
Skin Involvement and Breast Cancer: Are T4b Lesions of All Sizes Created Equal?



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BACKGROUND: Nonmetastatic, noninflammatory, invasive breast cancers with 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. Skin involved and non-SI tumors were reclassified using the American Joint Committee on Cancer, 7th edition groupings using tumor size and nodal involvement alone without considering SI (neostage). Disease-specific survival 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 to 2.0 cm, 2.1 to 5.0 cm, and >5.0 cm in 11.6%, 51.1%, and 37.3% of patients, respectively. There were no nodal metastases in 22.3%, 1 to 3 positive nodes in 31.7%, 4 to 9 positive in 28.6%, and ≥10 positive in 17.4% of patients. 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 non-SI 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 non-SI IIIC.

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. Skin involvement should be subordinate to T and N groupings to classify SI with non-SI lesions having similar prognoses. (J Am Coll Surg 2014;219:534–544. © 2014 by the American College of Surgeons)

Locally advanced breast cancers account for 5% to 10% of new breast cancer diagnoses in the United States and 60% to 70% of cases worldwide. According to the American Joint Committee on Cancer (AJCC) TNM classification (7th edition), 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

Disclosure Information: Nothing to disclose.

Supported, in part, by US Public Health Services grant P30 CA006927, by an appropriation from the Commonwealth of Pennsylvania, by American Cancer Society grant IRG-92-027-17, and by generous private donor support. This study used the linked SEER-Medicare database. The interpretation and reporting of these data are the sole responsibility of the authors. The authors acknowledge the efforts of the Applied Research Program, National Cancer Institute; the Office of Research, Development and Information, Centers for Medicare and Medicaid Services; Information Management Services, Inc.; and the SEER Program tumor registries in the creation of the SEER-Medicare database.

The collection of the California cancer incidence data used in this study was supported by the California Department of Public Health as part of the statewide cancer reporting program mandated by California Health and Safety Code Section 103885; the National Cancer Institute's SEER Program under contract N01-PC-35136 awarded to the Northern California Cancer Center, contract N01-PC-35139 awarded to the University of Southern California, and contract N02-PC-15105 awarded to the Public Health Institute; and the Centers for Disease Control and

Prevention's National Program of Cancer Registries, under agreement U55/CCR921930-02 awarded to the Public Health Institute. The ideas and opinions expressed herein are those of the authors and endorsement by the State of California, Department of Public Health, the National Cancer Institute, and the Centers for Disease Control and Prevention or their contractors and subcontractors is not intended nor should be inferred.

Presented, in part, at the Society of Surgical Oncology, 66th Annual Cancer Symposium, National Harbor, MD, March 2013.

Received November 22, 2013; Revised March 15, 2014; Accepted April 14, 2014.

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Abbreviations and Acronyms

AJCC	= American Joint Committee on Cancer
DSM	= disease-specific mortality
DSS	= disease-specific survival
EOD	= extent of disease
ER	= estrogen receptor
PR	= progesterone receptor
SI	= skin involvement

5-year overall survival ranges from 41% to 67%.² The 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 exist because of the low frequency of these tumors, however, if SI was not considered, earlier data suggest that nearly 60% of these tumors would be classified as T1 or T2, and 13% might 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 Because 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 noninflammatory breast cancers with 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 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 and older, they provide more specifics than SEER data alone about the surgical procedures, radiotherapy, and treatment dates. The SEER data provide no chemotherapy information and Medicare claims do.

Patients were included who were likely to have claims from 1 year before and after the SEER diagnosis month. Although patients were restricted to their first breast cancer, those with other earlier malignancies were not excluded. All 16 applicable SEER registries were used to increase the external generalizability of the results.

Included patients had a diagnosis of invasive breast cancer at 65 years of age or older from 1992 to 2005, and had cancer-directed surgery.

The SEER extent of disease (EOD) codes were used to identify confinement to breast tissue or involvement of skin or chest wall (see [Table 1](#) for definitions) and SEER stage is consistent with these codes. The following subgroups with pertinent EOD codes were included in this analysis: those having no SI (EOD codes 10, 11, 13, 14, 15, 16, 17, and 18) and those having extensive 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, and 28) or both extensive SI and chest wall involvement (EOD code 60) were excluded for a more definitive comparison between distinct SI and non-SI subgroups. Patients having metastatic, inflammatory cancer, and chest wall or extra-axillary nodal involvement were also excluded ([Fig. 1](#)).

After the subgroups were established, SI tumors were regrouped with AJCC 7th edition classifications using tumor size and nodal involvement, but without considering the SI that classified these tumors as T4b; these reclassifications are referred to as “neostage.” Patients having non-SI primaries were reclassified into the same neostage groupings using tumor size and nodal involvement for comparison, by updating to AJCC 7th edition classification from earlier 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 non-SI 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 were weighted by the inverse of the probability that the person was in their observed SI group. This is similar 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, sex, 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 non-SI group ($n = 896$ [1.4%]) because of insufficient overlap of the probabilities in the 2 groups. Age was included as a categorical variable in

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