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Current Trends in the Management of Phyllodes Tumors of the Breast

Taiwo Adesoye, MD MPH[1], **Heather B Neuman, MD MS**[1,2], **Lee G Wilke, MD**[2], **Jessica R Schumacher, PhD MS**[1], **Jennifer Steiman, MD**[2], and **Caprice C Greenberg, MD MPH**[1,2]

[1]Wisconsin Surgical Outcomes Research (WiSOR) Program, Department of Surgery, University of Wisconsin Hospitals and Clinics, Madison WI

[2]Division of Surgical Oncology, Department of Surgery, University of Wisconsin Hospitals and Clinics, Madison WI

Abstract

Introduction—National Comprehensive Cancer Network (NCCN) guidelines recommend wide excision without axillary staging to treat phyllodes tumors of the breast. Without prospective trials to guide management, NCCN also recommends consideration of radiation therapy (XRT). We describe current patterns of care for the multidisciplinary management of phyllodes tumors.

Methods—Using Surveillance, Epidemiology and End Results Program (SEER) data, we identified women diagnosed with phyllodes tumors between 2000 and 2012 who underwent surgical therapy. Trends in breast conserving surgery (BCS), nodal sampling and XRT were assessed using the Cochrane-Armitage test. Multivariable logistic regression was used to identify factors associated with treatment.

Results—Of 1,238 patients, 56.9% underwent BCS and 23.6% underwent nodal sampling (10.5% after BCS vs 40.9% after mastectomy). After surgery, 15.4% received adjuvant XRT (BCS, 12.9% and mastectomy, 18.8%). XRT utilization increased significantly over the study period (BCS, p=<0.0001; mastectomy, p=0.0003) while nodal sampling did not change significantly. Women were more likely to receive mastectomy if they were older or had larger tumors. Nodal sampling was also associated with older age, larger tumor size and receipt of mastectomy. Receipt of XRT was associated with later year of diagnosis, larger tumors and nodal assessment.

Conclusion—Over time, an increasing number of women received XRT after surgical management of phyllodes tumor, and one in four women underwent nodal sampling. While some of this practice can be attributed to concern about more advanced disease in the absence of strong data, there may be an educational gap regarding current guidelines and appropriate management.

Corresponding Author: Caprice C. Greenberg, MD, MPH, University of Wisconsin Hospitals & Clinics, Wisconsin Surgical Outcomes Research (WiSOR) Program, 600 Highland Avenue, BX7375 Clinical Science Center, K6/100, Madison, WI 53792-3284, Phone: (608)262-0395, greenberg@surgery.wisc.edu.

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INTRODUCTION

Phyllodes tumors of the breast are rare fibroepithelial lesions that comprise less than 1% of all breast malignancies.[1] An analysis of the Surveillance, Epidemiology, and End Results Program (SEER) data registry from 2000 to 2004 reported that 500 women are diagnosed with malignant phyllodes tumors in the United States annually.[2] Phyllodes tumors usually present as mobile painless breast masses, however, approximately 20% of tumors are identified on screening mammography and are non-palpable.[3] They are characterized by hypercellular stroma growth into epithelial lined cyst spaces and the epithelial element is responsible for the distinction from stromal sarcomas.[4,5] Although phyllodes tumors are similar to fibroadenomas, suspicion for a phyllodes tumor is based on large size, a rapid growth rate, and findings of stromal hyperplasia and atypia on microscopic examination.[3] Based on the degree of stromal hyperplasia and atypia, the World Health Organization (WHO) categorizes phyllodes tumors as benign, borderline and malignant with malignant tumors accounting for 25% of resected tumors.[1,5,6]

National Comprehensive Cancer Network (NCCN) guidelines for the management of phyllodes tumors recommend wide excision with margins ≥1cm and recommend against axillary staging.[7] Without randomized studies supporting the use of post-operative radiation (XRT), routine use of XRT is not recommended, except in specific circumstances where a local recurrence would result in significant morbidity. In this setting, guidelines recommend XRT, following a sarcoma treatment paradigm.[7] The objective of our study is to examine current patterns of care for the treatment of phyllodes tumors relative to current guideline recommendations and to assess temporal trends in management.

METHODS

Data Source and Study Subjects

The SEER program is comprised of 18 population-based cancer registries around the United States. Records from SEER registries are publicly available and managed by the National Cancer Institute.[8] It currently represents approximately 30% of the US population and is comparable to the general population with regards to poverty and education.[8] We utilized the SEER-18 submission spanning the following geographic regions: Metropolitan Atlanta, Connecticut, Detroit, Hawaii, Iowa, New Mexico, San Francisco-Oakland, Seattle-Puget Sound, Los Angeles, San Jose-Monterey, Utah, rural and greater Georgia, Alaska, greater California, Kentucky, Louisiana, and New Jersey. SEER routinely collects data on demographics (age at diagnosis, gender, race) tumor-specific information (primary site, stage, size, grade) and first course local-regional therapy defined as treatment plan at diagnosis, conducted prior to disease progression or recurrence.

We identified patients with a histologic diagnosis of malignant phyllodes tumors of the breast (International Classification of Diseases for Oncology, 3rd edition [ICD-O-3] histology codes 9020/3) diagnosed between 2000 and 2012. We limited our cohort to patients over the age of 18 who underwent breast surgery. We excluded patients with a prior history of cancer (n=266), who were diagnosed only at autopsy or on a death-certificate (n=89) and women with unknown XRT status (n=23). Patient factors examined include age,

race, year of diagnosis, and tumor size. Treatment factors include type of primary surgery (BCS vs mastectomy), nodal examination, and receipt of XRT.

Statistical Analysis

Patient and treatment characteristics were described stratified by type of breast surgery using summary statistics and p-values for comparing categorical data were computed using chi-square. We assessed changes in annual rates of BCS, lymph node evaluation and adjuvant XRT over time using the Cochran-Armitage test for trend. We utilized separate multivariable logistic regression models to identify factors independently associated with the receipt of BCS, nodal sampling and XRT. P-values were 2 sided and $p<0.05$ was used as threshold for statistical significance. Analyses were conducted using SEER*Stat 8.1.5 statistical software (National Cancer Institute, Bethesda, MD, USA) and SAS version 9.4 (SAS Institute, Cary, NC, USA).

RESULTS

Patient Characteristics

We identified 1,238 patients who were diagnosed with phyllodes tumor between 2000 and 2012 and underwent surgical therapy (Table 1). The mean age at diagnosis was 50.2 years and the median tumor size was 4.8cm (mean tumor size 6cm). In our cohort, 56.9% (n=705) underwent BCS while 43.1% (n=533) underwent mastectomy. Tumor size was greater in women undergoing mastectomy versus BCS (66.6% vs 28.7% with size ≥5cm). Nodal sampling was performed in 23.6% (n=292) of patients and was more common for patients receiving mastectomy compared with BCS (40.9%, n=218 vs 10.5%, n=74). Of the patients who had their nodes examined, 4.0% (n=12) had positive nodes. XRT was administered to 15.4% (n=191) of the cohort overall and was more common after mastectomy (18.8%, n=100) compared to BCS (12.9%, n=91) (Table 1).

Temporal Trends

There has been no change in the proportion of women who underwent BCS versus mastectomy (54.0% underwent BCS in 2000 and 48.0% in 2012, p= 0.58). Rates of nodal examination likewise did not change significantly during this time period, regardless of the surgery received (BCS, p=0.32; Mastectomy, p=0.80) (Figure 1). XRT utilization increased significantly after both BCS and mastectomy from 2000 to 2012, with a rate increase from 5.6% to 25.0% after BCS ($p<0.0001$) and 10.9% to 25.5% after mastectomy (p=0.0003) (Figure 1).

Multivariate Logistic Regression

In adjusted analysis, women were more likely to undergo mastectomy if they were older or had larger tumors (Table 2). Patients were more likely to receive nodal evaluation if they were older, had a larger tumor size, or underwent mastectomy. Receipt of mastectomy was the strongest predictor of nodal evaluation (OR 5.12; 95% CI 3.73–7.02). Receipt of post-BCS XRT was significantly associated with later years of diagnosis, larger tumor size, and nodal examination (Table 3). Similar associations were seen for receipt of post-mastectomy XRT.

DISCUSSION

Using a population-based cohort from the SEER database, we examined patterns of care in the local-regional management of patients diagnosed with phyllodes tumors of the breast. Our results demonstrate that approximately 50% of patients are treated with breast conservation. Our findings also demonstrate an increasing use of XRT over the study period after both BCS and mastectomy, despite the absence of Level 1 data supporting this practice. Finally, we determined that approximately one in four women receive axillary nodal staging despite guidelines recommending against this additional surgery.

BCS is appropriate treatment for a phyllodes tumor if a good cosmetic and oncologic outcome are feasible.[7,9] In an analysis of the SEER database from 1988–2002, Mcdonald et al suggested that BCS is equivalent to mastectomy and larger tumors can be effectively removed with wide excision without increasing the risk of cancer-specific death.[9] They also noted an increase in BCS rates in their analysis from 41% in 1988 to 56% in 2002. Our results suggest rates of BCS have remained relatively unchanged since that time. This stability in BCS rates may be related to the large average presenting tumor size for phyllodes tumors as well as the wider excision margins required, which can limit the surgeon's ability to achieve a good cosmetic outcome and negative margins with BCS alone. This is supported by our data, where the average tumor size was 6cm, and 45% of patients had a tumor ≥5cm in size, and is also consistent with prior literature.[1,10–13] We found that the type of surgical procedure varied with tumor size and 36% of patients with tumors ≥5cm received BCS compared to 75% of patients with tumors <5cm.

Over the study period, utilization of XRT more than doubled following both mastectomy and BCS. This is similar to trends previously reported by Gnerlich et al using the National Cancer Data Base (NCDB).[14] Currently, there are no randomized controlled trials that have examined the efficacy of XRT after margin-negative surgery for phyllodes tumors; however, the relatively high rate of local recurrence (LR) has generated interest in the potential role of XRT. There have been several retrospective studies examining the impact of XRT on local recurrence. The results of these single institution experiences are mixed however.[1,2,9,10,12,14] A retrospective study by Belkacemi et al evaluated 446 patients treated for phyllodes tumors with a 45% negative margin rate between 1971 and 2003. Adjuvant XRT was administered to 38 (8.5%) patients and they reported a significant decrease in 10 year LR rates from 86% to 56%.[12] In a study of 101 largely margin negative patients with phyllodes tumors by Chaney et al, local failure occurred in 4 (4%) patients. The authors here suggest that BCS with appropriate margins is sufficient primary therapy.[10] The only prospective study in the literature is from Barth et al who conducted a multi-institutional study of 46 patients where XRT was administered after margin-negative surgery for borderline and malignant tumors. No local recurrence occurred in this cohort after 56 months of follow up.[2] In the absence of better data, the NCCN recommends consideration of XRT if surgical management of a local recurrence would be especially morbid.[7] The increasing rate that we observe may reflect a propensity to utilize XRT for larger tumors where margins may be difficult to obtain. As a result, this may be in accordance with guidelines as larger tumors would most likely result in a morbid local recurrence.

In this cohort, one in four women underwent axillary nodal sampling despite guidelines recommending against it. Phyllodes tumors rarely metastasize to the lymph nodes, confirmed in this data by the low rate of positive nodes (0.1% and 2.1% after BCS and mastectomy, respectively). Because of the presumed hematogenous spread of these tumors if metastatic, it is uncertain what the goal of axillary surgery was in these cases. We identify four possible explanations for the unexpectedly high utilization of axillary sampling in this study. First, we identified an association between nodal sampling and mastectomy. Given limitations in the extent of axillary surgery variables, we used the number of nodes examined to determine whether axillary sampling was performed. It is possible that some of these cases represent removal of intramammary or inadvertent axillary lymph nodes during the mastectomy. A second explanation is that surgeons may be concerned about finding an occult primary invasive cancer in the mastectomy specimen and are therefore performing a prophylactic sentinel lymph node biopsy as is the standard recommendation for patients undergoing mastectomy for ductal carcinoma in situ (DCIS).[15–17] Another explanation is that patients are taken to the operating room with a presumed diagnosis of adenocarcinoma and undergo lymph node sampling. It is only on final pathology that the diagnosis of phyllodes is made. This etiology is supported by our observation that the utilization of lymph node sampling (24%) is greater than radiation (15%). However, if this were the case, we would have anticipated a temporal decrease in the utilization of lymph node sampling over time with the increasing utilization of percutaneous core biopsy and a higher rate with BCS as mastectomy is unlikely without a tissue diagnosis neither of which is observed. Finally, given the rarity of phyllodes tumors, it is possible some patients are being treated according to adenocarcinoma paradigms. This etiology is further supported by the strong association between nodal examination and XRT utilization in adjusted analysis for both BCS and mastectomy.

While SEER is a comprehensive and geographically representative registry, there are several limitations to this study. First, this is a retrospective study subject to bias as the allocation of patients to receive a particular intervention is not random. We were unable to evaluate diagnostic uncertainty prior to surgery, as histology in SEER is coded based on the final diagnosis obtained from a pathology report. Nodal examination is based on nodes removed during surgery rather than surgery type as discussed above. Several important prognostic data elements specifically relevant to phyllodes tumors, including grade, number of mitosis, cellular atypia, stromal overgrowth, and margin status, are either absent or incomplete in SEER. We therefore cannot assess how the presence of these factors may have influenced choice of XRT use in this cohort.[12,13,18] In addition, we lack data on comorbidities which can be a surrogate for overall health status and may significantly affect which patients are selected for certain treatments. SEER also lacks information on local or distant recurrence, preventing the assessment of the impact of XRT use on this outcome.

CONCLUSION

We determined that there is evidence of frequent nodal examination and increasing utilization of adjuvant XRT in patients diagnosed with phyllodes tumors of the breast. These findings have important implications for practice and policy. Continued efforts to increase pre-operative tissue diagnosis via core biopsy should be emphasized and may help to

decrease the rate of lymph node surgery for phyllodes tumors. Additionally, the majority of breast cancer surgery in the United States is performed at institutions treating less than 10 cases per year; thus, most centers will rarely encounter a phyllodes tumor due to its low incidence. As such, our findings may represent an educational gap in the surgical care of patients with phyllodes tumors. Improving the use of current guidelines in routine practice, such as those from the NCCN, for both common and rare conditions may help to ensure appropriate treatment, especially at institutions not routinely treating rare diseases such as phyllodes tumor.

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Synopsis

Using Surveillance, Epidemiology and End Results Program (SEER) data (2000–2012), we demonstrate a significant increase in the number of women received adjuvant radiation therapy after surgical management of phyllodes tumor. Additionally, one in four women underwent nodal sampling despite guidelines recommending against this procedure. These findings have implications for practice and policy highlighting the need for stronger evidence and education about current guidelines to inform practice and ensure appropriate care.

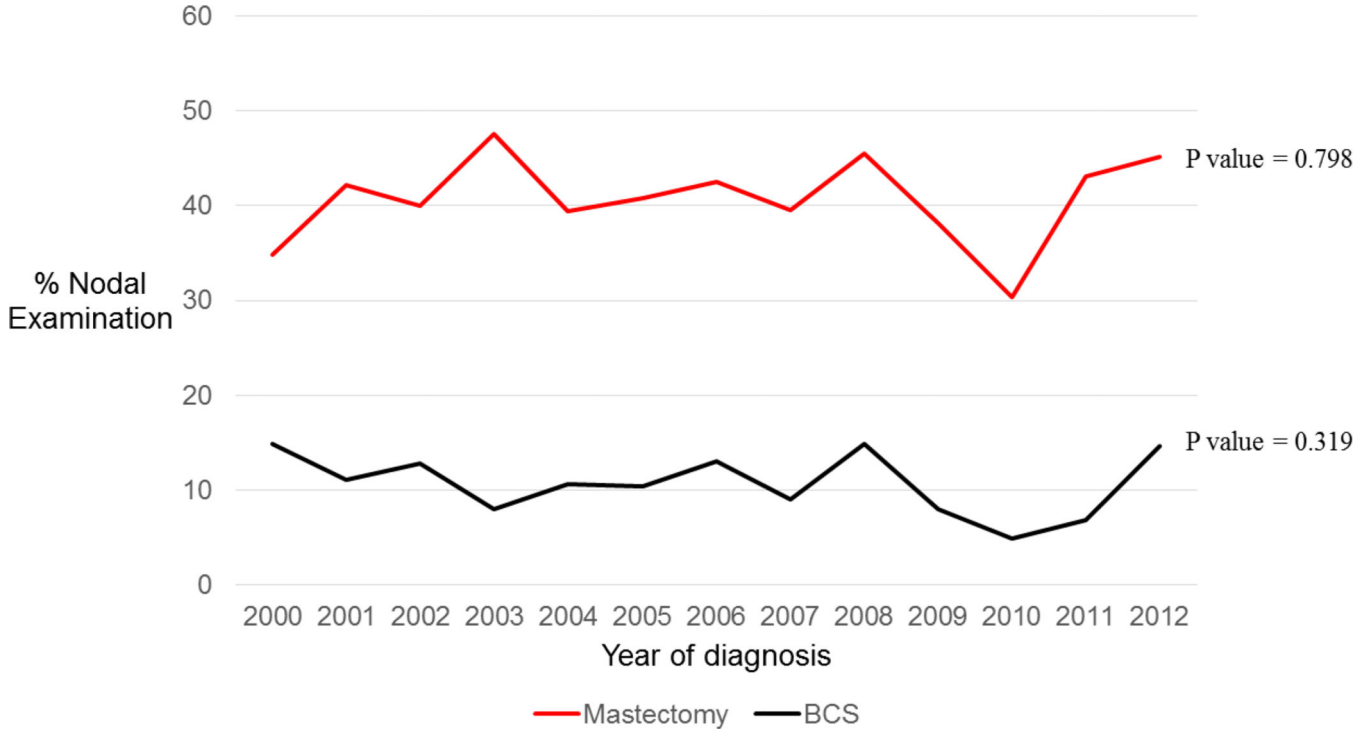

Figure 1.

Rate of nodal examination stratified by surgery type in patients diagnosed with phyllodes tumors from 2000 to 2012

Abbreviations: *BCS* Breast conserving surgery

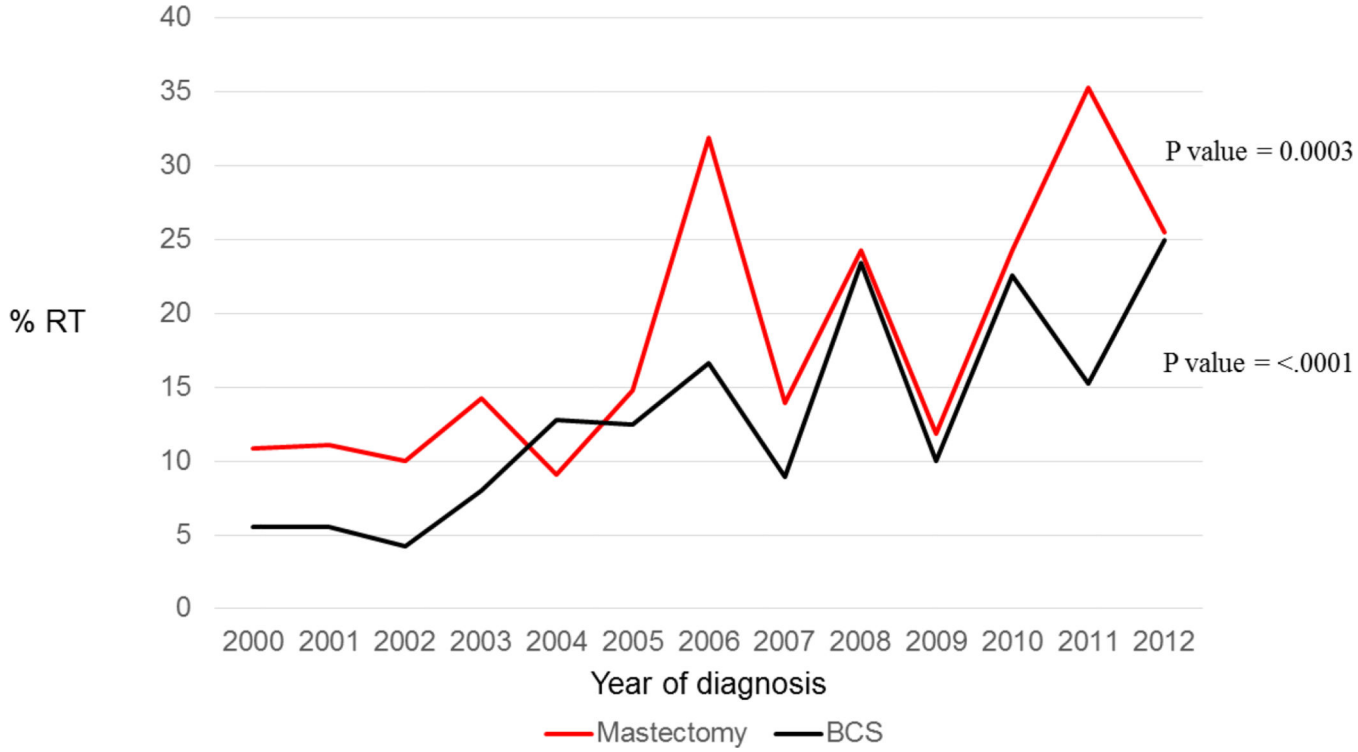

Figure 2.

Rate of radiotherapy utilization stratified by surgery type in patients diagnosed with phyllodes tumors from 2000 to 2012

Abbreviations: *BCS* Breast conserving surgery, *RT* radiotherapy

Table 1

Characteristics of women diagnosed with phyllodes tumors of the breast from 2000 to 2012 who underwent surgical therapy

Characteristic	Total (n = 1,238)	BCS (n = 705)	Mastectomy (n = 533)	P value
Age (years)				0.012
<40	254 (20.5)	166 (23.6)	88 (16.5)	
40–49	339 (27.4)	193 (27.4)	146 (27.4)	
50–59	376 (30.4)	207 (29.4)	169 (31.7)	
60 and older	269 (21.7)	139 (19.6)	130 (24.4)	
Race				0.746
White	907 (73.3)	519 (73.6)	388 (72.8)	
Other/unknown	331 (26.7)	186(26.4)	145 (27.2)	
Year of diagnosis				0.581
2000–2004	476 (38.5)	270 (38.3)	206 (38.7)	
2005–2008	366 (29.6)	216 (30.6)	150 (28.1)	
2009–2012	396 (31.9)	219 (31.1)	177 (33.2)	
Tumor size (cm)				<.0001
<5	593 (47.9)	443 (62.8)	150 (28.1)	
≥5	557 (45.0)	202 (28.7)	355 (66.6)	
Unknown	88 (7.1)	60 (8.5)	28 (5.3)	
Nodal Status				
Negative	280 (22.6)	73 (10.4)	207 (38.8)	<.0001
Positive	12 (1.0)	1 (0.1)	11 (2.1)	
Not examined	946 (76.4)	631 (89.5)	315 (59.1)	
Radiotherapy				
No	1047 (84.6)	614 (87.1)	433 (81.2)	<.0001
Yes	191 (15.4)	91 (12.9)	100 (18.8)	

Data are expressed as n(%)

Abbreviations: *BCS* Breast conserving surgery

Table 2

Adjusted odds ratio for receipt of breast conserving surgery in women diagnosed with phyllodes tumor who underwent surgical therapy, 2000 – 2012 (n = 1,238)

Characteristic	Adjusted OR (95% CI)
Age (years)	
<40	1
40–49	**0.66 (0.46 – 0.94)**[‡]
50–59	**0.59 (0.41 – 0.84)**[‡]
60 and older	**0.50 (0.34 – 0.73)**[‡]
Race	
White	1
Other/unknown	1.08 (0.82 – 1.43)
Year of diagnosis	
2000–2004	1
2005–2008	1.24 (0.92 – 1.67)
2009–2012	1.11 (0.83 – 1.49)
Tumor size (cm)	
<5	1
≥5	**0.18 (0.14 – 0.24)**[‡]
Unknown	0.69 (0.42 – 1.13)

Abbreviations: *BCS* Breast conserving surgery, *OR* odds ratio, *CI* confidence interval

[‡]Statistically significant (P<0.05) after adjusting for all other variables in the table

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Table 3

Adjusted odds ratio for receipt of radiotherapy (RT) in women diagnosed with phyllodes tumor who underwent surgical therapy, 2000 – 2012 (n = 1,238)

Characteristic	Post-BCS XRT (n=91) n (%)	*P* value	Adjusted OR (95% CI)	Post-mastectomy XRT (n=100) n (%)	*P* value	Adjusted OR (95% CI)
Age (years)		0.189			0.264	
<40	19 (20.9)		1	18 (18)		1
40–49	18 (19.8)		0.75 (0.37 – 1.52)	29 (29)		1.05 (0.53 – 2.09)
50–59	32 (35.2)		1.40 (0.75 – 2.63)	36 (36)		1.08 (0.55 – 2.12)
60 and older	22 (24.2)		1.45 (0.73 – 2.87)	17 (17)		0.53 (0.25 – 1.14)
Race		0.93			0.149	
White	67 (73.6)		1	67 (67)		1
Other/unknown	24 (26.4)		1.05 (0.62 – 1.76)	33 (33)		1.18 (0.72 – 1.92)
Year of diagnosis		0.001			0.001	
2000–2004	19 (20.9)		1	23 (23)		1
2005–2008	32 (35.2)		**2.28 (1.24 – 4.19)**‡	33 (33)		**2.12 (1.16 – 3.87)**‡
2009–2012	40 (43.9)		**2.99 (1.66 – 5.42)**‡	44 (44)		**2.43 (1.37 – 4.30)**‡
Tumor size (cm)		0.014			<.0001	
<5	54 (59.3)		1	12 (12)		1
≥5	35 (38.5)		**1.46 (0.90 – 2.37)**‡	85 (85)		**3.34 (1.74 – 6.39)**‡
Unknown	2 (2.2)		0.26 (0.26 – 1.11)	3 (3)		1.56 (0.40 – 6.06)
Nodal Status		0.001			0.04	
Not examined	72 (79.1)		1	50 (50)		1
Examined	19 (20.8)		**2.92 (1.59–5.36)**‡	50 (50)		**1.66 (1.05 – 2.62)**‡

Abbreviations: *BCS* Breast conserving surgery, *XRT* radiation therapy, *OR* odds ratio, *CI* confidence interval

‡Statistically significant (P<0.05) after adjusting for all other variables in the table