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Trends in Treatment Patterns and Clinical Outcomes in Young Women Diagnosed with Ductal Carcinoma In Situ

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Keywords

Ductal Carcinoma In Situ (DCIS), Breast Conserving Surgery (BCS), Radiation Therapy (RT), Mastectomy (MTX), Contralateral Prophylactic Mastectomy (CPM), Epidemiology

List of abbreviations

Ductal Carcinoma In Situ (DCIS), Breast Conserving Surgery (BCS), Radiation Therapy (RT), Mastectomy (MTX), Contralateral Prophylactic Mastectomy (CPM), Surveillance, Epidemiology and End Results (SEER)

Conflict of Interest

The authors declare that they have no conflicts of interest.

Microabstract

Younger women diagnosed with DCIS are more likely to receive a more aggressive treatment compared to older women. Our analysis of SEER data (n=3,648) showed that young women who received MTX +/- CPM did not have improved survival compared to BCS+RT. Thoughtful consideration should be given to treatment selection for DCIS in young women.

Abstract

Purpose: While it is known that the risk of a second breast cancer event among young women diagnosed with Ductal Carcinoma in Situ (DCIS) is higher than in older women, the impact of current treatment options on long-term outcomes in this subgroup of women remains poorly defined. We aimed to evaluate national treatment trends and determine their impact on second breast cancer risk and overall survival among young women diagnosed with DCIS. **Methods:** Surveillance, Epidemiology and End Results (SEER) data from 1998-2011 were used to analyze 3,648 DCIS patients under age 40. **Results:** Among all treatment options, Breast Conserving Surgery with Radiation Therapy (BCS+RT) was the most prevalent (36.1%) followed by Mastectomy (MTX) without Contralateral Prophylactic Mastectomy (CPM) (25.8%), BCS alone (22.2%) and MTX with CPM (15.8%). Risk of a second ipsilateral event was >5-fold and >2-fold lower within two years and five years of initial DCIS diagnosis, respectively, in women who received BCS+RT compared to BCS alone; and overall survival was 3-fold higher in women who received BCS+RT. However, MTX with or without CPM did not show an increase in overall survival compared to BCS+RT. In addition, while the percentage of young women getting MTX with CPM has increased in recent years, MTX with CPM did not show an increased benefit in survival compared to MTX without CPM. **Conclusions:** The results of our study suggest that more aggressive treatments do not offer survival benefits over BCS+RT; thus, clinical treatment options in young women with DCIS should be carefully considered.

Introduction

Ductal carcinoma in situ, also known as DCIS, is a non-invasive form of breast cancer which may be a potential precursor to invasive breast cancer. In women between the ages of 20-49, DCIS accounted for approximately 24% of breast cancers diagnosed in 2013. [1] Women younger than 45 are at a higher risk of a second event following diagnosis with DCIS compared to older women (27% vs. 11%). [2,3] and up to half of these second events after DCIS are invasive. [4,5] Treatment options for DCIS include breast-conserving surgery (BCS), breast conserving surgery and radiation therapy (BCS+RT), and mastectomy (MTX). In addition, some women opt to undergo MTX with prophylactic removal of the contralateral breast, or contralateral prophylactic mastectomy (CPM). [6]

The goal of treatment for DCIS is not only to minimize the development of a second breast cancer event but also reduce its impact on the patient's quality of life. [7,8] Among women diagnosed with DCIS, mental quality of life was significantly lower in younger women compared to older women diagnosed with DCIS. [9] Since overtreatment may have potential effects on patients' quality of life that are especially relevant in young women, in order to reach a balanced decision about which treatment option a young woman diagnosed with DCIS should take, it is important to understand the clinical benefits of the different treatment options in terms of developing a second breast cancer and survival in young women.

Studies comparing BCS+RT versus BCS alone have shown a survival benefit for DCIS patients overall who received BCS+RT, [10–12] and numerous clinical trials have

demonstrated that RT lowers the incidence for a second ipsilateral event. [13,14] Studies have also shown that there is no difference in survival between women overall treated with BCS+RT versus MTX for women with early stage breast cancer. [15–20] However, DCIS in young women specifically has been minimally studied in terms of second ipsilateral events and survival in the U.S. In addition, there has been an increase in the use of CPM in women diagnosed with DCIS, especially among young women in the U.S. [21–23]; however, the clinical benefits of CPM are not well understood in young women with DCIS and there have been controversial findings for young women diagnosed with low grade invasive breast cancer. [24,25] The current analysis focuses on recent trends in treatment options and clinical outcomes in young women with DCIS.

Methods

This is a retrospective population based study using Surveillance, Epidemiology, and End Results (SEER) data. The SEER program of the National Cancer Institute (NCI) contains approximately 97% of all incident cancer cases from population-based cancer registries covering approximately 28% of the U.S. population. The SEER Program Registries routinely collect data on patient demographics, primary tumor site, tumor morphology and stage, first course of treatment, and follow-up for vital status in 18 registries.
Our analysis included data on young women (age at diagnosis between 18 and 40 years old) diagnosed between January 1, 1998 and December 31, 2011 with primary ductal carcinoma in situ (DCIS) breast cancer as their first or only tumor in their lifetime.[26] Breast cancer was identified using SEER primary site recode 26000 with the median follow-up time of 7 years. International Classification of Disease for Oncology

(ICD-O) morphology codes categorized as DCIS included 85002, 85012, 85032, 85042, 85222, 85432, 80502 and 82012. Patients who were treated with mastectomy plus radiation consisted 0.7% of data and were excluded from analysis due to small sample size. There was one case identified by autopsy or death certificate only, which was excluded. The final analytic data set included 3,648 subjects.

Variables and statistical analysis

Treatment for DCIS was identified for each patient using the "surgery for primary site" and "radiation therapy" variables provided in SEER data. The four types of treatment were breast-conserving surgery alone (BCS alone), breast conserving surgery and radiation therapy (BCS+RT), mastectomy with contralateral prophylactic mastectomy (MTX with CPM), and mastectomy without contralateral prophylactic mastectomy (MTX without CPM).

Other covariates included demographic and tumor characteristics. Race/ethnicity of the patient was categorized into five groups: White, African American, Hispanic, Asian/Pacific Islander, or other/unknown. Patient marital status was categorized into married, not married or unknown. Registry region had four categories: Central (Detroit, Iowa, Utah, Kentucky, and Louisiana), Eastern (Connecticut, Georgia, and New Jersey), Western (Hawaii, New Mexico, Seattle and Alaska) and California. Tumor characteristics included tumor grade (low grade, high grade or unknown), tumor size (≤15mm, >15mm or unknown size), tumor histology (comedo or other histology), estrogen receptor status (ER), and progesterone receptor status (PR), all obtained from the SEER data.

Frequency distributions of patients' demographic and clinical characteristics were analyzed using χ^2 Test for categorical variables or ANOVA test for continuous variable in bivariate analysis. Multivariate logistic regression models were used to test for associations between receiving BCS+RT and the characteristics. The Kaplan-Meier method was used to determine the cumulative risk of a second ipsilateral breast tumor from the date of first DCIS diagnosis to the date of second ipsilateral tumor diagnosis. Incidence rates of a second ipsilateral breast tumor were calculated in BCS alone and BCS +RT treatment groups for follow-up times of 2 years, 5 years and the entire study period. After verifying the proportionality assumption, Cox proportional hazards model was fitted to evaluate the effects of additional RT on the risk of developing second ipsilateral breast cancer controlling for other characteristics. Patients' follow up time was defined as the time between diagnosis date and death from all causes or last follow-up date. After verifying proportionality assumption, proportional hazards model was fitted to evaluate the effects of treatment option and other predictor on overall survival, and possible interaction terms of main effects were also tested by comparing a reduced model to the full model. All statistical tests were two-sided. P-values <0.05 were considered statistically significant. All statistical analyses were performed on SAS 9.4 (SAS Institute, Cary, NC, U.S.A).

Results

Trends in treatment options

We identified 3,648 DCIS patients under the age of 40 who met the eligibility criteria. The greatest proportion of patients underwent BCS+RT (36.1%) followed by MTX

without CPM (25.8%), then BCS alone (22.2%) and MTX with CPM (15.8%). Treatment trends have significantly changed in the recent years going from 1998-1999 to 2005-2011. The percentage of women who received MTX with CPM increased (7% to 21.5%) whereas the percentages of women getting BCS+RT (38.8% to 35.3%), BCS alone (25.1% to 20%) and MTX without CPM (29.1% to 23.1%) decreased (Table 1). Women who were diagnosed with DCIS and got MTX in 2005-11 were 4.18-fold more likely to get CPM than women diagnosed in 1998-99 (Table 2). Among the same women, African Americans were significantly less likely to get CPM (OR = 0.29, 95% CI = 0.20 - 0.44), followed by Asians (OR =0.48, 95% Cl = 0.31 - 0.73) and Hispanics (OR =0.57, 95% Cl = 0.38 - 0.84) compared to Whites (Table 2).

Second ipsilateral breast tumor

Young women who got BCS alone were more likely to have a second ipsilateral breast tumor compared to women who received BCS+RT, both at 2 years and 5 years after DCIS diagnosis (HR = 5.36, 94% CI = 2.02 - 14.3, p=0.0008 and HR = 2.46, 95% CI = 1.47- 4.11, p=0.0006, respectively), after adjusting for year of diagnosis, race, registry region, tumor grade, histology, size and hormone receptor status (Table 3). The small numbers of second ipsilateral events limited our stratified analysis by second DCIS events, but the trend remained statistically significant for second invasive ipsilateral events within 5 years (HR = 2.06, 95% CI = 1.12 - 3.77, p=0.019).

Survival

Overall survival was 3-fold lower in young women who received BCS alone (HR = 3.26, 95% CI 1.58-6.73, p = 0.0014) compared to BCS+RT, after adjusting for potential confounders (Table 4). Overall survival in young women was not significantly different between those who received MTX with (HR = 1.16, 95% CI 0.38-3.56, p = 0.80) or without (HR = 1.65, 95% CI 0.79-3.46, p = 0.19) CPM compared to BCS+RT. The results were consistent after propensity weight scoring for adjusting for confounded and inverse probability weighting. There was also no significant difference in overall survival in young women who received MTX with CPM compared to without CPM (data not shown).

Discussion

With advancements in mammographic techniques, the incidence and detection of DCIS is on the rise. [27] Since only a limited number of studies on DCIS focus on women younger than 40, there is little clarity as to which treatment option is best for this age group of women. The trends in treatment patterns among young women diagnosed with DCIS observed in our study are different than in a previous analysis of women of all age groups which found that the greatest proportion opted for BCS+RT (43%), followed by BCS alone (26.5%), unilateral MTX (23.8%), and MTX with CPM (4.5%). [28] The rise in use of MTX with CPM among young women diagnosed with DCIS observed in our study is in agreement with previous studies, which have also shown that MTX is increasingly becoming a popular choice for women over the past decade. [21,22] Since young women are more likely to undergo MTX compared to women overall and the percent of young

women choosing MTX with CPM is increasing, it is imperative to study not only treatment trends but also clinical outcomes in this specific age group of women.

Our observation that young white women were more likely to get MTX with CPM compared to women of other race/ethnicities is consistent with a previous study done in women of all age groups diagnosed with DCIS which suggested that the trend towards getting a more aggressive treatment option is most prominent among white women in comparison to other ethnic groups. [28] An unexpected finding was that women with tumors >15 mm were less likely to get MTX with CPM than MTX without CPM compared to women with tumors up to 15 mm. This may be due to a large proportion of tumors classified with "unknown" size actually being smaller tumors that cannot be measured. Since we do not have data that this was actually the case, we allowed tumors of unknown size to remain as a separate category; however, if we combined women with tumors of unknown size and women with tumors up to 15 mm, there would have been no statistically significant difference in likelihood of undergoing the different treatments.

Consistent with previous studies which showed that women of all ages diagnosed with DCIS who got radiation therapy had a 60% decreased risk of second ipsilateral event compared to women who got BCS alone [29], our data also showed that young women with DCIS who got BCS+RT also had a >5-fold and >2-fold lower risk of a second ipsilateral event within two years and five years of initial DCIS diagnosis, respectively. These are important parameters because previous long-term studies have shown that approximately half of the recurrences following DCIS diagnosis occurred within the first 5 years. [30,31]

However, considering all second ipsilateral events that occurred in our study cohort, which had up to 13 years of follow-up, there was no difference in risk, suggesting that the protective effect of radiation decreases over time, which is consistent with recent findings on women with DCIS in the Netherlands. [32]

While our data indicate that, after adjusting for potential confounders, young women who received BCS alone were more than 3-fold likely to die compared to women who received BCS+RT, there does not appear to be a survival benefit associated with undergoing MTX with or without CPM over BCS+RT. There are other reasons women may opt for MTX with or without CPM. For example, a woman may choose MTX because of physician advice, personal fear of developing a second breast cancer event, high levels of stress and anxiety related to future breast cancer screening of the remaining breast(s), family history and others reasons. [33,34] Some women may opt for MTX with CPM in part due to desire for better cosmetic symmetry. [34] In addition, the use of MRI preoperatively allows for a better interpretation of the contralateral breast, and women who get an MRI are more likely to choose CPM. [35] In young women, these issues are particularly relevant because they have a longer expected number of years to live and also tend to overestimate their risk of having a contralateral breast cancer in the future. [36] Thus, even though a survival benefit is not evident, MTX with or without CPM may offer young women diagnosed with DCIS better outcomes in terms of alleviating anxiety of a second breast cancer in the future and a general piece of mind. Since the rate of young women diagnosed with DCIS choosing to undergo MTX with CPM has recently increased, future studies are needed to better understand the long-term effects of this

treatment in relation to overall and breast cancer-free survival. In addition, the increasing trend warrants studies on other aspects of women's health including quality of life and well-being.

Limitations of this study include the lack of family history, BRCA mutation status, genetic testing and hormone therapy results available in the SEER database. Because our study focused on DCIS in young women, our results are also limited by sample size and follow-up time. However, despite these limitations, SEER data account for a large diverse set of patients from all parts of the United States, thus making our findings broadly applicable to overall breast cancer trends in the country. To our knowledge, this study is unique in that it uses the most recent patient data from the SEER database (diagnosed between 1998-2011) to study both risk of second ipsilateral events and survival between young women diagnosed with DCIS who received different clinical treatments. Further studies on large populations with longer follow-up time and risk factor and treatment information are warranted to better understand the most clinically beneficial treatment option for young women with DCIS.

Conclusions

Young women with DCIS and their physicians should give thoughtful consideration to all treatment options because although young women choose MTX more so than in older women, there appears to be no significant difference in overall survival between young women who received MTX compared to BCS+RT. In addition, there was no significant difference in overall survival between young women who received MTX with CPM

compared to without CPM. Young women with DCIS should carefully consider all treatment options before making an informed decision, as more aggressive treatments (MTX with or without CPM) do not appear to confer survival benefit over BCS+RT.

Clinical Practice Points

- In 2013, DCIS accounted for approximately 24% of breast cancers in women between the ages of 20-49.
- Studies comparing BCS+RT versus BCS alone have shown that RT lowers the incidence for a second ipsilateral event and increases survival in DCIS patients overall.
- Previous studies have also shown that there are no differences in survival between women treated with BCS+RT versus MTX for women overall with early stage breast cancer.
- The present study found that treatment trends for young women (under age 40) diagnosed with DCIS have significantly changed in the recent years from 1998-1999 to 2005-2011, with a significant increase in the percentage of young women who received MTX with CPM in recent years.
- Overall survival in young women with DCIS who received BCS+RT was significantly higher compared to BCS alone.
- There was no difference in overall survival between young women with DCIS who received MTX with or without CPM compared to BCS+RT.

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Tables

Table 1. Patient demographics and tumor characteristics by treatment in study population, 1998-2011†*

	Total		BCS alone		BCS + RT		MTX with CPM		MTX without CPM	
	n	%	n	%	n	%	n	%	n	%
Total	3648	100.0	811	22.2	1318	36.1	577	15.8	942	25.8
Age at first DCIS diagnosis										
Mean age ± SD	37.2 ± 3.4		37.1 ± 3.8		37.7 ± 3.0		36.6 ± 3.6		37.1 ± 3.3	
Year DX										
1998-1999	402	11.0	101	25.1	156	38.8	28	7.0	117	29.1
2000-2004	1528	41.9	366	24.0	555	36.3	179	11.7	428	28.0
2005-2011	1718	47.1	344	20.0	607	35.3	370	21.5	397	23.1
Race										
White	2350	64.4	485	20.6	835	35.5	442	18.8	588	25.0
African American	462	12.7	110	23.8	164	35.5	39	8.4	149	32.3
Hispanic	379	10.4	94	24.8	131	34.6	50	13.2	104	27.4
Asian/Pacific Islander	415	11.4	111	26.7	172	41.4	39	9.4	93	22.4
Marital status										
Married	2449	67.1	508	20.7	857	35.0	427	17.4	657	26.8
Not married	1061	29.1	261	24.6	419	39.5	130	12.3	251	23.7
Unknown	138	3.8	42	30.4	42	30.4	20	14.5	34	24.6
Registry region										
California	1303	35.7	343	26.3	420	32.2	204	15.7	336	25.8
Central	782	21.4	120	15.3	297	38.0	142	18.2	223	28.5
Eastern	1230	33.7	288	23.4	464	37.7	194	15.8	284	23.1
Western	333	9.1	60	18.0	137	41.1	37	11.1	99	29.7
Grade										
Low grade (I or II)	1428	39.1	390	27.3	555	38.9	201	14.1	282	19.7
High grade (III or higher)	1428	39.1	201	14.1	485	34.0	270	18.9	472	33.1
Unknown	792	21.7	220	27.8	278	35.1	106	13.4	188	23.7
Histology										
Comedo	654	17.9	85	13.0	247	37.8	114	17.4	208	31.8
All others	2994	82.1	726	24.2	1071	35.8	463	15.5	734	24.5
Size										
<=15mm	1455	39.9	364	25.0	693	47.6	177	12.2	221	15.2
>15mm	948	26.0	146	15.4	237	25.0	188	19.8	377	39.8
unknown	1245	34.1	301	24.2	388	31.2	212	17.0	344	27.6
Laterality										
Right side	1808	49.6	407	22.5	641	35.5	296	16.4	464	25.7
Left side	1836	50.4	402	21.9	677	36.9	281	15.3	476	25.9
Hormone status										
Either ER or PR is positive	1568	43.0	284	18.1	611	39.0	303	19.3	370	23.6
Both ER and PR are negative	254	7.0	35	13.8	78	30.7	52	20.5	89	35.0
Unknown	1826	50.1	492	26.9	629	34.4	222	12.2	483	26.5

†dataset excludes MTX, NOS (not otherwise specified)
*P-values for Chi Square tests and ANOVA test are all <0.05, except for Laterality (p=0.72)
BCS: Breast conserving surgery
RT: Radiation therapy
CPM: Contralateral prophylactic mastectomy

Table 2. Logistic regression models of factors associated with treatment in subsets of young women with DCIS

	(2A) Factors associated with receiving BCS+RT, among subset of patients who had BCS+RT or BCS alone		(2B) Factors associated with receiving BCS+RT, among subset of patients who had BCS+RT or MTX (with or without CPM)		(2C) Factors associated with receiving MTX+CPM, among subset of patients who had MTX with or without CPM	
	O.R. (95% C.I.)	p value	O.R. (95% C.I.)	p value	O.R. (95% C.I.)	p value
Age DX	1.05 (1.02- 1.08)	0.0003	1.08 (1.05-1.11)	<.0001	0.94 (0.91-0.97)	0.0003
Year DX						
1998-1999	1.00	-	1.00	-	1.00	-
2000-2004	1.00 (0.74-1.34)	0.98	0.85 (0.65-1.12)	0.25	1.68 (1.06-2.65)	0.027
2005-2011	0.85 (0.60-1.19)	0.34	0.67 (0.50-0.91)	0.011	4.18 (2.57-6.79)	<.0001
Race						
White	1.00	-	1.00	-	1.00	-
African American	0.87 (0.65-1.16)	0.34	1.10 (0.85-1.41)	0.47	0.29 (0.20-0.44)	<.0001
Hispanic	1.04 (0.76-1.42)	0.80	1.27 (0.97-1.68)	0.088	0.57 (0.38-0.84)	0.0051
Asian/Pacific Islander	1.08 (0.81-1.44)	0.61	1.75 (1.33-2.30)	<.0001	0.48 (0.31-0.73)	0.0006
Other	1.32 (0.56-3.10)	0.53	1.70 (0.80-3.63)	0.17	1.22 (0.41-3.62)	0.73
Marital status						
Married	1.00	-	1.00	-	1.00	-
Not married	1.04 (0.85-1.27)	0.74	1.47 (1.22-1.76)	<.0001	0.91(0.70-1.19)	0.51
Unknown	0.60 (0.37-0.95)	0.03	0.90 (0.58-1.39)	0.63	0.85 (0.46-1.56)	0.60
Registry region						
California	1.00	-	1.00	-	1.00	-
Central	2.20 (1.66-2.91)	<.0001	1.12 (0.89-1.40)	0.34	0.88 (0.65-1.20)	0.43
Eastern	1.51 (1.20-1.89)	0.0005	1.28 (1.04-1.58)	0.019	1.00	0.99
Western	1.89 (1.33-2.69)	0.0004	1.21 (0.90-1.63)	0.20	0.60 (0.39-0.94)	0.024
Grade						
Low grade (I or II)	1.00	-	1.00	-	1.00	-
High grade (III or higher)	1.47 (1.16-1.84)	0.0012	0.70 (0.58-0.85)	0.0002	0.85 (0.66-1.11)	0.23
Unknown	0.95 (0.75-1.20)	0.66	0.93 (0.75-1.16)	0.52	0.93 (0.67-1.29)	0.67
Histology						
Comedo	1.00	-	1.00	-	1.00	-
All others	0.59 (0.44-0.78)	0.0002	0.94 (0.76-1.15)	0.52	1.03 (0.78-1.36)	0.85
Size						
<=15mm	1.00	-	1.00	-	1.00	-
>15mm	0.81 (0.63-1.05)	0.11	0.27 (0.22-0.33)	<.0001	0.63 (0.47-0.83)	0.0012
unknown	0.68 (0.55-0.84)	0.0003	0.41 (0.34-0.49)	<.0001	0.86 (0.65-1.15)	0.31
Hormone receptor status						
Either ER or PR is +	1.00	-	1.00	-	1.00	-
Both ER and PR are -	0.87 (0.56-1.36)	0.55	0.80 (0.58-1.11)	0.19	0.75 (0.50-1.12)	0.16
Unknown	0.56 (0.45-0.71)	<.0001	0.87 (0.71-1.07)	0.19	0.92 (0.69-1.23)	0.57

O.R.: Odds ratio; C.I.: Confidence interval; ER: Estrogen receptor; PR: Progesterone receptor; BCS: Breast conserving surgery; RT: Radiation therapy; CPM: Contralateral prophylactic mastectomy

Table 3. Comparison of number of second ipsilateral events, incidence rates and hazard ratios during follow-up in BCS and BCS+RT treatment groups

	BCS alone			BCS + RT			Hazard ratio and p value for BCS+RT compared to BCS alone group from multivariable Cox model†	
	Person-Yrs.	cases	Incidence rate (%) and 95% C.I.	Person-Yrs.	cases	Incidence rate (%) and 95% C.I.		
2 year ipsilateral breast tumor	1486	19	1.28 (0.71-1.85)	2470	6	0.24 (0.05-0.44)	5.36 (2.02-14.30)	0.0008
2 year ipsilateral in situ		8	-		1	-	-	-
2 year ipsilateral invasive		11	-		5	-	-	-
5 year ipsilateral breast tumor	3275	45	1.37 (0.98-1.77)	5479	29	0.53 (0.3- 0.72)	2.46 (1.47-4.11)	0.0006
5 year ipsilateral in situ		17	-		5	-	-	-
5 year ipsilateral invasive		28	0.86 (0.54-1.17)		24	0.44 (0.26-0.61)	2.06 (1.12-3.77)	0.019
All ipsilateral breast tumor	5444	72	1.32 (1.02-1.63)	8984	88	0.98 (0.78-1.18)	1.03 (0.81-1.33)	0.79
All ipsilateral in situ		23	0.42 (0.25-0.59)		26	0.29 (0.18-0.40)	1.17 (0.76-1.81)	0.48
All ipsilateral invasive		49	0.90 (0.65-1.15)		62	0.69 (0.52-0.86)	0.97 (0.71-1.32)	0.85

†Hazard ratios are for BCS+RT group comparing to BCS-alone group from multivariable proportional hazards models on time to second ipsilateral breast cancer controlling for age, year of diagnosis, race, registry region, tumor grade, histology, size and hormone receptor status.

Table 4. Results from survival analysis on overall survival using three methods

	Multivariable proportion hazards cox model				With propensity score covariate adjustment				With inverse probability weighting			
	H.R.	95% C.I.		p value	H.R.	95% C.I.		p value	H.R.	95% C.I.		p value
Treatment												
BCS alone	3.26	1.58	6.73	0.0014	3.24	1.553	6.763	0.0017	3.43	1.667	7.041	0.0008
BCS + RT	1.00	-	-	-	1.00	-	-	-	1.00	-	-	-
MTX with CPM	1.16	0.38	3.56	0.7995	1.17	0.38	3.65	0.7865	1.04	0.40	2.90	0.9676
MTX without CPM	1.65	0.79	3.46	0.1855	1.68	0.79	3.54	0.1765	1.77	0.84	3.75	0.1351

*Multivariable cox model also controlled for race, registry region, tumor grade, histology, size and hormone receptor status. Age at diagnosis and diagnosis year were included in the model as strata.

BCS: Breast conserving surgery

RT: Radiation therapy

CPM: Contralateral prophylactic mastectomy