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Skin Involvement and Breast Cancer: Are T4B Lesions of All Sizes Created Equal?

Diana Silverman, DO^{*}, Karen Ruth, MS[†], Elin R. Sigurdson, MD, PhD^{**}, Brian L. Egleston, PhD[†], Lori J. Goldstein, MD[†], Yu-Ning Wong, MD, MPH[†], Marcia Boraas, MD, FACS^{**}, and Richard J. Bleicher, MD, FACS^{**§}

^{*}Department of Surgery, Saint Francis Hospital and Health Center, Poughkeepsie, NY

^{**}Department of Surgical Oncology, Fox Chase Cancer Center, Philadelphia, PA

[†]Department of Biostatistics, Fox Chase Cancer Center, Philadelphia, PA

[†]Department of Medical Oncology, Fox Chase Cancer Center, Philadelphia, PA

Abstract

Background—Nonmetastatic non-inflammatory invasive breast cancers having skin involvement (SI) are classified as T4b, regardless of size. This study evaluated disease specific survival (DSS) to determine whether size should be considered for these lesions, rather than grouping them all into Stage III.

Study Design—Surveillance Epidemiology and End Results data linked to Medicare claims were reviewed. SI and nonSI tumors were reclassified using AJCC 7th Edition groupings using tumor size and nodal involvement alone without considering SI (neostage). DSS was adjusted for demographics, histology and treatment using competing risk methods with propensity score-based weighting and bootstrap standard errors.

Results—Among 924 SI patients diagnosed between 1992 and 2005, tumors were 0.1–2.0, 2.1–5.0, and >5.0 cm in 11.6%, 51.1%, and 37.3% of cases, respectively. There were no nodal metastases in 22.3%, 1–3 positive nodes in 31.7%, 4–9 positive in 28.6% and 10 positive in 17.4% of cases. For SI patients, adjusted 5-year DSS was 95.8% [95%CI: 95.6–96.0] for neostage I, declining progressively to 36.4% [95%CI: 33.8–39.2] for neostage IIIC patients. Adjusted 5-year DSS for SI and nonSI tumors ($n=66,185$) was similar for neostage I, IIA, and IIB, and markedly lower for IIIA and IIIC. Adjusted DSS for SI IIIA was similar to nonSI IIIC.

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[§]Corresponding author Richard J. Bleicher, MD, Department of Surgical Oncology, 333 Cottman Avenue, Fox Chase Cancer Center, Room C-308, Philadelphia, PA 19111, richard.bleicher@fccc.edu, (215) 728–2596 voice, (215) 728–2773 facsimile.

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Conclusions—Noninflammatory SI breast cancers have widely varied DSS that differs by tumor size and nodal involvement, and therefore should not all be stage III. SI should be subordinate to T and N groupings to classify SI with nonSI lesions having similar prognoses.

INTRODUCTION

Locally advanced breast cancers account for 5–10% of new breast cancer diagnoses in the United States and 60–70% of cases worldwide. According to the American Joint Committee on Cancer (AJCC) TNM 7th edition classification, breast cancer lesions with direct extension to skin beyond the dermis are considered locally advanced and grouped as T4b primaries. Regardless of tumor size and involvement of regional lymph node basins, the presence of significant skin involvement (SI) places any tumor into Stage III (1), where 5-year overall survival ranges from 41 to 67% (2). TNM staging criteria were created to provide groupings for prognosis and treatment of patients with breast cancer. However, because the SI characteristic is the primary determinant for classification overriding size and nodal status, the heterogeneity of the T4b category is significant. A paucity of data exists because of the low frequency of these tumors, however if the SI were not considered, prior data suggest that nearly 60% of these tumors would be classified as T1 or T2, and 13% can be node-negative (3).

A few small studies have analyzed patients with T4b tumors, however they have all suggested that this subset of breast cancers has widely varied prognoses (3–8). Since cancer normally invades surrounding structures, logic suggests that a small invasive tumor that, by chance, arises close to skin and grows through it, does not necessarily have a worse prognosis than a similarly sized tumor arising and growing distant from skin. The lack of data, however, has prohibited any such assertion.

This study was performed to describe the diversity among non-inflammatory breast cancers having SI that would be classified as T4b by using a large population-based dataset to determine whether tumor size and nodal status should play a more prominent role in staging such lesions.

METHODS

Data were derived from the Surveillance, Epidemiology, and End Results (SEER)-Medicare linked claims database with approval from the National Cancer Institute (9, 10) and our institutional IRB. Although SEER-Medicare linked data are limited to patients ≥ 65 years old, they provide more specifics than SEER data alone about the surgical procedures, radiotherapy, and treatment dates. SEER provides no chemotherapy information while Medicare claims do.

Patients were included who were likely to have claims from one year before and after the SEER diagnosis month. Although patients were restricted to their first breast cancer, those with other prior malignancies were not excluded. All sixteen applicable SEER registries were used to increase the external generalizability of the results. Included patients had a diagnosis of invasive breast cancer ≥ age 65 from 1992–2005, and had cancer-directed surgery.

SEER extent of disease (EOD) codes were used to identify confinement to breast tissue or involvement of skin or chest wall (Table 1 for definitions) and SEER stage is consistent with these codes. Two subgroups having pertinent EOD codes were included in this analysis: those having no SI ('nonSI,' EOD codes 10, 11, 13, 14, 15, 16, 17, 18) and those having extensive SI ('SI,' EOD codes 50, 51, and 52), fulfilling criteria for T4b classification. Patients having involvement of subcutaneous tissue and dermis (limited SI not extensive enough to be T4b, EOD codes 20, 21, 23, 24, 25, 26, 27, 28) or both extensive SI and chest wall involvement (EOD code 60) were excluded for a more definitive comparison between distinct SI and nonSI subgroups. Patients having metastatic, inflammatory cancer, and chest wall or extra-axillary nodal involvement were also excluded (Figure 1).

After the subgroups were established, SI tumors were regrouped with American Joint Committee on Cancer (AJCC) 7th Edition classifications using tumor size and nodal involvement but without considering SI that classified these tumors as T4b; these reclassifications are referred to as "neostage." Patients having nonSI primaries were reclassified into the same neostage groupings using tumor size and nodal involvement for comparison, by updating to 7th Edition from prior staging classifications. Mean tumor size by SI group was compared within neostage using *t*-tests, adjusted for multiple comparisons using the Benjamini-Hochberg method.

Propensity score-based weighting was used to adjust for differences in the SI and nonSI groups (11). This method has been used and described previously (12, 13). The propensity score is the probability of being in the SI group within stage, generated from a logistic regression model, including potential confounders. Within each stage, each person's data was weighted by the inverse of the probability that the person was in their observed SI group. This is akin to survey weighting, and creates an adjusted population in which the distribution of confounding factors across SI groups is similar, thereby reducing the impact of confounding. Confounding factors, including age, race, gender, histology, grade, estrogen and progesterone receptor status (ER, PR), surgery, chemotherapy, and radiotherapy, were included in a logistic regression model for each neostage to estimate the probability of being in the SI group. Patients were excluded from the nonSI group (n=896 or 1.4%) because of insufficient overlap of the probabilities in the two groups. Age was included as a categorical variable in 5 year intervals, ER and PR grouped as positive/borderline versus negative/unknown, and chemotherapy and radiotherapy each included as being administered or not. Procedural data were derived from physician claims, supplemented by outpatient and inpatient hospital claims.

Although oral chemotherapeutic agents were not covered by Medicare until 2006, most agents are intravenously administered, and chemotherapy claims are most accurate for breast cancer agents (10). Preoperative chemotherapy (between first breast-related doctor visit and surgery), and postoperative claims within 1 year were identified. Radiotherapy claims were identified within 1 year after surgery. Differences in treatment by SI group were examined using logistic regression with adjustment for neostage. Increases in chemotherapy use over time were evaluated with the Cochran-Armitage trend test. Charlson Comorbidity Index (14) (CCI) was estimated from diagnosis codes using the method of Klabunde (15, 16).

Disease specific survival (DSS) was the primary outcome. To account for competing risk of other causes of death, disease specific mortality (DSM) was estimated within neostage using cumulative incidence estimators with bootstrap standard errors. DSS was calculated as $1 - \text{DSM}$. Covariate-adjusted DSM was estimated using propensity score weighting. Subdistribution hazard ratios were estimated for each neostage using Fine and Gray competing risks regression (17, 18) with propensity score weighting. Plots of DSS ($1 - \text{DSM}$) were based on cumulative incidence estimates accounting for death from other causes. Survival estimations were from the first therapeutic surgery date (19). Patients remaining alive were censored as of 12/31/2006. Statistical significance was set at $p=0.05$ (two-sided). Analyses were performed using SAS software, version 9.2 (SAS Institute) and Stata software, release 12 (StataCorp 2011).

RESULTS

Among breast cancer patients having significant SI diagnosed from 1992 to 2005, 924 remained after all exclusions (Figure 1). These patients were compared to 66,185 patients having nonSI tumors. Mean age was 78.8 and 75.0 years for SI and nonSI patients. Male breast patients accounted for 3.5% of the SI and 0.8% of the nonSI tumors, while a greater proportion of SI patients were Black, with cohort characteristics listed in Table 2. Most patients with SI cancers were originally stage III-B (95.9%) with only a small percentage categorized as III-C (4.1%). When restaging SI tumors based upon T and N alone (neostage), only 57.0% of SI patients would remain as neostage III, while 4.5% would be reclassified as neostage I, and 38.4% as neostage II (Table 3).

Mean ($\pm$ standard deviation) and median tumor sizes were 5.0 (± 2.8) and 4.2 cm for SI primaries [interquartile (IQ) range 1.0–2.4 cm] and 1.9 (± 1.3) and 1.5 cm [IQ range 3.0–6.5 cm] for nonSI primaries, respectively. Among SI patients, neostage T1 and T2 tumors accounted for 43.0% of cases but 91.4% of the nonSI patients. Patients known to be ER-negative, PR-negative accounted for 15.6% of SI vs. 12.1% of nonSI patients ($p=0.0015$). Within each neostage, the mean tumor sizes were significantly larger for SI tumors than nonSI tumors (Table 3).

There were 77.7% of SI and 26.6% of nonSI patients having positive nodes. The mean number of positive nodes ($\pm$ standard deviation) was 6.4 (± 6.1) for SI and 3.6 (± 4.4) for nonSI tumors ($p<0.0001$). There were no positive nodes in 22.3% of SI cases ($n = 206$), 1–3 positive in 31.7% ($n = 293$), 4–9 positive in 28.6% ($n = 264$) and 10 positive in 17.4% ($n = 161$). The proportion of patients having SI tumors in neostage IIA and IIB was lower than for nonSI tumors ($p<0.01$), and the median number of positive nodes among those having positive nodes was similar between the two groups (Table 3). Conversion of original nonSI tumor stage to neostage (i.e. updating to AJCC 7th edition) changed the stage for 4,338 nonSI tumors (6.6%). In redistributing SI tumors using neostage reclassifications, 4.5% became neostage I, 38.4% became neostage II, and 57.0% became neostage III (Table 3).

Mastectomy was performed on 51.4% of nonSI and 90.7% of SI tumors overall with surgery the sole treatment (no radiotherapy or chemotherapy) in 50.2% and 49.2% of SI and nonSI cases, respectively ($p=0.52$). Neostage I patients underwent BCS in 35.7% of SI and 57.4%

of nonSI tumors ($p=0.0045$) and neostage II patients underwent BCS in 10.1% of SI, and 40.0% of nonSI tumors ($p<0.0001$). Radiotherapy was added to BCS in 66.3% of SI and 75.3% of nonSI tumors ($p=0.0537$), and chemotherapy and radiotherapy were both administered to 16.5% of SI and 9.4% of nonSI tumors ($p<0.0001$). Chemotherapy use increased from 10.4% in 1992 to 21.4% in 2005 (trend test, $p<0.0001$). Treatment is summarized in Table 4.

Survival is presented in Figure 2 and Table 5. For the 924 patients with SI, the adjusted 5 y DSS was 95.8% for patients having restaged tumors now classified as neostage I, 90.3% for IIA, 82.3% for IIB, and 68.4% for IIIA, declining to 36.4% for IIIC patients. These 5 y DSS were similar to nonSI tumors restaged as neostage I, IIA, and IIB, respectively, but SI tumors restaged as neostage IIIA and IIIC had a far greater disparity in their DSS than their similarly restaged nonSI counterparts ($p = 0.023$ and $p<0.001$, respectively). SI tumors reclassified as neostage IIIA had a DSS closer to nonSI tumors of neostage IIIC. Subdistribution hazard ratios (sHRs) calculated from competing risk regression for DSM for SI vs nonSI were not different for tumors of neostage I, IIA and IIB, but were significantly elevated at 1.54 and 1.85 for neostage IIIA and IIIC, respectively (Table 5). Furthermore, competing risk regression models were performed to assess DSM for tumors receiving chemotherapy (SI vs nonSI), and not receiving chemotherapy (SI vs nonSI). For neostages I, IIA, and IIB, DSM was not different between SI and nonSI tumors receiving chemotherapy, and not different between SI and nonSI tumors not receiving chemotherapy. However, SI tumors had a higher mortality regardless of use or nonuse of chemotherapy as vs nonSI tumors for neostages IIIA and IIIC (data not shown).

DISCUSSION

The TNM classification system was designed to group tumors having similar prognoses and provides clarity for treatment and research (2). Breast tumors having significant SI have been classified as T4b (and thus stage III) since the first edition of the AJCC staging system, published in 1977 (20), irrespective of size. SI is most frequently a result of larger tumor infiltration of overlying skin, but tumors that would be classified as T2 (>2.0–5.0 cm) account for approximately half of them, and smaller lesions account for another 11.6%. The low frequency of tumors exhibiting significant SI is one reason why this study, with 924 such patients, is the largest of its kind to date, with little change in the classification of these lesions over the past 36 years.

If staging is designed to group tumors of similar prognosis, then the data presented here suggest that the current classification of SI tumors diverges from this principle. Historically, breast carcinomas that were large, visible, and that invaded skin, had frequent nodal involvement on initial presentation. These classic cases comprised the majority of such breast carcinomas and were appropriately classified as advanced stage lesions when the staging system was defined. As early as 1943 Haagensen and Stout (21) noted that dermal involvement with edema conferred a 5 year cure rate of 0 to 18.2%, although many of these cases would later be classified as inflammatory carcinoma. That same year, the physical signs of inoperability defined by these authors (22) were: size >10 cm, skin ulceration, skin

edema, chest wall fixation, and axillary lymph nodes ≥ 2.5 cm in transverse diameter or fixed to chest wall or skin. A few of these still classify a tumor as “unresectable” to this day.

Our series notes that the characteristics and outcomes of tumors having SI are heterogeneous and can demonstrate DSS as high as 96% when stratified purely by tumor size and nodal status, similar to early stage tumors having no SI, with hazard ratios for death that do not significantly differ from those without SI. While SI tumors more commonly have adverse features, adjustment in our models demonstrates that these measurable features contribute, but the SI itself has less prognostic importance than current staging suggests. This finding is consistent with small series noting that some of these tumors are large and have no regional metastatic involvement. In 1981 Zucali and colleagues (23) demonstrated that among 66 patients, T4 tumors <3 cm had a better overall survival at 5 years than tumors of 3–5 cm (71.3% vs 34.7%). Similar results were obtained by Wieland *et al* (24) who noted that the 5-year survival rate for T4b, N0–3 patients <3 cm was 81% (95% CI 65–97%), which was also consistent with the 36–80% 5 year survival range (25) for all tumors classified as stage III at the time (26). More recently, in 2005 Guth and colleagues noted that in 119 patients, SI for breast tumors ≥ 5.0 cm had no effect on DSS compared to controls of similar sizes (8), and recommended completely abandoning the use of SI in staging outside of inflammatory carcinoma. They updated their findings a year later with similar results (27).

These outcomes are consistent with our demonstration of similar DSS between SI and nonSI lesions reclassified as neostage T2N0 (IIA), and T2N1 (IIB), but not for T2N2 (IIIA) or T2N3 (IIIC) where SI did confer a higher mortality. This is further reinforced by our finding that only neostage IIIA and IIIC SI patients were at increased risk of disease-specific mortality as versus nonSI patients of similar stage and treatment (i.e. whether or not they had chemotherapy), suggesting that the increased risk is due to SI differences, rather than from use or nonuse of systemic therapy. Duraker and colleagues (28) noted in a series of 180 patients that disease-free survival for patients with “classic” clinical T4b signs, having adjuvant or neoadjuvant chemotherapy, was significantly worse than those who only had histologic SI. All of these data reinforce the notion that there may be prognostic importance to significant SI, but that this should be subordinate to tumor size and nodal metastases, while still being maintained as part of staging.

In our study, the early neostage tumors (neostage I-II) had overall survival similar to those without any SI, suggesting that the term “locally advanced” is misleading for these smaller skin-involved lesions as this incorrectly suggests a poor prognosis. We must also consider that the use of the surgical term “unresectable,” frequently used for any skin-involved lesion, may not be appropriate for all such lesions as this connotes an inability to provide a surgical benefit when chemotherapy is not used. The data presented here contradict that by noting a low disease-specific mortality even when some lesions are resected in the absence of nonsurgical therapy. The multimodal standard of care for small SI lesions, whose indications need to be refined, has traditionally been used for any lesion involving skin. This stems from the fact that SI lesions more commonly are large and have nodal involvement, and benefit from such therapy.

Although inflammatory breast cancer has become a clear contraindication to breast conservation therapy (29) and extensive SI is also considered “unresectable,” there remains no standard for the smaller T1 and small T2 skin-involved primaries. The benefit of neoadjuvant chemotherapy has not been scrutinized for such tumors and there is no data to our knowledge that address which SI lesions might undergo breast conservation therapy alone without a compromise in outcomes. Studies of neoadjuvant chemotherapy for breast conservation still typically exclude any SI lesions and some maintain, even without evaluation, that breast conservation is contraindicated when SI exists from tumors of any size (30). Although our data are retrospective, the multivariable adjustment that includes chemotherapy suggests that the smaller lesions might have a negligible benefit if SI is the sole adjuvant therapy indication. The lower frequency of such tumors, however, makes it unlikely that a prospective trial for such lesions will ever occur.

It is also difficult to infer a standard of care for small SI lesions, because our data suggest that actual practice is highly variable. Series in the literature that review the need for multimodal therapy for lesions deemed “unresectable” or “inoperable” typically include either few smaller SI lesions (31) or provide few or no details about the sizes of those primaries at presentation (32, 33). We question the necessity of preoperative chemotherapy for the smallest of these lesions and believe that specific investigation is warranted if sufficient power could be achieved. Shen and colleagues (34) found that patients having SI breast tumors had a benefit from neoadjuvant chemotherapy by affording the ability to undergo breast conservation. These patients had a 5-year disease-free survival rate of 70%, but the median initial tumor size was 7.0 cm, and 67% had nodal metastases, limiting the applicability to this subset. Unfortunately, larger prospective trials such as National Surgical Adjuvant Breast and Bowel Project studies rigorously excluded patients with SI, making subset analysis impossible (35–38).

In light of our findings, we believe that the addition of a SI category, analogous to the grade (G) category for sarcoma (TNMG), to refine the TNM stage should be considered. A tumor (T), node (N), metastasis (M), skin involvement (S) classification for breast cancers could allow for more homogeneous groupings than currently exist. For example, these data suggest that T1, N0, M0, S0 or S1 would remain Stage I, while T1, N1, M0, S0 or S1 and T2, N0, M0, S0 or S1 would remain Stage IIA. Although Guth and colleagues (5) suggested a more complex stratification for SI lesions, we do not believe that even our study, which is the largest of its kind, would have sufficient power to justify further subdividing patients based upon the extent of epidermal involvement, even if such data were available.

Our study is limited by its retrospective nature and the inaccuracies inherent to coding claims as well as the limitations of registry data which includes missing data, changing coding standards, changes in expertise, and changes in staging. Although only 1.4% of tumors here were notable for SI, SEER-Medicare data are generalizable to the US population in this age group (39). Younger age is poorly prognostic in breast cancer patients, but outcome differences have not been significant enough to incorporate age into staging. Although this study evaluated only women ≥ 65, there is little to suggest that the relationship between women having and not having SI would be different from younger women not analyzed here. Available treatment data are also limited by a lack of endocrine therapy data

but inclusion of receptor status should mitigate this. While it is possible to assess outcomes from retrospective data, further conclusions regarding variations in treatment cannot be definitively made without a prospective study.

Ultimately these data suggest a need to consider revising the current TNM classification to allow for more uniform prognostic grouping of breast tumors. These findings demonstrate that the outcome is correlated to the local tumor burden. Therefore, we recommend that consideration be given to classifying T4b (skin involved) tumors according to size and lymph node status which will group them with lesions of similar prognosis, while adding a staging descriptor to subclassify significant SI. Since it also appears that no current standard for treatment of small skin-involved lesions exists, further investigation may be warranted if a cohort of sufficient size can be garnered.

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Figure 1.

Cohort exclusion criteria. AJCC, American Joint Committee on Cancer; HMO, health maintenance organization; EOD codes = Surveillance Epidemiology End Results extent of disease codes. EOD codes X+ refers to all digits within that decile: e.g., 30+ = 30, 31, 32... 39.

Figure 2.

Disease-specific survival (DSS) curves adjusted for competing risks (CR) for SI vs nonSI lesions. **Panel A:** Neostage I and II. Five-year DSS for SI vs nonSI lesions was 95.8% vs 97.7% for Neostage I, 90.3% vs 93.4% for Neostage IIA, and 82.3% vs 86.3% for Neostage IIB, respectively. **Panel B:** Five-year DSS for SI vs nonSI lesions was 68.4% vs 78.8% for Neostage IIIA and 36.4% vs 62.0% for Neostage IIIC, respectively.

Table 1

Extent of disease (EOD) codes and skin involvement (SI). Also see Figure 1 under exclusions.

1992–2003		2004–2005	
EOD 00	IN SITU: noninfiltrating; intraductal WITHOUT infiltration; lobular neoplasia		
EOD 05	Paget's disease (WITHOUT underlying tumor)		
EOD 10+ (11,13,14,15, 16,17,18)	<ul style="list-style-type: none"> Confined to the breast tissue and fat including nipple and/or areola 	EOD 10+ (11,13,14,15, 16,17,18)	<ul style="list-style-type: none"> Confined to the breast tissue and fat including nipple and/or areola
EOD 20+ (21, 23,24, 25,26,27,28)	<ul style="list-style-type: none"> Invasion of subcutaneous tissue Skin infiltration of primary breast including skin of nipple and/or areola Local infiltration of dermal lymphatics adjacent to primary tumor involving skin by direct extension Skin infiltration of primary breast including skin of nipple and/or areola 	EOD 20	<ul style="list-style-type: none"> Invasion of subcutaneous tissue Local infiltration of dermal lymphatics adjacent to primary tumor involving skin by direct extension Skin infiltration of primary breast including skin of nipple and/or areola
EOD 30+ (31,33,34,35 36,37,38)	Invasion of (or fixation to) pectoral fascia or muscle or underlying tissue		
EOD 40	Invasion of (or fixation to) chest wall, ribs, intercostal or serratus anterior muscles		
EOD 50	Extensive skin involvement: Skin edema, peau d'orange, "pigskin," en cuirasse, lenticular nodule(s), inflammation of skin, erythema, ulceration of skin of breast, satellite nodule(s) in skin of primary breast.	EOD 51, 52	Extensive skin involvement, including: Satellite Nodule(s) in skin of primary breast, ulceration of breast skin, any of the following described as involving not more than 50% or % not stated (EOD51) or at least 50% but not inflammatory (EOD52) of the breast: skin edema, en cuirasse, erythema, skin inflammation, peau d'orange.
EOD 60	(50) + (40)		
EOD 70	Inflammatory carcinoma, incl. diffuse (beyond that directly overlying the tumor) dermal lymphatic permeation or infiltration		
EOD 80	FURTHER contiguous extension: Skin over sternum, upper abdomen, axilla or opposite breast		
EOD 85	Metastasis: Bone, other than adjacent rib, Lung, Breast, Contralateral – if stated as metastatic, Adrenal Gland, Ovary, Satellite nodule(s) in skin other than primary breast		
EOD 99	UNKNOWN if extension or metastasis		

Table 2

Patient demographics and tumor characteristics for SEER-Medicare patients fulfilling criteria, diagnosed between 1992 and 2005.

	Extent of Disease				<i>p</i>
	No SI (n = 66,185)		SI (n = 924)		
	<i>n</i>	%	<i>n</i>	%	No SI vs SI
Gender					
Female	65646	99.2	892	96.5	<0.0001
Male	539	0.8	32	3.5	
Race (Medicare)					
White	59209	89.5	784	84.8	<0.0001
Black	3745	5.7	80	8.7	
Other/Unknown	3231	4.9	60	6.5	
Age at Diagnosis (y) Mean (±Std Dev):		75.0 (±6.1)		78.8 (±7.3)	
65–69	14621	22.1	116	12.6	<0.0001
70–74	18944	28.6	164	17.7	
75–79	17305	26.1	222	24.0	
80–84	10481	15.8	227	24.6	
85+	4834	7.3	195	21.1	
Charlson Comorbidity Score					
0	46067	69.6	631	68.3	0.0061
1	13712	20.7	177	19.2	
2	4216	6.4	68	7.4	
3 to 10	2190	3.3	48	5.2	
Original AJCC Stage*					
I	37401	56.5	.	.	<0.0001
IIA	18330	27.7	.	.	
IIB	8084	12.2	.	.	
IIIA	2148	3.2	.	.	
IIIB	.	.	886	95.9	

	Extent of Disease				<i>p</i>
	No SI (n = 66,185)		SI (n = 924)		
	<i>n</i>	%	<i>n</i>	%	No SI vs SI
IIIC	222	0.3	38	4.1	
Positive lymph nodes					
0	48577	73.4	206	22.3	<0.0001
1–3	12464	18.8	293	31.7	
4–9	3586	5.4	264	28.6	
10+	1558	2.4	161	17.4	
Tumor size (cm)					
0.1–2.0	45730	69.1	107	11.6	<0.0001
2.1–5.0	18556	28.0	472	51.1	
5.1–20.0	1899	2.9	345	37.3	
Histology					
Ductal	57274	86.5	769	83.2	<0.0001
Lobular	7058	10.7	77	8.3	
Other/Unknown	1853	2.8	78	8.4	
Tumor Grade					
1	13499	20.4	48	5.2	<0.0001
2	27030	40.8	319	34.5	
3	17103	25.8	455	49.2	
Unknown	8553	12.9	102	11.0	
ER+					
Negative/Unknown	18248	27.6	309	33.4	<0.0001
Positive/Borderline	47937	72.4	615	66.6	
PR+					
Negative/Unknown	26538	40.1	416	45.0	0.0024
Positive/Borderline	39647	59.9	508	55.0	
Surgery					
Breast Conservation	32193	48.6	86	9.3	<0.0001

	Extent of Disease				<i>p</i>
	No SI (n = 66,185)		SI (n = 924)		
	<i>n</i>	%	<i>n</i>	%	No SI vs SI
Mastectomy	33992	51.4	838	90.7	
Postoperative Radiotherapy					
No	40193	60.7	614	66.5	<0.0004
Yes	25992	39.3	310	33.5	
Chemotherapy					
Yes	12182	18.2	262	28.4	<0.0001

* Staging listed here is the cohort as originally staged in the AJCC 3rd/6th Editions prior to conversion in this study to Neostage.

Std Dev=Standard Deviation

Table 3

Tumor sizes and nodal status by neostage for SI and NonSI tumors.

Neostage	Non SI (n = 66,185)		SI (n = 924)		Non SI	SI	p Value*
	n	%	n	%			
Distribution of pts					Mean Tumor Size, mm (±SD)		
IA	37,447	56.6	42	4.5	11.8 (±4.7)	13.9 (±5.3)	0.0045
IIA	17,100	25.8	127	13.7	23.3 (±9.6)	30.5 (±11.8)	<0.0001
IIIB	5,957	9.0	228	24.7	35.3 (±16.7)	48.9 (±26.1)	<0.0001
IIIA	4,123	6.2	366	39.6	35.2 (±21.4)	58.5 (±29.2)	<0.0001
IIIC	1,558	2.4	161	17.4	34.7 (±21.0)	57.5 (±27.0)	<0.0001
Positive nodes, %					Mean Number of Positive Nodes (±SD)		
IA	All are node negative				--	--	--
IIA	6,683	39.1	35	27.6	1.4 (±0.7)	1.7 (±0.8)	0.0769
IIIB	5,244	88.0	156	68.4	1.6 (±0.8)	1.8 (±0.9)	0.0364
IIIA	All are node positive				5.2 (±2.1)	4.8 (±2.4)	0.0136
IIIC	All are node positive				15.3 (±5.5)	15.6 (±5.8)	0.5068

Non-SI neostage reflects nonSI tumors reclassified into the AJCC 7th Edition staging system for uniform comparison.

* p Values calculated using t-test, corrected for multiple comparisons.

SI, skin involvement; Non SI, No skin involvement.

Table 4

Treatment given by neostage for SI and NonSI tumors. Numbers represent n (%). Numbers here represent each treatment independently, and so differences between SI and nonSI tumors may be interdependent. For instance, differences reflected in radiotherapy may result in part from differences in surgical treatment, and so radiotherapy administration by surgery type is also delineated. In contrast, outcomes in Table 5, adjust for all modalities combined.

Treatment (Referent)	SI Status	Neostage					p-value for SI
		Neostage I	Neostage IIA	Neostage IIB	Neostage IIIA	Neostage IIIC	
Total patients	SI	42	127	228	366	161	
	NonSI	37,447	17,100	5,957	4,123	1,558	
Surgery (Mastectomy)	SI	27 (64.3)	109 (85.8)	210 (92.1)	338 (92.3)	154 (95.7)	<0.0001
	NonSI	15,952 (42.6)	9,860 (57.7)	3,985 (66.9)	2,990 (72.5)	1,205 (77.3)	
Radiotherapy (Given)	SI	13 (31.0)	35 (27.6)	67 (29.4)	154 (42.1)	81 (50.3)	0.0003
	NonSI	16,891 (45.1)	5,929 (34.7)	2,035 (34.2)	2,031 (49.3)	818 (52.5)	
BCS (Given)	SI	* (*)	15 (83.3)	12 (66.7)	14 (50.0)	* (*)	0.1704
	NonSI	16,436 (76.5)	5324 (73.5)	1398 (70.9)	820 (73.4)	254 (72.0)	
Mastectomy (Given)	SI	* (*)	20 (18.4)	55 (26.2)	140 (41.4)	75 (48.7)	0.0006
	NonSI	455 (2.9)	605 (6.1)	637 (16.0)	1211 (40.5)	564 (46.8)	
Chemotherapy (Given)	SI	* (*)	27 (21.3)	47 (20.6)	116 (31.7)	68 (42.2)	<0.0001
	NonSI	3,034 (8.1)	4,154 (24.3)	2,104 (35.3)	2,020 (49.0)	870 (55.8)	

* As per NCI SEER-Medicare requirements, cells containing fewer than 11 individuals have been censored.

SI = Skin involvement; nonSI = no skin involvement; BCS=Breast Conservation Surgery

Table 5

Disease-specific survival by neostage reclassification, with and without SI.

Neostage	SI Status	n (%) SI n = 66,185 nonSI n = 924	Unadjusted 5y DSS (%)	95% CI (%)	Adjusted** 5y DSS (%)	95% CI (%)	SubHazard Ratio for DSS: SI vs nonSI		
							sHR	sHR 95%CI	p-value
I	nonSI	37,447 (56.6)	97.7	97.5–97.8	97.7	97.4–97.9	1.00	Referent	
	SI	42 (4.5)	94.6	84.2–99.0	95.8	86.7–98.8	1.36	0.30–6.34	0.6957
IIA	nonSI	17,100 (25.8)	93.4	93.0–93.8	93.4	93.0–93.8	1.00	Referent	
	SI	127 (13.7)	87.3	80.2–92.7	90.3	81.8–95.1	1.45	0.78–2.69	0.2458
IIB	nonSI	5,957 (9.0)	86.5	85.5–87.4	86.3	85.2–87.3	1.00	Referent	
	SI	228 (24.7)	77.8	71.5–83.5	82.3	74.1–88.2	1.31	0.90–1.91	0.1653
IIIA	nonSI	4,123 (6.2)	79.0	77.6–80.4	78.8	77.5–80.1	1.00	Referent	
	SI	366 (39.6)	63.9	58.5–69.3	68.4	60.9–75.1	1.54	1.22–1.94	0.0002
IIIB	Inflammatory and chest wall involvement excluded; SI reclassified.								
IIIC	nonSI	1,558 (2.4)	64.4	61.8–66.9	62.0	58.9–65.1	1.00	Referent	
	SI	161 (17.4)	44.7	36.4–53.9	36.4	25.4–49.0	1.85	1.45–2.36	<0.0001

* % of SI or nonSI cohort

SI = Skin involvement; nonSI = no skin involvement; DSS = disease specific survival, estimated as 100% x (1 – cumulative incidence of disease-specific mortality); CI = confidence interval

** Adjusted using propensity score weights for gender, age, race, ER status, PR status, grade, histology, type of surgery (breast conservation vs mastectomy), chemotherapy, and postoperative radiotherapy administration.

sHR = subHazard Ratio for breast cancer mortality, comparing risk of SI to nonSI, estimated using competing risk regression within each Stage^a group. Propensity score weighting was used to adjust for covariates. Analyses were performed separately for each neostage.