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The Role of Skin Ulceration in Breast Carcinoma Staging and Outcome

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Abstract

Breast carcinoma with skin ulceration (SU) is considered a locally advanced disease. The purpose of the study is to investigate if SU is an independent adverse factor. Breast carcinoma patients with SU (n=111) were included in the study. A subset (n=38, study cohort) was matched with cases that had no SU (n=38, matched cohort); the survival analyses were compared between these groups. Then, cases (n=80) were staged independent from SU into stage I, II or III. Disease free survival (DFS) and overall survival (OS) were analyzed. Patients with larger tumors tended to present with distant metastases more often than patients with smaller tumors (p=0.004). In the matched cases, the 5-year DFS probability was 53% for the study cohort and 58% for the matched cohort; and for OS 75% for the study cohort and 84% for the matched cohort with no statistical significant difference. However, there was a trend towards worse DFS for the patients whose tumors had SU. When the cases were staged based on tumor size and node status (I, II or III), the OS was statistically significant (p=0.047) but not the DFS (p=0.195). Relatively small tumors with SU had an extent of disease similar to that observed in patients with early stages disease. The survival analysis suggests that SU may not be an adverse factor. However, more cases are needed to further examine this finding.

Keywords

Breast carcinoma; skin ulceration; staging; survival

INTRODUCTION

It has been long thought that non-inflammatory skin involvement is a pathologic variable that places breast carcinoma (BC) in categories with most advanced loco-regional extent (1). The most recent American Joint Committee on Cancer (AJCC) (2010) staging guidelines considered BC with skin ulceration (SU) vis a vis erosion as pT4b. This designation would signify the tumor as a more advanced tumor stage of either IIIB or IIIC, depending upon the number of involved lymph nodes (IIIB when pN is 0, 1 or 2 and IIIC when pN is 3) (2). However, recent studies have suggested that T4 designation should be restricted to inflammatory carcinoma (T4d) only, with the consideration that T4 a, b, and c categories have outcomes similar to those in the T3 category, and substantially better than those with true inflammatory BC if carefully defined (3–8). In this situation, the other subcategories (T4a, T4b, and T4c) would then be categorized based on the size of the tumor in each case, regardless of skin or chest wall involvement. Although the AJCC task force acknowledged these studies, they did not change the staging system due to insufficient data to recommend this change at that time, but they did advocate further study and future consideration (2).

This situation has created confusion among practicing pathologists as well as treating physicians. Rarely, BC can present with a relatively small tumor ulcerates the skin. The large difference in the staging of these tumors (stage I vs. stage III) puts these patients into different treatment groups. Stage III disease (locally advanced) is treated either with neoadjuvant therapy or with surgical excision with subsequent adjuvant chemotherapy, radiation therapy with or without hormonal therapy. Early stage tumors are usually treated with surgical excision with or without adjuvant therapy depends upon other clinical, pathological or molecular factors (9).

We hypothesize that pathologists do not strictly follow the AJCC staging guidelines, particularly for relatively small tumors; tumor size correlates directly proportional to distant metastases; and SU may not be an independent factor in predicting worse clinical outcomes. In order to examine these hypotheses, we pooled a large number of BC cases with SU treated in the adjuvant setting from different academic institutions and correlate with the clinical outcomes.

METHODS

In order to evaluate how the pathologists stage BC with SU, T-stage was abstracted from the original pathology report. To investigate if tumor size correlates directly proportional to distant metastases, tumor size was correlated with M-stage. Further, we attempted to investigate if tumor size plays a role in the disease free survival (DFS) and the overall survival (OS). In order to evaluate the role of SU in tumor behavior a subset from the clinical set designated as study cohort was clinically and pathologically matched with cases without SU, designated as matched cohort and survival outcomes were compared.

Clinical Set

The pathology database from each institution was searched using key words “breast”, “carcinoma”, “skin ulceration”, “extending to skin”, and “erosion” to retrieve a total number of 111 cases fulfilling the inclusion criteria. The contributing institutions were Roswell Park Cancer Institute (RPCI) at Buffalo, NY (n=16); Magee Women’s Hospital of the University of Pittsburgh Medical Center (UPMC) at Pittsburgh, PA (n=55); Washington University (Wash U.) at Saint Louis, MO (n=18); Montefiore Medical Center (MMC) at Bronx, NY (n=6); Ohio State University (OSU) at Columbus, OH (n=5); Vanderbilt University (VU) at Nashville, TN (n=3); and University of Texas Southwest (UTSW) at Dallas, TX (n=8).

The cases were identified at RPCI through a computer-based search in PowerPath between 1994 and 2014 [under Institutional Review Board (IRB) #BDR 054114]. The Text Information Extract System (TIES) natural language processing system was used to retrieve UPMC cases from 2000 to 2014 (under IRB #PRO07050292). Cases were retrieved from Wash. U. through a computer-based search in CoPath between 2004 and 2014 (under IRB #201203144), for OSU through CoPath between 1999 and 2014 (under IRB #2014E0671), for VU through CoPath and Triple-G software systems between 2000 and 2014 (under IRB #141863). Cases were retrieved from MMC through a computer-based search in CoPath between 2004 and 2014 (under IRB #2015-5518, Reference # 012257), and for UTSW through CoPath between 2007 and 2014 in one institution and through Cerner millennium between 2010 and 2014 in another institution (under IRB #STU102015-068). No patient consent was required as this study was performed retrospectively on existing data with no human tissue utilization.

The exclusion criteria were neoadjuvant therapy, SU due to Paget disease, chest wall involvement, tumor recurrence, ulceration due to biopsy procedure or infection, small skin biopsy procedure (shave or punch), concurrent contralateral BC, and/or clinical inflammatory carcinoma (cT4d). The total number of candidate cases was 111. Clinicopathologic information were obtained including patients’ age at diagnosis, gender, menopausal status, race, tumor size, Nottingham grade, histologic type, node status [procedure (sentinel vs. axillary lymph node dissection), total number, and number of positive lymph nodes], reported pathology stage, distant metastases (M0 vs. M1), margin status (positive vs. negative), biomarkers status [estrogen receptor (ER) progesterone receptor (PR) and *HER2*], therapy modality [chemotherapy (CT) (anti-*HER2*-yes vs. no), hormonal therapy (HT), and radiation therapy (RT)]. We also obtained survival data including DFS and OS.

When the slides were available, breast biomarkers (ER, PR and *HER2*-immunohistochemistry) were scored following the ASCO-CAP guidelines (10,11). In brief, ER or PR were considered positive when the percentage of stained cells was >1% (10). *HER2* was considered positive by immunohistochemistry when >10% of the cells had 3+ staining (intense, complete and circumferential). When *HER2* fluorescence in situ hybridization (FISH) report was available, the cases were scored following the ASCO-CAP 2013 guidelines. In brief, *HER2* was considered positive by FISH when *HER2/CEP17* ratio 2.0 or when the absolute number of *HER2* signals was ≥ 6 regardless of the ratio (11).

There were 77 cases diagnosed using immunohistochemistry, 27 using FISH, and 7 had no HER2 assay performed.

Study and Matched Cohorts

The study cohort is defined as a group of cases from the clinical set that has met certain inclusions criteria. The inclusion criteria were stage I, II or III, tumor size ≤ 5.0 -cm, not lost to follow-up; and the following information are available, biomarkers status (ER, PR or *HER2*), therapy modality including CT, anti-*HER2* therapy, RT or HT. The number of cases that met these inclusion criteria was (n=43).

The matched cohort is defined as a group of cases from the clinical BC database at RPCI or UPMC with certain exclusion criteria and clinically and pathologically matching to the study cohort. The exclusion criteria were bilateral BC, history of BC in any breast within the last five years or patients who had or developed carcinoma in other organs (other than skin). We selected the best single matching case for each case in the study cohort from RPCI or UPMC breast cancer database cases after applying the exclusion criteria. Matching criteria included: age (50 years cutoff), gender, histologic type, tumor size (≤ 2 -cm, and 2.1-cm to 5.0-cm), lymph node stage (pN0 to pN3), molecular subtype [hormone receptors (ER/PR)/*HER2*], margin status, CT including anti-*HER2* therapy, RT and HT. When multiple cases were found to match a single case in the study cohort, the matched case was selected to have the closest value in this order, tumor size, age, and then time of follow-up. The final number of cases with successful matched cases was (n=38).

Statistical analysis

Overall Clinical Set—Survival curves of OS and DFS were visualized by Kaplan Meyer (KM) method. Differences between the groups were assessed using the log-rank statistic. The univariate and multivariate survival analyses were performed by Cox proportional hazard model to evaluate the survival prognosis ability of the clinical and pathologic characteristics of patients. The clinical and pathologic characteristics included age at diagnosis, gender, race, menopause status, histology type, Nottingham grade, tumor size (in cm), TNM-stage, DCIS, focality, margin status, ER, PR, *HER2*, and therapy modality (CT, anti-*HER2* therapy, RT, HT). The tumors were staged in multiple ways and KM curve was created for each to correlate with the DFS and OS. First we staged the cases based on the tumor size into T1 (≤ 2.0 -cm), T2 (2.1 to 5.0-cm) and T3 (>5.0 -cm), once including stage-IV cases and once excluding them. Then, reclassification was undertaken to assess the tumor stage [tumor size (T1, T2 and T3) and lymph node involvement (N0, negative nodes; N1, 1 to 3 positive lymph nodes; N2, 4 to 9; and N3 >9)] of tumors independent from the morphologic SU. Finally, all cases were considered as pT4b and node-stage was incorporated to stage cases into either IIIB or IIIC. Further, a multivariate cox model was fit with all significant univariate predictors. The cases could not be stratified based on the therapy modality, as the number of cases in each subgroup became too small, mainly in the MBC cases. The backward model selection by Akaike information criterion (AIC) method was used to eliminate the non-significant variables. Two tailed p values less than 0.05 was deemed as statistically significant. Data analysis was performed using R version 3.2.1.

Study Cohort vs. Matched Cohort—Fisher's test was used to examine the difference in the categorical parameters between the two groups, and logistic regression was used for the continuous parameters. OS and DFS were analyzed by KM methods to evaluate the survival difference between the two groups. 5-year probabilities for DFS and OS were also calculated.

RESULTS

Overall Clinical Set

In all included cases (n=111), the mean (range) of tumor size was 5.85 (0.2, 18.6) cm with 19 (17.1%) tumors measuring 2.0-cm and 41 (36.9%) 2.1-cm to 5.0-cm. The histologic type in the majority (90.1%) of the tumors was of no special type (ductal). 90.1% of the patients had total mastectomy procedure and 73% had axillary lymph node dissection. There were 55 (49.6%) patients who had local (n=31) or distant recurrence (n=23) and 43 (38.7%) who died of disease (table 1). The median and range of follow up was 38 (1, 232) months. Fourteen of 28 (50%) *HER2* positive patients received anti-*HER2* therapy, 11 (39.3%) did not and 3 (10.7%) with unknown status. One patient with negative *HER2* received anti-*HER2* therapy. There were 22 (19.8%) patients who had distant metastases (stage-IV) and 9 (8.1%) patients could not be staged due to the lack of lymph node sampling. Patients with larger tumors tended to present with distant metastases more often than patients with smaller tumors [median (range) 7.0 (2.5,18.0) cm vs. 4.0 (0.2,18.6) cm, respectively (p=0.004)].

The reported T-stage was pT4b in 88 (79.3%) cases and non-pT4b in 23 (20.7%) cases. The tumors were staged as pT1 in 9 of 19 (47.4%) cases that measured 2.0-cm, pT2 in 9 of 41 (22%) cases that measured 2.1-cm to 5.0-cm, and pT3 in 5 of 51 (9.8%) cases that measured >5.0-cm (p=0.003). After excluding stage-IV (n=22) and stage-X cases (n=9), 17 of 79 (21.5%) were incorrectly staged (6, IA; 4, IIA; 2, IIB; and 5, IIIA) (p<0.0001) (table 2).

Survival Analyses

Subset Analysis of Study vs. Matched Cases—Table 3 illustrates the clinicopathologic characteristics of the patients in the study cohort (with SU) and matched cohort (with no SU). The mean (range) of patients' age in the study cohort and matched cohort was 68 (38 to 84) and 59 (42 to 86), respectively. The mean (range) of the tumor size in the study cohort and matched cohort was 30 (2 to 50) and 23 (5 to 46), respectively. The median (range) of follow up time for the study cohort was 50 (4, 232) months and for the matched cohort 62 (11,164) months. Nine (23.7%) patients died of disease in each cohort. While 20 (52.6%) patients developed recurrence in the study cohort, 17 (44.7%) developed recurrence in the matched cohort. The 5-year DFS probability was 53% for the study cohort and 58% for the matched cohort; and for OS 75% for the study cohort and 84% for the matched cohort with no statistical significant difference. There was no statistical significant difference in the OS or DFS between the two cohorts. However, the survival had a trend towards worse DFS for patients with SU (figure 1a and 1b). Using different tumor size cutoffs (2.0-cm and 3.0-cm), there was no statistical significant difference between the two groups.

Additional survival analyses—When the tumors were staged as T1, T2 or T3 (table 2), patients with larger tumors had worse OS ($p=0.009$) and a trend towards worse DFS ($p=0.067$) (figure 2a and 2b). When stage-IV cases were excluded, tumor size did not correlate with OS ($p=0.165$) or DFS ($p=0.8$) (figure 2c and 2d). However, when the cases (excluding stage-IV) were staged based on tumor size (independent from SU) and node involvement into stage I, II or III, the OS was statistically significant ($p=0.047$) but not the DFS ($p=0.195$) (figure 3a and 3b). There was a trend in 5 year survival by size of tumor and number of positive lymph nodes, though was not statistically significant due to the small number of cases (figure 4). We then recalculated, following the AJCC staging guidelines considering all cases as pT4b. There were only two stages, IIIB (pT4b/pN0, pN1 or pN2) or IIIC (pT4b/pN3) (table 2). There was no statistical significant difference between these two stages for the OS ($p=0.265$) (figure 5a) but was significant for the DFS ($p=0.012$) (figure 5b).

In the univariate analysis (table 4) older patients had shorter OS with Cox Proportional HR of 1.05 and confidence interval (1 to 1.1) ($p=0.01$) (figure 6a). Patients with *HER2*⁺ and treated with anti-*HER2* therapy had better OS than patients with *HER2*⁺ and with no anti-*HER2* therapy ($p=0.029$) (figure 6b). However, Cox Proportional HR ratio could not be calculated because none of the treated patients died from disease. Patients with a single focus disease had lower risk of recurrence than patients with multiple foci with Cox Proportional HR of 0.46 and confidence interval of (0.216 and 0.986) ($p=0.036$) (figure 6c). Positive margins carry higher risk of tumor recurrence than negative margins ($p<0.0001$) (figure 6d). Higher number of positive lymph nodes carries higher risk of recurrence with borderline significance ($p=0.056$) (figure 6e). None of the patients ($n=13$) who had a tumor size 1.7-cm died from disease with median (range) of follow up 54.5 (4, 108) months (figure 6f). In the multivariate analysis none of the examined variables was statistically significant.

DISCUSSION

Surgical staging of breast carcinoma patients should be based on their risk for tumor recurrence as it influences recommendations for systemic therapies. In ER positive tumors, a change from an early stage I/II tumor to a stage III tumor, may lead to recommendation of treating with systemic chemotherapy independent of Oncotype DX testing (12,13). This could result in administering a treatment with potential for multiple side effects without much benefit in decreasing a risk of recurrence for the patient. Similarly, in *HER2* amplified carcinomas there is increasing evidence that relatively small tumors with no lymph node spread can be treated with less aggressive systemic chemotherapy (14). Based on the current AJCC staging system, these relatively small ulcerating tumors would most certainly be treated more aggressively, therefore incurring the risk of more serious toxicities. This study demonstrates the benefits of analyzing risk for a rare breast carcinoma phenotype (e.g. ulceration) across multiple institutions. Better prediction of risk of tumor recurrence and more personalized systemic therapy is a critical component of informed decision making for patients.

We first intended to explore if the scenario where a relatively small tumor that ulcerates the skin poses a staging dilemma for the reviewing pathologist. This study showed that the pathologists are not uniformly staging BC with SU following the AJCC staging guidelines, which we have observed in our clinical practices. We found that the number of pathologists who staged a tumor in clinical practice (abstracted reports in the clinical set) as non-T4 was 20.7%. More specifically, about half (47.4%) of the tumors that measured ≥ 2.0 -cm were staged based on tumor size as pT1. Our results suggest that many pathologists believe that relatively small tumors should not be staged as locally advanced disease only because the tumor ulcerates the skin.

In order to address this particular question, “does a relatively small tumor with SU present with advanced stage (stage IV)?”, we collected a large number of cases (n=111) from seven academic institutions and correlated the tumor size with the overall stage. We found that larger tumors present with more advanced disease than smaller tumor, where the median (range) for stage-IV cases vs. stage (I, II and III) were 7.0 (2.5 to 18.0) cm vs. 4.0 (0.2 to 18.6) cm, respectively (p=0.004). That is consistent with a previous study by Güth et al (3). It is worth noting that many patients presented with locally advanced disease. Therefore, they underwent aggressive surgical procedures such as total mastectomy (90.1%) and axillary dissection (73%).

There have been few studies that investigated if there is a justification to categorize any non-inflammatory BC as pT4, such as clinical skin change including ulceration, skin nodules, or pathologic skin involvement (3–8). We intended to nullify all these variables except for pathology-proven SU, in order to evaluate if SU is an adverse factor and to investigate if these tumors should be staged as pT4. All the studies that addressed the staging issue of tumors with skin involvement did not separate skin involvement (dermis and/or epidermis) from BC with only SU (3–8). Some clinical pictures of skin involvement are unclear and cannot be easily classified based on the definitions of the TNM classification (4). In order to ensure consistency among the participating institutions, we restricted our selection to cases with pathology-proven SU. In addition we excluded all cases that had neoadjuvant therapy, SU due to Paget disease, chest wall involvement with SU (pT4c) or without it (pT4a), tumor recurrence, ulceration due to biopsy procedure or infection, small skin biopsy procedure (shave or punch), concurrent contralateral BC, and/or clinical inflammatory carcinoma (cT4d). Cases with secondary Paget disease (n=18) were included in the study, as the SU is considered due to the direct extension of the tumor to the skin. To answer the question “does SU play a role in the tumor outcome?” we selected a subset (n=38) with tumors measuring ≥ 5.0 -cm ($\geq$ stage-T3) and matched them with cases that had similar clinical and pathologic variables. Then we analyzed the DFS and OS. We could not stratify the patients based on therapy modality due to the small number of cases in each subgroup. Therefore, we think that using matching process is a way to minimize the effect of therapy modality among other confounding factors.

When we separated the cases based on the tumor size following the T-staging (T1, T2, T3) independent from SU, patients with larger tumors had higher risk of dying of disease or developing tumor recurrence (figure 2). Güth et al studied 119 patients who presented with histologically proven non-inflammatory skin involvement accompanied by macroscopic and

typical, readily discernible, “classic” skin changes, such as ulceration, edema, peau d’orange, and satellite skin nodules. They found that DFS and OS correlated with the AJCC tumor size. The advantage of this study over ours is that they followed up all patients for at least 5-years or until death. Our median follow-up time is 38-months. However, there are two advantages in our study over Güth’s et al study. First, the inclusion criteria in Güth et al study were clinical and pathologic skin involvement. It is known that there is difficulty in staging certain cases based on the skin changes in the absence of pathology-proven SU (4). In our study only patients with pathology-proven SU were included. Second, Güth et al did not perform survival analyses after excluding stage-IV cases (3). In our study, we found that when cases with stage-IV (n=22) were excluded from the survival analyses, tumor size did not play a role in DFS or OS (figure 2c and 2d). However, when the cases were restaged based on the tumor size and lymph node involvement (I, II, or III), patients with more advanced TN-stage had higher risk of dying of disease (figure 3a).

The AJCC task force acknowledged the issue of tumors that ulcerate to the skin being over-staged. Therefore, they requested an analysis of 5 year survival rate in T4 tumors in the National Cancer database from 1998 to 2000. In this analysis of 9,865 cases, significantly different outcomes were observed for each of the T4 categories (T4a= 47%, T4b= 40%, T4c= 28%, and T4d= 34%; $p<0.0001$, all pair-wise comparisons). They also found that there is statistically significant difference in the 5-year survival based on the tumor size and node involvement. They created a barplot that is similar to ours (figure 4) except that the number of cases in our study is too small to reach a statistical significance (2). There are two issues with this particular analysis. First, there was no comprehensive comparison to tumors of similar size/stage but <T4 which was acknowledged by the AJCC task force. We clinically and pathologically matched cases (n=38) with no SU all measuring ≤ 5.0 -cm and found that these tumors had no statistically significant difference in the OS or DFS, though the later had a trend. The second issue with the AJCC approach was that there was no verification of the accuracy of T4b staging in this database. Inaccurate reporting of the tumor stage for small tumors occurred in our study in about half of the cases that measured ≤ 2.0 -cm. It is worth noting that we did not perform our search for the candidate cases using a keyword “pT4” but we used “ulceration”/“erosion” keywords. That is in order to avoid selection bias and include all cases that had SU. Excluding the cases with relatively small tumor size from the National Cancer database would potentially influence the result of the study.

The AJCC staging system is a continuation of prior classification systems such as Columbia Clinical classification first published in 1943 by Haagensen and Stout. At that point in time BC with SU was more common and more homogenous as a group than the current time (15). We found that BC with SU is a heterogeneous group mainly due to the wide range of tumor size, a factor we and others found to be significantly correlating with the clinical outcome (3,7,8). In fact we found that 54.1% of the clinical set measured ≤ 5.0 -cm, while others found that approximately 65% of the patients had tumor size <5.0 -cm (5,8,16). It should be noted that in our study and in others the data suffers from selection bias. Patients that had truly advanced disease with large tumor size and/or multiple clinically positive lymph nodes (usually patients with large tumor size present with multiple positive lymph nodes and/or stage-IV disease) undergo neoadjuvant or palliative therapy. These cases are excluded from these studies. This would shift the data towards less clinically advanced cases.

In conclusion, our data suggest that relatively small tumors with SU had an extent of disease similar to that observed in patients with early stages disease. Although SU does not appear to be an independent factor in predicting worse clinical outcomes, there was a trend towards worse DFS. However, the sample size was too small to withdraw a more definitive conclusion. Therefore, more similar studies like ours are encouraged to accumulate additional evidence supporting the notion that these tumors should not be staged as locally advanced disease. Meanwhile, we suggest that a relatively small size tumor with SU, particularly a tumor measuring 2.0-cm be staged more conservatively as non-locally advanced disease and discussed with the treating physician to avoid over-treatment.

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Figure 1. Survival curves for study and matched cohorts; A, OS and B, DFS.

Figure 2. Survival curves based on tumor size (T1, T2, T3) including stage-IV cases (A and B) and excluding stage-IV (C and D); A, OS including stage-IV; B, DFS including stage-IV; C, OS excluding stage-IV; and D, DFS excluding stage-IV.

Figure 3.
Survival curves based on tumor stage (stage I, II and III); A, OS and B, DFS.

Figure 4.
Barplot of 5 year survival by size of tumor and number of positive lymph nodes.

Figure 5.
Survival curves based on tumor stage considering all cases as pT4b; A, OS and B, DFS.

Figure 6. Survival curves; A, OS based on age; B, OS based on Anti-HER2 therapy; C, DFS based on tumor focality (multifocal vs. unifocal); D, DFS based on margin status (positive vs. negative); E, DFS based on lymph node status (negative vs. at least one positive); F, OS based on best tumor size cutoff (1.7-cm)

Table 1

Clinicopathologic information on the study set (n=111)

Variable		Mean (range)
Age (years)		67.6(34–92)
Size (cm)		5.85(0.2–18.6)
No. positive lymph nodes		4.1(0–21)
		Frequency (%)
Race	African American	18(16.2)
	Asian	2(1.8)
	Asian Indian	1(0.9)
	Caucasian	83(74.8)
	Hispanic	7(6.3)
Menopause	Post-	94(84.7)
	Pre-	17(15.3)
Histologic type	Lobular	1(0.9)
	Pleomorphic lobular	1(0.9)
	Metaplastic	8(7.2)
	Mucinous	1(0.9)
	No special type	100(90.1)
Nottingham grade	1	6(5.4)
	2	30(27)
	3	75(67.6)
Lymph node sampling procedure	Axillary dissection	81(73)
	Excision	4(3.6)
	Intramammary	1(0.9)
	No lymph node sampling	15(13.5)
	Sentinel	10(9)
Lymphovascular invasion	Yes	83(74.8)
	No	28(25.2)
Ductal carcinoma in situ	Yes	64(57.7)
	No	47(42.3)
Focality	Multifocal	25(22.5)
	Single	86(77.5)
Margins	Negative	102(91.9)
	Positive	9(8.1)
ER	Negative	31(27.9)
	Positive	79(71.2)
	Unknown	1(0.9)
PR	Negative	41(36.9)
	Positive	69(62.2)

Variable		Mean (range)
	Unknown	1(0.9)
HER2	Negative	76(68.5)
	Positive	28(25.2)
	Unknown	7(6.3)
Surgery procedure	Mastectomy	100(90.1)
	Segmental mastectomy	11(9.9)
Chemotherapy	Yes	55(49.6)
	No	53(44.7)
	Unknown	3(2.7)
Anti-HER2 therapy	Yes	15(13.5)
	No	84(75.7)
	Unknown	12(10.8)
Radiation therapy	Yes	60(54.1)
	No	48(43.2)
	Unknown	3(2.7)
Hormonal therapy	Yes	69(62.2)
	No	39(35.1)
	Unknown	3(2.7)
Death	Alive	50(45.1)
	Deceased	43(38.7)
	Unknown	18(16.2)
Recurrence	No	34(30.6)
	Yes	55(50.0)
	Unknown	22(19.4)

Table 2

Tumor staging based on reported T-stage, following AJCC guidelines, and independent from SU

T-stage (reported)	T-stage		N-stage		M-stage		TNM-Stage	
	T1a	3(2.7)*	0	21(18.9)	0	89(80.2)	IA	6(5.4)
	T1b	3(2.7)	1	25(22.5)	1	22(19.8)	IIA	4(3.6)
	T1c	3(2.7)	1mi	3(2.7)			IIB	2(1.8)
	T2	9(8.1)	2	27(24.3)			IIIA	5(4.5)
	T3	5(4.5)	3	20(18)			IIIB	49(44.2)
	T4b	88(79.3)	X	15(13.5)^			IIIC	14(12.6)
							IV	22(19.8)
							X	9(8.1)
T-stage following AJCC	T4b	111(100%)	0	21(18.9)	0	89(80.2)	IIIB	66(59.5)
			1	25(22.5)	1	22(19.8)	IIIC	14(12.6)
			1mi	3(2.7)			IV	22(19.8)
			2	27(24.3)			X	10(9)
			3	20(18)				
			X	15(13.5)^				
T-stage independent from SU	1	17(15.3)	0	21(18.9)	0	89(80.2)	IA	9(8.1)
	2	43(38.7)	1	25(22.5)	1	22(19.8)	IIA	10(9.0)
	3	51(46)	1mi	3(2.7)			IIB	16(14.4)
			2	27(24.3)			IIIA	31(28)
			3	20(18)			IIIC	14(12.6)
			X	15(13.5)^			IV	22(19.8)
							X	9(8.1)

* N(%); note N-stage and M-stage is the same for all three staging results;

^ 6 of 15 cases with Nx had stage M1, staged as stage-IV.

Table 3

Clinicopathologic characteristics of the study cohort and matched cohort

		Study cohort (with SU; n=38)	Matched cohort (No SU; n=38)	P value
Age mean (range) in years *		68 (38 to 84)	59 (42 to 86)	1
Size-mean (range) in cm *		3.0 (0.2 to 5.0)	2.3 (0.5 to 4.6)	1
Gender *	Female	36(94.7)	36(94.7)	1
	Male	2(5.3)	2(5.3)	
Histologic type	Pleomorphic lobular	2(5.3)	2(5.3)	1
	Metaplastic	2(5.3)	2(5.3)	
	No special type	34(89.4)	34(89.4)	
N-stage	0	9(23.7)	9(23.7)	1
	1	12(31.6)	12(31.6)	
	1mi	1(2.6)	1(2.6)	
	2	10(26.3)	10(26.3)	
	3	6(15.8)	6(15.8)	
ER	Positive	27(71.1)	27(71.1)	1
	Negative	11(28.9)	11(28.9)	
PR	Positive	27(71.1)	23(60.5)	0.4686
	Negative	11(28.9)	15(39.5)	
HER2	Positive	14(36.8)	14(36.8)	1
	Negative	24(63.2)	24(63.2)	
Margins	Positive	5(13.2)	5(13.2)	1
	Negative	33(86.8)	33(86.8)	
Chemotherapy	Yes	19(50)	19(50)	1
	No	19(50)	19(50)	
Anti-HER2 therapy	Yes	9(23.7)	9(23.7)	1
	No	29(76.3)	29(76.3)	
Radiation therapy	Yes	18(47.4)	19(50)	1
	No	20(52.6)	19(50)	
Hormonal therapy	Yes	24(63.2)	24(63.2)	1
	No	14(36.8)	14(36.8)	
Died of disease	No	29(76.3)	29(76.3)	1
	Yes	9(23.7)	9(23.7)	
Recurrence	No	18(47.4)	21(55.3)	0.6466
	Yes	20(52.6)	17(44.7)	

* p-value was calculated by Wald test in the logistic model. The rest of p-values were calculated by Fisher exact test.

Table 4

Univariate analysis of the OS and DFS by the Cox proportional hazards model (excluding stage-IV and stage-X cases).

	P value for OS	P value for DFS
Age	0.01	0.848
Race	0.282	0.905
Menopause status	0.110	0.414
Histologic type	0.578	0.339
Nottingham grade	0.497	0.205
Ductal carcinoma in situ	0.941	0.799
Focality	0.774	0.036
Margins	0.273	<0.0001
Triple negative	0.508	0.77
ER+ and/or PR+ and <i>HER2</i> –	0.97	0.354
<i>HER2</i> +	0.566	0.445
Size (T1, T2, T3)	0.165	0.784
Positive lymph nodes	0.115	0.056
Lymphovascular invasion	0.0508	0.135
Stage based on SU (T4b)	0.272	0.089
Stage independent from skin ulceration	0.165	0.335
Type of surgery	0.836	0.384
Chemotherapy	0.073	0.367
Anti- <i>HER2</i> therapy	0.041	0.187
Radiation therapy	0.375	0.551
Hormonal therapy	0.537	0.387