Ann Surg Oncol (2015) 22:3308–3316
DOI 10.1245/s10434-015-4664-3

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

CrossMark

ORIGINAL ARTICLE – BREAST ONCOLOGY

Modern Trends in the Surgical Management of Paget's Disease

Stephanie M. Wong, MD[1,2], Rachel A. Freedman, MD[3], Emily Stamell, MD[1,3], Yasuaki Sagara, MD[5], Jane E. Brock, MBBS, PhD[4], Stephen D. Desantis, BS[3,5], and Mehra Golshan, MD[5]

[1]Harvard School of Public Health, Boston, MA; [2]Department of Surgery, McGill University Health Centre, Montreal, QC, Canada; [3]Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA; [4]Department of Pathology, Brigham and Women's Hospital, Boston, MA; [5]Department of Surgery, Brigham and Women's Hospital, Dana Farber Cancer Institute, Boston, MA

ABSTRACT

Purpose. We examined the incidence and modern national trends in the management of Paget's disease (PD), including the use of breast-conserving surgery (BCS), mastectomy, axillary surgery, and receipt of radiotherapy.

Methods. Using surveillance, epidemiology and end results (SEER) data, we identified 2631 patients diagnosed with PD during 2000–2011. Of these patients, 185 (7 %) had PD of the nipple only, 953 (36.2 %) had PD with ductal carcinoma in situ (PD-DCIS), and 1493 (56.7 %) had PD with invasive ductal carcinoma (PD-IDC). Trends in age-adjusted incidence, primary surgery, sentinel lymph node biopsy (SLNB), and axillary lymph node dissection were examined. Multivariable logistic regression was used to evaluate factors associated with receipt of BCS and radiotherapy.

Results. A decrease in the age-adjusted incidence of PD occurred from 2000 to 2011 (−4.3 % per year, $p < 0.05$). The overall rates of mastectomy in the PD only, PD-DCIS, and PD-IDC groups were 47, 69, and 88.9 %, respectively. Only in the PD-IDC group did the proportion of patients undergoing BCS increase significantly, from 8.5 % in 2000 to 15.7 % in 2011 ($p = 0.01$). Of those who underwent axillary surgery, the proportion of patients undergoing SLNB increased from 2000 to 2011. In adjusted analyses, Paget's subgroup, older age, central tumor location, low/intermediate grade, tumor size <2.0 cm, SEER region, and year of diagnosis after 2006 were significantly associated with receipt of BCS.

Conclusions. The incidence of Paget's disease has decreased over time while modern trends in local therapy suggest that BCS, SLNB, and adjuvant radiotherapy remain underutilized.

© Society of Surgical Oncology 2015

First Received: 21 February 2015;
Published Online: 23 July 2015

M. Golshan, MD
e-mail: mgolshan@partners.org

Paget's disease of the breast is an uncommon clinical entity characterized by an eczematous eruption and ulceration of the nipple that may secondarily affect the areola.[1,2] Described by Sir James Paget in 1874, it is associated with an underlying invasive or in situ carcinoma in 82–94 % of cases.[3–6] In the past, due to concern that a patient may harbor multifocal, multicentric or occult malignancy in breast tissue distant from the nipple, mastectomy was offered as the standard surgical management of Paget's disease. In the modern era of diagnostic breast imaging and breast-conserving surgery (BCS), however, surgical options have evolved to include central lumpectomy (with removal of the nipple) and whole breast radiation, a less invasive alternative with equivalent survival outcomes albeit slightly higher rates of local recurrence.[5,7–9]

In addition to BCS, the role of axillary staging and the use of sentinel node biopsy in Paget's disease remains an area of evolving interest.[6] Based on current standards, sentinel node biopsy should be recommended in all patients with Paget's disease for whom mastectomy is performed or for those undergoing breast conservation with a known underlying invasive carcinoma, yet little is known as to whether surgeons have incorporated this recommendation into modern day practice.[10,11]

METHODS

Data Source

The SEER database is maintained by the National Cancer Institute and contains publically available records

of 18 population-based cancer registries whose catchment areas represent approximately 28 % of the United States population.[12] We used the November 2013 submission for this study. Information from SEER includes patient demographics, pathologic information, type of surgical therapy, and receipt of radiation. Because the study used de-identified, pre-existing data, the protocol was considered exempt from the Institutional Review board of the Dana-Farber Cancer Institute.

Study Cohort

We identified a cohort of patients with Paget's disease within SEER using the *International Classification of Diseases for Oncology*, 3rd edition (ICD-O-3) histopathology codes corresponding to mammary Paget's disease (PD) (code 8540), Paget's disease with intraductal carcinoma (PD-DCIS) (code 8543), and Paget's disease with invasive ductal carcinoma (PD-IDC) (code 8541). Women who were older than aged 18 years with a pathologic diagnosis between January 1, 2000 and December 31, 2011 were included ($n = 4064$). We restricted our analysis to women who had no prior history of any cancer ($n = 2926$) and excluded patients with stage IV disease ($n = 79$). In the Paget's only group (code 8540), we further excluded women who did not have "tumor size" or "extent of disease" variables defined as "Paget's disease of the nipple with no demonstrable/underlying tumor" ($n = 125$). Because our analyses focused on local therapy, we excluded women who did not undergo surgery ($n = 68$).

Outcome of Interest

Our primary outcome of interest was local therapy, categorized as breast-conserving surgery (BCS), total (simple) mastectomy, or modified radical mastectomy (MRM). Nodal evaluation also was of interest. Women who underwent the following surgical procedures were deemed to have undergone BCS: partial mastectomy, partial mastectomy with nipple resection, lumpectomy, excisional biopsy, re-excision of biopsy site, quadrantectomy, and segmental mastectomy. The remaining women who underwent unilateral or bilateral mastectomy were subcategorized as having undergone total mastectomy or MRM. To define surgical management of the axilla, extent of disease codes for the number of regional lymph nodes examined and positive were used. Because SEER does not report the type of axillary surgery performed, surrogates of 1–5 lymph nodes and >5 lymph nodes removed were used to dichotomize patients who underwent nodal evaluation into sentinel lymph node biopsy (SLNB) and axillary lymph node dissection (ALND) groups, as in previous studies.[13]

Control Variables

Control variables included age, race, marital status, Paget's subtype, SEER region, and year of diagnosis as categorized in Table 1. Additional control variables included primary site of the tumor within the breast, tumor size, histologic grade, and hormone-receptor status [defined as positive if estrogen receptor (ER) or progesterone receptor (PR)-positive, negative if both ER- and PR-negative, or borderline/unknown]. Human epidermal receptor-2 (Her2) status was only available for select cases diagnosed after 2010 and therefore was excluded from analysis.

Statistical Analysis

The SEER*Stat 8.1.5 statistical software (National Cancer Institute, Bethesda, MD) was used to derive incidence rates for all cases of Paget's disease of the Breast, which were age-adjusted according to the 2000 U.S. standard population (19 age groups—Census P25-1130). Age adjusted trends were determined by the annual percent change (APC) in incidence rates. Significance testing was then performed using the null hypothesis that the APC was equal to zero.[14] Using SAS version 9.4 (SAS Institute, Cary, NC), the SEER 18 Registries database was then retrieved in American Standard Code for Information Interchange (ASCII) format. After applying prespecified inclusion and exclusion criteria, we analyzed demographic and clinicopathologic differences across the three Paget's subgroups using Pearson's χ^2 test for categorical data, and one-way ANOVA for continuous variables. To determine if there had been a significant change in surgical management over time, we calculated the annual rates of BCS and mastectomy for each year for 2000–2011 and compared them using the Cochran-Armitage Test for trend. We performed analyses for those undergoing axillary evaluation via SLNB or ALND. Finally, to evaluate which factors were independently associated with receipt of BCS, we constructed a multivariable logistic regression model, adjusting for the control variables described. For model building, we created indicator variables for missing data and included them into the model. Lastly, we tested the sensitivity of our results to changes in cohort construction by repeating the above analyses after inclusion of women with prior cancers, producing similar results and effect estimates (data not shown). For all statistical tests, p values were two-sided; $p < 0.05$ was used to indicate statistical significance.

RESULTS

Incidence of Paget's Disease

Between 2000 and 2011, there was a significant decline in age-adjusted incidence rates for all female Paget's

TABLE 1 Patient characteristics within Paget's subgroups

Characteristic	Paget's only ($N = 185$)	Paget's + DCIS ($N = 953$)	Paget's + IDC ($N = 1493$)	P value*
Age—*n*, (%) (years)				**<0.0001**
<40 (*n*, %)	6 (3.3)	51 (5.4)	115 (7.7)	
40–59	60 (32.4)	328 (34.4)	628 (42.1)	
60–79	94 (50.8)	431 (45.2)	551 (36.9)	
>80	25 (13.5)	143 (15.0)	199 (13.3)	
Marital status—*n*, (%)				0.701
Married	99 (53.5)	488 (51.2)	752 (50.3)	
Not married[a]	86 (46.5)	465 (48.8)	741 (49.6)	
Race—*n*, (%)				**0.0015**
White	157 (84.9)	803 (84.3)	1178 (78.9)	
Black	11 (5.9)	71 (7.4)	177 (11.9)	
Other/unknown	17 (9.2)	79 (8.3)	138 (9.2)	
SEER region[b]				**0.026**
California[†]	79 (42.7)	466 (48.9)	785 (52.5)	
Georgia[‡], Louisiana, Kentucky	36 (19.5)	146 (15.3)	233 (15.6)	
Connecticut, New Jersey	12 (6.5)	116 (12.2)	151 (10.1)	
Seattle (Puget Sound), Hawaii, Alaska	23 (12.4)	96 (10.1)	122 (8.2)	
Detroit, Iowa	22 (11.9)	74 (7.8)	126 (8.4)	
Utah, New Mexico	13 (7.0)	55 (5.8)	76 (5.1)	
Tumor location—*n*, (%)				**<0.0001**
Central/NAC	179 (96.8)	610 (64.0)	446 (29.9)	
Upper inner quadrant	0 (0)	10 (1.1)	57 (3.8)	
Lower inner quadrant	0 (0)	16 (1.7)	57 (3.8)	
Upper outer quadrant	3 (1.6)	41 (4.3)	216 (14.5)	
Lower outer quadrant	0 (0)	21 (2.2)	64 (4.3)	
Overlapping Quadrants	1 (0.54)	77 (8.1)	256 (17.2)	
Breast NOS	2 (1.08)	178 (18.7)	397 (26.6)	
Tumor grade—*n*, (%)				**<0.0001**
Low/intermediate grade/grade I–II	3 (1.6)	112 (11.7)	524 (35.1)	
High grade/grade III	13 (7.0)	540 (56.7)	858 (57.5)	
Unknown/not applicable	169 (91.4)	301 (31.6)	111 (7.4)	
Tumor size, cm—*n*, (%)				**<0.0001**
0–2.0	25 (13.5)	366 (38.4)	794 (53.2)	
2.1–5.0	2 (1.1)	115 (12.1)	488 (32.7)	
>5.0	1 (0.5)	58 (6.1)	136 (9.1)	
Paget's disease NOS/unknown	157 (84.9)	414 (43.4)	75 (5.0)	
ER status—*n*, (%)				**<0.0001**
Positive	21 (11.3)	190 (19.9)	656 (43.9)	
Negative	27 (14.6)	337 (35.4)	655 (43.9)	
Borderline/not performed/unknown	137 (74.1)	426 (44.7)	182 (12.2)	
PR status—*n*, (%)				**<0.0001**
Positive	12 (6.5)	112 (11.8)	483 (32.4)	
Negative	33 (17.8)	389 (40.8)	815 (54.6)	
Borderline/not performed/unknown	140 (75.7)	452 (47.4)	185 (12.4)	

TABLE 1 continued

Characteristic	Paget's only ($N = 185$)	Paget's + DCIS ($N = 953$)	Paget's + IDC ($N = 1493$)	P value*
Lymph node status—*n*, (%)				**<0.0001**
Positive	0 (0)	39 (4.1)	703 (47.1)	
Negative	75 (40.5)	561 (58.9)	686 (45.9)	
Axillary surgery not performed/unknown	110 (59.5)	353 (37.0)	104 (7.0)	

NOS not otherwise specified; *DCIS* ductal carcinoma in situ; *IDC* invasive ductal carcinoma

* P values calculated by Pearson Chi squared testing; Bold if statistically significant, $p < 0.05$

† Includes San-Francisco-Oakland, San Jose-Monterey, Los Angeles, and Greater California

‡ Includes Metropolitan Atlanta, Rural Georgia, and Greater Georgia

[a] Single, separated, divorced, widowed, or other groups collapsed

[b] Regions combined due to small sample sizes

disease. The annual rate was found to be highest at 0.89 per 100,000 woman-years in 2001 and decreased steadily to 0.44 per 100,000 woman-years by 2011 [APC −4.3; 95 % confidence interval (CI) −6.2 to −2.3; $p < 0.05$; Fig. 1]. When stratifying by subgroup, both the PD-IDC and PD-DCIS groups demonstrated a significant decrease in incidence rates, with an APC of −4.53 (95 % CI −6.6 to −2.42), and −4.89 (95 % CI −7.75 to −1.94), respectively. In contrast, the age-adjusted incidence rate for Paget's of the nipple only did not demonstrate a statistically significant decrease over time (APC −1.8; 95 % CI −4.99 to 1.52).

Patients Characteristics and Group Comparisons

Our cohort included 2631 patients with Paget's disease of the breast, comprised of 185 (7.0 %) patients with PD only, 953 (36.2 %) patients with PD-DCIS, and 1493 (56.7 %) patients with PD-IDC. Patient demographic and clinicopathologic characteristics are shown in Table 1. Among all patients, those with PD of the nipple only tended to be older (mean age 65.1 years, 95 % CI 63.1–67.1), followed by PD-DCIS (mean age 63.5 years, 95 % CI 62.6–64.4) and patients with PD-IDC, who were the youngest of the cohort (mean age 60.3 years, 95 % CI 59.5–61.1; $p < 0.001$). In cases of PD-DCIS, lesions were centrally located in 64 % of cases compared with only 30 % of patients with PD-IDC ($p < 0.001$). In both groups, there was a tendency to be of high histologic grade (56.7 % high grade in PD-DCIS, 57.5 % grade III in PD-IDC). Patients with underlying invasive or in situ carcinoma were more commonly hormone-receptor negative. With respect to nodal disease, 47.1 % of cases of PD-IDC had nodal involvement. Lymph node metastasis was also reported in 4.1 % of cases of PD-DCIS, suggesting the presence of undocumented occult invasive disease.

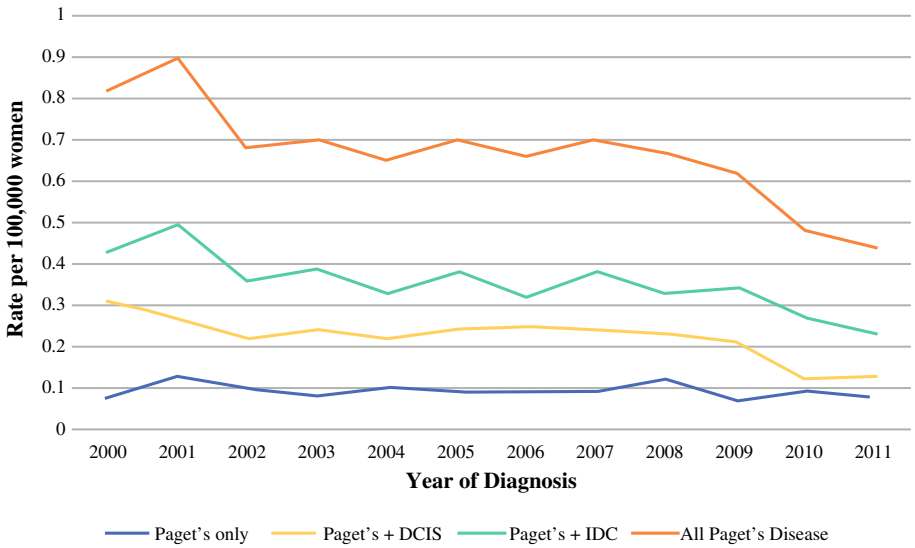

FIG. 1 Age-adjusted incidence rates for Paget's disease of the breast per 100,000 women over time, according to subgroup and adjusted to the age distribution of women 18 years or older in the 2000 U.S. Census

Trends in Surgical Management and Radiotherapy

In examining the rates of primary surgery over time, only the PD-IDC group demonstrated a significant trend towards increasing use of BCS during the study period, from 8.5 % in 2000 to 15.6 % in 2011 ($p = 0.012$; Fig. S1a, supplemental). The PD and PD-DCIS group saw no significant change, with breast conservation being more common in these groups, at overall rates of 53 and 31 %, respectively (Table 2).

For adjuvant radiotherapy in the setting of breast conservation, just more than half of patients with an underlying invasive or in situ carcinoma received radiation (51.2 % of cases of PD-DCIS, and 53.6 % of cases of PD-IDC). Of those with PD confined to the nipple only, 33.7 % underwent adjuvant radiation therapy after excision. The proportion of patients receiving post-BCS adjuvant radiotherapy declined with increasing age: 73.3 % of women younger than 40 years, 64.5 % of women 40–60 years, 49.4 % of women 60–80 years, and 29.2 % of women older than 80 years ($p < 0.0001$). In the postmastectomy population, adjuvant radiotherapy was seen in 4.7 % of patients with PD-DCIS and 21.4 % of patients with PD-IDC.

Of the 1491 patients who underwent BCS or total mastectomy, 63.3 % underwent axillary node assessment, with SLNB or ALND performed in 30 % of patients with PD only, 53 % of PD-DCIS, and 84 % of PD-IDC. Of patients undergoing axillary surgery, the proportion undergoing SLNB increased between 2000 and 2011, from 40 to 66.6 % in PD only ($p = 0.13$), 33.3 to 82.4 % in PD-DCIS ($p < 0.001$), and 14.2 to 43.2 % in the PD-IDC group ($p < 0.001$; Fig. S1b, supplemental). Similarly, the proportion of patients undergoing ALND with node-positive disease increased over time, from 18.5 % of ALND patients in 2000 to 60 % of ALND patients in 2011 ($p = 0.002$).

Logistic Regression Analysis

In adjusted analyses, older age at diagnosis, SEER region, central tumor location, low/intermediate tumor, smaller tumor size, and diagnosis after 2006 were associated with receipt of BCS. Compared with PD-IDC, patients diagnosed as PD-DCIS had a 2.6-fold increased odds of receiving BCS, whereas patients with PD alone were the most likely of all groups to undergo breast conservation [odds ratio (OR) 4.5; 95 % CI 2.80–7.24; Table 3].

After adjusting for patient and tumor characteristics as well as year of diagnosis, receipt of radiation following BCS remained significantly associated with younger age group ($p < 0.0001$), tumor location ($p = 0.002$), and geographic (SEER) region ($p = 0.001$; Table 4).

DISCUSSION

In this large population-based cohort of women diagnosed with Paget's disease of the breast, we found a significant decline in the incidence of Paget's disease, namely due to decreasing rates of Paget's disease with underlying carcinoma. In addition, our analysis of the surgical management of Paget's disease demonstrated significant temporal trends, with increasing use of SLNB for axillary staging, as well as a subtle but significant increase in the use of BCS for PD-IDC.

Our findings are consistent with a previous analysis performed by Chen et al.[5] who demonstrated a decrease in the age-adjusted incidence of Paget's disease between 1988 and 2002 using SEER data. Chen et al. hypothesized that this decrease could be explained by increasing rates of

TABLE 2 Overall rates of axillary surgery and adjuvant radiation therapy for patients with Paget's disease, 2000–2011

	PD only ($n = 185$)	PD-DCIS ($n = 953$)	PD-IDC ($n = 1493$)
Breast-conserving surgery (BCS)	98 (53.0)	295 (31.0)	166 (11.1)
With SLNB	14 (14.3)	71 (24.1)	76 (45.8)
With ALND	4 (4.1)	19 (6.4)	43 (25.9)
With adjuvant radiotherapy	33 (33.7)	151 (51.2)	89 (53.6)
Total (simple) mastectomy	58 (31.3)	432 (45.3)	442 (29.6)
With SLNB	24 (41.3)	245 (57.4)	253 (57.2)
With ALND	5 (8.6)	50 (11.7)	140 (31.7)
With adjuvant radiation therapy	1 (1.7)	16 (3.7)	58 (13.1)
Modified radical mastectomy	29 (15.7)	226 (23.7)	885 (59.3)
With adjuvant radiation therapy	0 (0.0)	15 (6.6)	226 (25.5)

PD Paget's disease, *PD-DCIS* Paget's disease with ductal carcinoma in situ, *PD-IDC* Paget's disease with invasive ductal carcinoma, *BCS* breast-conserving surgery, *SLNB* sentinel lymph node biopsy (defined as removal of 1–5 lymph nodes), *ALND* axillary lymph node dissection (defined as removal of >6 lymph nodes)

TABLE 3 Adjusted odds ratios for receipt of BCS in women with Paget's disease who underwent surgery ($n = 2631$)

Characteristic	Cohort	Proportion undergoing BCT		Adjusted odds ratio for BCS (95 % confidence interval)**
	No. (%)	%	*P* value*	
Histology			<0.001	
Paget's + IDC	1493 (56.7)	11.1		1.00
Paget's + DCIS	953 (36.2)	30.9		**2.61 (1.97–3.47)**
Paget's of the nipple only	185 (7.0)	53.0		**4.50 (2.80–7.24)**
Age group (years)			<0.001	
<40 (*n*, %)	172 (6.5)	8.7		1.00
40–59	1016 (38.6)	15.6		1.43 (0.79–2.60)
60–79	1076 (40.9)	24.6		**1.96 (1.09–3.54)**
>80	367 (14.0)	33.0		**3.24 (1.74–6.06)**
Marital status			0.06	
Not married[a]	1292 (49.1)	22.7		1.00
Married	1339 (50.9)	19.8		0.96 (0.77–1.20)
Race			0.001	
White	2138 (81.3)	22.6		1.00
Black	259 (9.8)	16.2		1.01 (0.68–1.50)
Other/unknown	234 (8.9)	14.1		**0.63 (0.41–0.97)**
SEER region[b]			0.01	
California[†]	1330 (50.6)	20.5		1.00
Georgia[‡], Louisiana, Kentucky	415 (15.8)	19.3		**0.66 (0.48–0.91)**
Connecticut, New Jersey	279 (10.6)	29.0		**1.45 (1.04–2.00)**
Seattle (Puget Sound), Hawaii, Alaska	241 (9.2)	22.0		0.97 (0.66–1.42)
Detroit, Iowa	222 (8.4)	23.0		0.90 (0.61–1.32)
Utah, New Mexico	144 (5.5)	15.3		**0.51 (0.30–0.85)**
Tumor location[c]			<0.001	
Central/NAC	1235 (46.9)	36.1		1.00
Peripheral	485 (18.4)	7.7		**0.34 (0.23–0.49)**
Overlapping areas/breast NOS	911 (34.6)	8.7		**0.26 (0.20–0.35)**
Tumor grade			<0.001	
Low/intermediate grade/grade I–II	639 (24.3)	20.2		1.00
High grade/grade III	1411 (53.6)	15.5		**0.62 (0.47–0.83)**
Unknown/not applicable	581 (22.1)	36.5		0.80 (0.56–1.13)
Tumor size (cm)			<0.001	
0–2.0	1185 (45.0)	22.6		1.00
2.1–5.0	605 (23.0)	9.75		**0.53 (0.38–0.73)**
>5.0	195 (7.4)	2.56		**0.14 (0.06–0.34)**
Paget's disease NOS/unknown	646 (24.6)	33.5		0.77 (0.60–1.02)
Hormone receptor status[d]			<0.001[e]	
Negative	958 (36.4)	16.9		1.00
Positive	936 (35.6)	17.6		1.21 (0.91–1.60)
Unknown	737 (28.0)	31.4		1.19 (0.90–1.60)

TABLE 3 continued

Characteristic	Cohort	Proportion undergoing BCT		Adjusted odds ratio for BCS (95 % confidence interval)**
	No. (%)	%	*P* value*	
Year of diagnosis			0.02	
2000–2005	1438 (54.7)	19.6		1.00
2006–2011	1193 (45.3)	23.2		**1.36 (1.09–1.70)**

Paget's disease NOS Paget's disease not otherwise specified, *BCS* breast-conserving surgery, *NOS* not otherwise specified

* *P* values calculated by Pearson Chi squared testing

** Using multivariable logistic regression, adjusting for all variables listed; Bold if statistically significant, $p < 0.05$

† Includes San-Francisco-Oakland, San Jose-Monterey, Los Angeles, and Greater California

‡ Includes Metropolitan Atlanta, Rural Georgia, and Greater Georgia

[a] Single, separated, divorced, widowed, or other groups collapsed

[b] Regions combined due to small sample sizes

[c] Upper inner, upper outer, lower inner, and lower outer quadrant groups collapsed due to small sample sizes

[d] Defined as the following: negative if estrogen receptor and progesterone receptor reported as negative; positive if estrogen or progesterone receptor (or both receptors) reported as positive; unknown if both receptors unknown or negative/unknown

[e] No significant difference in pairwise testing between HR-negative and -positive ($p = 0.76$)

screening mammography, with earlier detection of tumors prior to the development of clinically evident Pagetoid spread. An additional reason for this decline may be related to decreased recognition of clinically occult Paget's disease, a pathologic entity defined by tumor infiltration of the nipple epidermis that is seen only on detailed evaluation of the nipple/areolar complex. Prior studies have suggested that a fraction of patients, between 15 % and 46 %, harbor clinically undetectable Paget's disease yet are incidentally diagnosed following microscopic examination of mastectomy specimens performed for another indication.[4,6,15,16] With U.S. mastectomy rates steadily declining between 1988 and 2004, these patients may have remained undocumented.[17]

Although mastectomy has long been regarded as standard therapy for Paget's disease, the use of breast conservation is oncologically safe for breast cancer associated with or without Paget's disease of the breast. While early studies examining the use of local excision alone reported high local recurrence rates for PD-IDC, equivalent disease-free and overall survival rates have since been documented in several retrospective series comparing mastectomy to BCS with adjuvant radiation.[2,5,9,18–23] One prospective study performed by Bijker et al. reported adequate local control and a 5-year recurrence rate of 5.2 % following BCS and adjuvant radiation for PD-DCIS.[8] In turn, some have called for breast conservation with radiation to become the preferred treatment for Paget's disease with underlying carcinoma.[19] Despite this, our study found that national rates of BCS in Paget's disease remain quite low. While we did see a modest increase in the use of BCS for PD-IDC, the overall rate for this subgroup was only 11.1 %, with less than one fifth of patients treated with this approach during 2011. Our adjusted analysis further supports the notion that women with PD-IDC are less likely to receive BCS, given that Paget's subgroup remained a significant predictor after controlling for factors such as age, tumor size, location, and histologic grade. One could surmise that this may be due to a variety of factors, such as the surgeon or patient feeling that if the nipple and areola are to be removed then the utility of the maintaining the breast mound may not be as important, leading women to choose mastectomy with or without reconstruction.

Unexpectedly, we found low rates of adjuvant radiation following BCS; our data suggest that just over half of cases of Paget's disease with underlying carcinoma receive radiation following BCS. These findings may be partially justified by delayed initiation of therapy and other factors that result in radiotherapy under-ascertainment in SEER.[24] However, if we assume the results are valid for PD-IDC patients, where receipt of radiation following BCS is considered an indicator for quality of care, then the low rates seen may represent undertreatment.[25]

In the current study, we found increasing use of SLNB across all Paget's subgroups, reflecting part of a broader adoption in breast cancer therapy in the modern era. Using SEER-Medicare data, Black et al. demonstrated widespread adoption of the sentinel node technique, with rates of ALND declining from 43.5 % in 2002 to 15.6 % in 2007 for pathological node-negative women.[26] Interestingly, amongst this cohort of patients with Paget's disease undergoing ALND

TABLE 4 Adjusted odds ratios for receipt of radiotherapy in women with Paget's disease undergoing BCS ($n = 548$)

Characteristic	Adjusted odds ratio for receipt of radiotherapy, OR (95 % CI)[†]
Histology	
Paget's + IDC	1.00
Paget's + DCIS	1.14 (0.69–1.90)
Paget's of the nipple only	0.59 (0.27–1.29)
Age group (years)	
<40 (*n*, %)	1.00
40–59	0.62 (0.17–2.20)
60–79	0.33 (0.09–1.15)
>80	**0.12 (0.03–0.45)**
Marital status	
Not married[a]	1.00
Married	1.10 (0.74–1.61)
Race	
White	1.00
Black	0.83 (0.40–1.73)
Other/unknown	1.11 (0.50–2.50)
SEER region[b]	
California[†]	1.00
Georgia[‡], Louisiana, Kentucky	**2.34 (1.32–4.14)**
Connecticut, New Jersey	**2.03 (1.17–3.50)**
Seattle (Puget Sound), Hawaii,	1.86 (0.96–3.61)
Alaska	**3.82 (1.88–7.78)**
Detroit, Iowa	1.14 (0.41–3.20)
Utah, New Mexico	
Tumor location[c]	
Central/NAC	1.00
Peripheral	**0.29 (0.14–0.63)**
Overlapping areas/breast NOS	**0.51 (0.29–0.92)**
Tumor grade	
Low/intermediate Grade/grade I–II	1.00
High grade/grade III	0.87 (0.47–1.64)
Unknown/not applicable	0.83 (0.49–1.40)
Tumor size (cm)	
0–2.0	1.00
2.1–5.0	1.21 (0.64–2.31)
>5.0	1.09 (0.15–8.11)
Paget's disease NOS/unknown	0.71 (0.44–1.13)
Hormone receptor status[d]	
Negative	1.00
Positive	1.29 (0.77–2.19)
Unknown	1.09 (0.15–8.11)
Year of diagnosis	
2000–2005	1.00
2006–2011	0.736 (0.49–1.11)

BCS breast-conserving surgery, *NOS* not otherwise specified. Patients with unknown radiation therapy status excluded from the analysis

[†] Bold if statistically significant, $p < 0.05$

[†] Includes San-Francisco-Oakland, San Jose-Monterey, Los Angeles, and Greater California

[‡] Includes Metropolitan Atlanta, Rural Georgia, and Greater Georgia

[a] Single, separated, divorced, widowed, or other groups collapsed

[b] Regions combined due to small sample sizes

[c] Upper inner, upper outer, lower inner, and lower outer quadrant groups collapsed due to small sample sizes

[d] Defined as the following: negative if estrogen receptor and progesterone receptor reported as negative; positive if estrogen or progesterone receptor (or both receptors) reported as positive; unknown if both receptors unknown or negative/unknown

with BCS or mastectomy, 53.8 % were node-negative. While this trend decreased over time concomitant with increasing use of SLNB, a significant minority (approximately 40 %) of node-negative women continued to undergo ALND in the final years of this study. Although the role of sentinel lymph node biopsy has not been well established in the management of Paget's disease, studies over the past decade have shown SLNB to be safe and feasible and have recommended its consideration for patients with PD-IDC or all patients with Paget's disease of the breast.[6,10,11,27,28] Current National Comprehensive Cancer Network (NCCN) guidelines encourage axillary staging in the context of Paget's disease with an underlying invasive breast cancer, although axillary evaluation is not considered necessary for PD-DCIS treated with BCS.[29] Despite this, at our institution we routinely perform SLNB on all cases of Paget's disease with underlying IDC or DCIS, with the rationale that removal of the nipple-areola complex precludes the use of future subareolar mapping injections should an invasive component be identified on the excised specimen.

To our knowledge, this is the largest study of Paget's disease in the modern era and one of the first to assess patterns of local therapy. Apart from one prior population-based study containing data to 2002, most of the available literature on Paget's disease has been derived from single-institution cohorts or case-series.[5] Yet, this study does have

several limitations. First, the SEER database has no measures in place for central pathology review, which increases the possibility of misclassification bias. Secondly, we were unable to incorporate Paget's disease associated with non-ductal histologies (such as lobular carcinoma) into our cohort due to limitations in SEER coding that do not allow for this distinction. Additionally, we did not have specific information on type of axillary surgery performed and thus required the use of surrogates derived from the number of lymph nodes excised. In doing so, a fraction of women who underwent sentinel node biopsy procedures yielding greater than five axillary nodes would have been assigned to the ALND group, and vice versa. Finally, we lacked data on a number of potentially relevant factors that may influence choice of therapy, including radiologic findings, multifocality, and patient preference. As a result, we were unable to explore some of the central reasons patients and their surgeons may have opted for specific types of local therapy when examining temporal trends.

In summary, we found that as incidence continues to decrease, trends in local therapy suggest that BCS, SLNB, and adjuvant radiation remain underutilized in the management of Paget's disease. Further guidelines are needed to minimize variation in patterns of care and standardize approach to management.

ACKNOWLEDGMENT The authors thank Ellen McCarthy, PhD, MPH, Harvard Medical School, for her guidance and expertise with SEER database programming. S.W. thanks the Cedars Cancer Institute Henry R. Shibata Fellowship, Montreal, QC, Canada

REFERENCES

1. Ashikari R, Park K, Huvos AG, Urban JA. Paget's disease of the breast. *Cancer*. 1970;26:680–5.
2. Dixon AR, Galea MH, Ellis IO, et al. Paget's disease of the nipple. *Br J Surg*. 1991;78:722–3.
3. Yim JH, Wick MR, Philpott GW, et al. Underlying pathology in mammary Paget's disease. *Ann Surg Oncol*. 1997;4:287–92.
4. Kollmorgen DR, Varanasi JS, Edge SB, Carson WE 3rd. Paget's disease of the breast: a 33-year experience. *J Am Coll Surg*. 1998;187:171–7.
5. Chen CY, Sun LM, Anderson BO. Paget disease of the breast: changing patterns of incidence, clinical presentation, and treatment in the U.S. *Cancer*. 2006;107:1448–58.
6. Dominici LS, Lester S, Liao GS, et al. Current surgical approach to Paget's disease. *Am J Surg*. 2012;204:18–22.
7. Singh A, Sutton RJ, Baker CB, Sacks NP. Is mastectomy overtreatment for Paget's disease of the nipple? *Breast*. 1999;8:191–4.
8. Bijker N, Rutgers EJ, Duchateau L, et al. Breast-conserving therapy for Paget disease of the nipple: a prospective European Organization for Research and Treatment of Cancer study of 61 patients. *Cancer*. 2001;91:472–7.
9. Kawase K, Dimaio DJ, Tucker SL, et al. Paget's disease of the breast: there is a role for breast-conserving therapy. *Ann Surg Oncol*. 2005;12:391–7.
10. Laronga C, Hasson D, Hoover S, et al. Paget's disease in the era of sentinel lymph node biopsy. *Am J Surg*. 2006;192:481–3.
11. Sukumvanich P, Bentrem DJ, Cody HS 3rd, et al. The role of sentinel lymph node biopsy in Paget's disease of the breast. *Ann Surg Oncol*. 2007;14:1020–3.
12. National Cancer Institute. SEER Cancer Statistics Review, 1975–2011. Bethesda, MD: 2014. http://seer.cancer.gov/csr/1975_2011/. Accessed Dec 2014.
13. Wang J, Mittendorf EA, Sahin AA, et al. Outcomes of sentinel lymph node dissection alone vs. axillary lymph node dissection in early stage invasive lobular carcinoma: a retrospective study of the surveillance, epidemiology and end results (SEER) database. *PLoS One*. 2014;9:e89778.
14. Kleinbaum D KL, Muller K. Applied regression analysis and other multivariable models. Boston, MA: PWS-Kent; 1988.
15. Ling H, Hu X, Xu XL, et al. Patients with nipple-areola Paget's disease and underlying invasive breast carcinoma have very poor survival: a matched cohort study. *PLoS One*. 2013;8:e61455.
16. Sakorafas GH, Blanchard K, Sarr MG, Farley DR. Paget's disease of the breast. *Cancer Treat Rev*. 2001;27:9–18.
17. Freedman RA, He Y, Winer EP, Keating NL. Trends in racial and age disparities in definitive local therapy of early-stage breast cancer. *J Clin Oncol*. 2009;27:713–9.
18. Polgar C, Orosz Z, Kovacs T, Fodor J. Breast-conserving therapy for Paget disease of the nipple: a prospective European Organization for Research and Treatment of Cancer study of 61 patients. *Cancer*. 2002;94:1904–5.
19. Caliskan M, Gatti G, Sosnovskikh I, et al. Paget's disease of the breast: the experience of the European Institute of Oncology and review of the literature. *Breast Cancer Res Treat*. 2008;112:513–21.
20. Dalberg K, Hellborg H, Warnberg F. Paget's disease of the nipple in a population based cohort. Breast Cancer Res Treat. 2008;111:313–9.
21. Joseph KA, Ditkoff BA, Estabrook A, et al. Therapeutic options for Paget's disease: a single institution long-term follow-up study. *Breast J*. 2007;13:110–1.
22. Marshall JK, Griffith KA, Haffty BG, et al. Conservative management of Paget disease of the breast with radiotherapy: 10- and 15-year results. *Cancer*. 2003;97:2142–9.
23. Pierce LJ, Haffty BG, Solin LJ, et al. The conservative management of Paget's disease of the breast with radiotherapy. *Cancer*. 1997;80:1065–72.
24. Jagsi R, Abrahamse P, Hawley ST, et al. Underascertainment of radiotherapy receipt in Surveillance, Epidemiology, and End Results registry data. *Cancer*. 2012;118:333–41.
25. Hershman DL, Buono D, McBride RB, et al. Surgeon characteristics and receipt of adjuvant radiotherapy in women with breast cancer. *J Natl Cancer Inst*. 2008;100:199–206.
26. Black DM, Jiang J, Kuerer HM, et al. Racial disparities in adoption of axillary sentinel lymph node biopsy and lymphedema risk in women with breast cancer. *JAMA Surg*. 2014;149:788–96.
27. Trebska-McGowan K, Terracina KP, Takabe K. Update on the surgical management of Paget's disease. *Gland Surg*. 2013;2:137–42.
28. Siponen E, Hukkinen K, Heikkila P, et al. Surgical treatment in Paget's disease of the breast. *Am J Surg*. 2010;200:241–6.
29. NCCN Guidelines Version 2.2015 Breast cancer updates. Special situations: Paget's disease. In. MS-58: 2015. http://www.nccn.org/professionals/physician_gls/pdf/breast.pdf. Accessed 10 Mar 2015.