.0)			-
Metropolitan Detroit	2689 (7.0)	97 (4.4)			-
Connecticut	2655 (6.9)	109 (4.9)			-
Iowa	1917 (5.0)	80 (3.6)			-
New Jersey	4955 (12.9)	210 (9.5)			-
Greater California	7331 (19.0)	352 (15.9)			-
Los Angeles	2834 (7.4)	143 (6.5)			-
Seattle (Puget Sound)	2946 (7.6)	156 (7.1)			-
Utah	587 (1.5)	32 (1.4)			-
San Jose-Monterey	1284 (3.3)	76 (3.4)			-
Kentucky	1685 (4.4)	110 (5.0)			-
Rural Georgia	56 (0.1)	4 (0.2)			-
Louisiana	1823 (4.7)	152 (6.9)			-
New Mexico	440 (1.1)	37 (1.7)			-
Greater Georgia	2359 (6.1)	281 (12.7)			-
Metropolitan Atlanta	1584 (4.1)	303 (13.7)			-

WBI=whole breast irradiation, APBIb=accelerated partial breast irradiation through brachytherapy, ER=estrogen receptor, PR=progesterone receptor. 95% CI=95% confidence interval

[‡] ORs were estimated in a two-level multivariable logistic regression analysis in which patients were nested within counties to account for the non-independence of treatment selection among patients from the same county. All variables (except SEER registry) were simultaneously included in the model.

[‡] SEER registry was not included in the two-level logistic regression model because the counties in which patients lived were accounted for.

Table 2

Comparison of baseline characteristic of DCIS patients by type of radiation therapy before and after propensity score matching.

	Before matching		After matching		Standardized difference
	APBIB (n=2043)	WBI (n=36471)	APBIB (n=1962)	WBI (n=7203)	
Median (IQR) age, years	60 (52, 68)	57 (50, 66)	60 (52, 68)	60 (52, 68)	0.002
Age categories, No (%)					0.028
<50 years	330 (16.2)	9101 (25.0)	627 (32.0)	2343 (32.5)	
50–59 years	655 (32.1)	11483 (31.5)	609 (31.0)	2218 (30.8)	
60–69 years	635 (31.1)	9502 (26.1)	339 (17.3)	1277 (17.7)	
70–79 years	347 (17.0)	5197 (14.2)	72 (3.7)	262 (3.6)	
80 years	76 (3.7)	1188 (3.3)	315 (16.1)	1103 (15.3)	
Race and ethnicity, No (%)					0.027
Non-Hispanic white	1597 (78.2)	25886 (71.0)	1523 (77.6)	5518 (76.6)	
Non-Hispanic black	218 (10.7)	3647 (10.0)	213 (10.9)	829 (11.5)	
Non-Hispanic Asian	88 (4.3)	3279 (9.0)	88 (4.5)	328 (4.5)	
Hispanic	122 (6.0)	3194 (8.8)	120 (6.1)	450 (6.2)	
Others	18 (0.9)	465 (1.3)	18 (0.9)	78 (1.1)	
Tumor size, No (%)					0.035
10 mm	966 (47.3)	14979 (41.1)	909 (46.3)	3340 (46.4)	
11–20 mm	376 (18.4)	7335 (20.1)	365 (18.6)	1346 (18.7)	
21–30 mm	108 (5.3)	2362 (6.5)	108 (5.5)	382 (5.3)	
>30 mm	54 (2.6)	1943 (5.3)	54 (2.7)	183 (2.5)	
Unknown	539 (26.4)	9852 (27.0)	526 (26.8)	1952 (27.1)	
Nuclear grade, No (%)					0.018
Well differentiated	228 (11.2)	3947 (10.8)	219 (11.2)	827 (11.5)	
Moderately differentiated	785 (38.4)	12645 (34.7)	753 (38.4)	2748 (38.2)	
Poorly differentiated	805 (39.4)	15151 (41.5)	776 (39.6)	2828 (39.3)	
Unknown	225 (11.0)	4728 (13.0)	214 (10.9)	800 (11.1)	
Histological subtype, No (%)					0.021
Not otherwise specified	1338 (65.5)	24835 (68.1)	1300 (66.3)	4832 (67.1)	

	Before matching			After matching		
	APB1b (n=2043)	WBI (n=36471)	Standardize d difference	APB1b (n=1962)	WBI (n=7203)	Standardized difference
Comedo	240 (11.8)	3804 (10.4)		220 (11.2)	765 (10.6)	
Papillary	72 (3.5)	1603 (4.4)		65 (3.3)	235 (3.3)	
Cribiform	219 (10.7)	3661 (10.0)		212 (10.8)	760 (10.6)	
Solid	174 (8.5)	2568 (7.0)		165 (8.4)	611 (8.5)	
Hormone receptor status, No (%)			0.364			0.021
ER+/PR+	1290 (63.1)	18319 (50.2)		1225 (62.4)	4480 (62.2)	
ER+/PR-	169 (8.3)	2711 (7.4)		165 (8.4)	589 (8.2)	
ER-/PR+	12 (0.6)	238 (0.7)		11 (0.6)	41 (0.6)	
ER-/PR-	206 (10.1)	3595 (9.9)		197 (10.0)	715 (9.9)	
Unknown	366 (17.9)	11608 (31.8)		364 (18.6)	1378 (19.1)	
Quartiles of county-level socioeconomic deprivation, No (%)			0.194			0.026
Q1 (Least deprived)	894 (43.8)	14078 (38.6)		824 (42.0)	2902 (40.3)	
Q2	667 (32.7)	11176 (30.6)		660 (33.6)	2522 (35.0)	
Q3	239 (11.7)	6420 (17.6)		235 (12.0)	832 (11.6)	
Q4 (Most deprived)	243 (11.9)	4797 (13.2)		243 (12.4)	947 (13.2)	
Urban/rural residence, No (%)			0.130			0.030
Urban	1433 (70.1)	23408 (64.2)		1361 (69.4)	4974 (69.1)	
Near metropolis	522 (25.6)	11253 (30.9)		85 (4.3)	1937 (26.9)	
Rural	88 (4.3)	1810 (5.0)		516 (26.3)	292 (4.1)	
Year of diagnosis of first DCIS, No (%)			0.955			0.025
2002-2004	116 (5.7)	10458 (28.7)		116 (5.9)	442 (6.1)	
2005-2007	599 (29.3)	11656 (32.0)		588 (30.0)	2160 (30.0)	
2008-2011	1328 (65.0)	14357 (39.4)		1258 (64.1)	4601 (63.9)	

WBI=whole breast irradiation, APB1b=accelerated partial breast irradiation through brachytherapy

Table 3

Hazard ratios (HRs) of second breast tumors in the ipsilateral and contralateral breasts in DCIS patients receiving breast-conserving surgery and radiation therapy.

	Ipsilateral breast tumor recurrence			Contralateral breast tumors		
	No. of patients	No. of events	HR (95% CI)	P	No. of events	HR (95% CI)
Propensity score matching						
WBI	7203	52	1.00 (reference)		106	1.00 (reference)
APB1b	1962	22	1.74 (1.06, 2.85)	0.03	25	0.91 (0.59, 1.41)
Propensity score adjustment						
WBI	36471	539	1.00 (reference)		837	1.00 (reference)
APB1b	2043	23	1.68 (1.13, 2.49)	0.01	25	0.87 (0.65, 1.15)

WBI=whole breast irradiation, APB1b=accelerated partial breast irradiation through brachytherapy, 95% CI=95% confidence interval