Original Study

Patterns of Care and Efficacy of Chemotherapy and Radiotherapy in Skin-Involved Breast Cancers of All Sizes

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Abstract

A retrospective review of skin-involved (SI) breast cancers of all sizes was performed using the National Cancer Data Base. Systemic therapy and radiotherapy demonstrated efficacy, but variability in their application for SI and non-SI cancers.

Background: The management of small skin-involved (SI) invasive breast cancers is controversial because although they are considered unresectable, their prognosis is far better than their stage III classification. This study was undertaken to determine how SI lesions are treated in the United States and to discern the benefit of systemic therapy. **Patients and Methods:** Data of patients diagnosed with stage I-III breast cancer in the National Cancer Data Base between 2004 and 2011 were reviewed. Treatment patterns were examined and overall survival assessed. **Results:** A total of 3485 patients had SI and 456,287 patients had non-SI breast cancers. Chemotherapy was administered to 68.5% of SI and 45.9% of non-SI tumors ($P < .001$), including 77.2% of SI and 33% of non-SI tumors < 2 cm ($P < .001$). After adjusting for patient and tumor characteristics, SI patients were 19.4% more likely to receive chemotherapy than non-SI patients. Radiotherapy was provided to 61.1% of SI and 64.3% of non-SI tumors ($P < .001$), including 65.5% of SI and 66.5% non-SI tumors < 2 cm ($P = .711$). After adjusting for patient and tumor characteristics, SI patients were 76.6% more likely to receive radiotherapy than non-SI patients. Chemotherapy and radiotherapy provided an overall survival benefit for stage II and III SI and non-SI tumors. **Conclusion:** Despite controversy regarding staging and prognosis of SI tumors, the majority of patients are provided systemic therapy and radiotherapy. Varied patterns of chemotherapy administration for SI tumors suggests that further treatment guidance and standardization are required, especially because chemotherapy and radiotherapy are equally efficacious in SI and non-SI tumors alike.

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Introduction

The American Joint Committee on Cancer (AJCC) staging system is the authoritative standard for cancer staging, as its universal language allows clinicians to assess the extent of malignancy uniformly. Since its inception in 1977, the AJCC breast cancer staging classifications have seen many adaptations from that original edition.[1] With each revision, the staging system has categorized tumors into more homogeneous groups, allowing treatments to be better tailored to the extent and prognosis of disease.

The AJCC 7th and 8th edition staging systems classify T4b breast tumors as those lesions having ulceration, ipsilateral satellite nodules, and/or edema of the skin that do not meet the criteria for inflammatory breast cancer.[2,3] Skin and dermal tumor satellite nodules only identified on microscopic examination, in the absence of epidermal ulceration or edema, do not qualify as T4b disease.[3] Stage IIIB and IIIC tumors, where skin-involved (SI) tumors are

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Figure 1 Cohort Exclusion Criteria

categorized, are classified by the National Comprehensive Cancer Network (NCCN) as inoperable locoregional advanced carcinomas.[4] These locoregional or locally advanced breast cancers (LABC) account for 5% to 10% of breast cancer diagnoses in the United States.[2]

We previously evaluated SI lesions of all sizes to determine disease-specific survival (DSS) using Surveillance Epidemiology and End Results (SEER)-Medicare data. In that investigation, SI tumors were compared to non-SI lesions by ignoring their skin involvement and reclassifying their T stage using tumor size alone.[5] That study found that basing T stage on tumor size more accurately predicted outcomes in SI primary lesions < 2 cm, as their DSS was similar to those not having skin involvement.[5]

This study was performed with two objectives: first, to assess national practice patterns of treatment for SI tumors, specifically reviewing current management of tumors < 2 cm, and second, to assess how SI tumors, and specifically smaller SI tumors, are best treated. It remains unclear whether adjuvant therapy is favored in SI breast cancers of any size, especially because small SI tumors having prognoses similar to non-SI tumors of similar sizes. With no data (to our knowledge) specifically assessing treatment of these lesions, we sought to determine whether there is a differential benefit of

Table 1 Cohort Characteristics

Characteristic	Variable	Non-SI	SI	*P*
Age	N	456,287	3485	< .001
	Mean (SD)	59.5 (12.96)	64.3 (14.98)	
	Median (min, max)	59.0 (18.0, 90.0)	64.0 (23.0, 90.0)	
Race	White	387,359 (84.9)	2730 (78.3)	< .001
	Black	47,516 (10.4)	613 (17.6)	
	Other	21,412 (4.7)	142 (4.1)	
Hispanic	No	401,764 (88.1)	3085 (88.5)	.3
	Yes	21,408 (4.7)	170 (4.9)	
	Missing	33,115 (7.3)	230 (6.6)	
Insurance	Medicaid	26,122 (5.7)	415 (11.9)	< .001
	Medicare	149,911 (32.9)	1566 (44.9)	
	Not insured	8855 (1.9)	154 (4.4)	
	Other government/unknown	9387 (2.1)	53 (1.5)	
	Private insurance/managed care	262,012 (57.4)	1297 (37.2)	
Education (% of adults who did not graduate high school)	21% or more	63,492 (13.9)	688 (19.7)	< .001
	13-20.9%	106,827 (23.4)	1023 (29.4)	
	7-12.9%	149,978 (32.9)	1064 (30.5)	
	< 7%	129,336 (28.3)	665 (19.1)	
	Missing	6654 (1.5)	45 (1.3)	
Income (median household income for patient's residence)	< $38,000	67,495 (14.8)	736 (21.1)	< .001
	$38,000-$47,999	97,665 (21.4)	888 (25.5)	
	$48,000-$62,999	121,162 (26.6)	889 (25.5)	
	$63,000 +	163,115 (35.7)	925 (26.5)	
	Missing	6850 (1.5)	47 (1.3)	
Setting	Large metropolitan	236,595 (51.9)	1784 (51.2)	.001
	Small metropolitan	136,316 (29.9)	1011 (29.0)	
	Suburban	41,852 (9.2)	340 (9.8)	
	Rural	25,915 (5.7)	250 (7.2)	
	Missing	15,609 (3.4)	100 (2.9)	
Distance (miles between patient's residence and facility)	≤ 10 miles	252,248 (55.3)	2082 (59.7)	< .001
	11-20 miles	103,575 (22.7)	695 (19.9)	
	21-50 miles	65,802 (14.4)	470 (13.5)	
	> 50 miles	28,222 (6.2)	194 (5.6)	
	Missing	6440 (1.4)	44 (1.3)	
Facility location	New England	26,282 (5.8)	177 (5.1)	< .001
	Middle Atlantic	63,696 (14.0)	573 (16.4)	
	South Atlantic	99,587 (21.8)	747 (21.4)	
	East North Central	87,671 (19.2)	662 (19.0)	
	East South Central	29,377 (6.4)	256 (7.3)	
	West North Central	36,422 (8.0)	262 (7.5)	
	West South Central	34,127 (7.5)	337 (9.7)	
	Mountain	22,740 (5.0)	122 (3.5)	
	Pacific	56,385 (12.4)	349 (10.0)	
Facility type	Community cancer program	51,264 (11.2)	524 (15.0)	< .001
	Comprehensive community	273,474 (59.9)	1996 (57.3)	
	Academic/research program	130,931 (28.7)	963 (27.6)	
	Other/missing	618 (0.1)	2 (0.1)	
Year of diagnosis	2004	27,842 (6.1)	300 (8.6)	< .001
	2005	30,580 (6.7)	271 (7.8)	
	2006	33,814 (7.4)	285 (8.2)	

Table 1 Continued

Characteristic	Variable	Non-SI	SI	*P*
	2007	42,036 (9.2)	321 (9.2)	
	2008	68,685 (15.1)	522 (15.0)	
	2009	79,495 (17.4)	521 (14.9)	
	2010	84,566 (18.5)	598 (17.2)	
	2011	89,269 (19.6)	667 (19.1)	
Charlson comorbidity score	0	389,980 (85.5)	2804 (80.5)	< .001
	1	55,378 (12.1)	510 (14.6)	
	2+	10,929 (2.4)	171 (4.9)	
Histology	Ductal	402,786 (88.3)	3039 (87.2)	< .001
	Lobular	40,416 (8.9)	254 (7.3)	
	Other	13,085 (2.9)	192 (5.5)	
Tumor grade	1	105,205 (23.1)	242 (6.9)	< .001
	2	190,406 (41.7)	1219 (35.0)	
	3-4	142,602 (31.3)	1845 (52.9)	
	Unknown	18,074 (4.0)	179 (5.1)	
ER	Negative	84,652 (18.6)	1100 (31.6)	< .001
	Positive/borderline	363,402 (79.6)	2318 (66.5)	
	Missing	8233 (1.8)	67 (1.9)	
PR	Negative	129,139 (28.3)	1492 (42.8)	< .001
	Positive/borderline	318,328 (69.8)	1926 (55.3)	
	Missing	8820 (1.9)	67 (1.9)	
Tumor size	Mean (SD)	20.1 (21.39)	63.8 (72.98)	< .001
	Median (Min, max)	15.0 (1.0, 989.0)	50.0 (1.0, 989.0)	
T neostage	T1	280,681 (61.51)	280 (8.03)	
	T2	150,628 (33.01)	1266 (36.33)	
	T3	24,978 (5.47)	1939 (55.64)	
No. of tumors < 2 cm	< 2 cm	280,681 (61.51)	280 (8.03)	
	≥ 2 cm	175,606 (38.49)	3205 (91.97)	
No. of positive nodes	0	320,615 (70.3)	797 (22.9)	< .001
	1-3	98,344 (21.6)	1222 (35.1)	
	4-9	26,236 (5.7)	931 (26.7)	
	10+	11,092 (2.4)	535 (15.4)	
Surgery type	Breast-conserving surgery	278,459 (61.0)	330 (9.5)	< .001
	Mastectomy	177,828 (39.0)	3155 (90.5)	
Chemotherapy	Yes	209,524 (45.9)	2388 (68.5)	< .001
	No	246,763 (54.1)	1097 (31.5)	
Radiotherapy	Yes	293,612 (64.3)	2129 (61.1)	< .001
	No	162,675 (35.7)	356 (38.9)	
Neoadjuvant chemotherapy	Yes	36,860 (8.08)	1597 (45.82)	< .001
Adjuvant chemotherapy	Yes	172,664 (37.84)	791 (22.70)	< .001

Abbreviations: ER = estrogen receptor; PR = progesterone receptor; SD = standard deviation.

chemotherapy and radiotherapy in SI tumors of differing sizes in light of their varied prognoses, which is based more on size than skin involvement.

Patients and Methods

We retrieved data from the National Cancer Data Base (NCDB) with approval from our institutional review board and the American College of Surgeons. The NCDB is a nationwide data set that captures 70% of all newly diagnosed malignancies in the US at Commission on Cancer–accredited hospitals, including 66% of all breast cancers.[6] Data of patients diagnosed with stage I, II, or III breast cancer in the NCDB between 2004 and 2011 were reviewed to allow for adequate follow-up.

In order to capture the purest subset for which to perform our analysis, both the Collaborative Stage (CS) Extension codes and the AJCC 7th edition tumor, node, metastasis classification system (TNM) were used to identify skin involvement. Skin involvement is defined as the following: breast tumors with gross epidermal lesions, edema, and ulcerations not meeting criteria for inflammatory cancer as defined by the AJCC 7th edition T4b, and CS Extension code definition. Collaborative staging was developed as a method of conversion between the TNM staging systems of the AJCC and the

SEER staging system.[7] Such conversions would eliminate duplicate data collection from cancer registries.[7] The AJCC 7th edition staging was used to classify disease in the NCDB before 2018. Cases with conflicting codes were excluded from the analysis. In patients receiving neoadjuvant chemotherapy, AJCC clinical T staging was used to identify T4b tumors. AJCC pathologic T staging was used for all other patients. T4b tumors were defined as having macroscopically/clinically apparent skin involvement. Most were coded using CS version 2, while a small subset (2664 patients) diagnosed before 2009 used CS version 1. Each tumor underwent T-stage reclassification by tumor size alone and was reassigned into a neostage on the basis of the AJCC TNM classifications without incorporating SI (which in itself would mandate that it be classified as T4b). This was done for uniform comparison of SI versus non-SI tumors.

Patient exclusions are provided in Figure 1. SI and non-SI groups were compared by the chi-square and Wilcoxon rank sum tests. Multivariable logistic regression was used to identify predictors of receipt of chemotherapy and receipt of radiotherapy separately for SI and non-SI cohorts. In order to create comparable groups, propensity score and exact matching methods were used to match SI and non-SI patients (1:3) separately when analyzing chemotherapy and radiotherapy in the whole cohort as well as within neostage II and III (neostage I was not analyzed because of inadequate sample size). Groups were matched on patient and tumor characteristics, including age, race, ethnicity, insurance status, education, income, geographic region, size of metropolitan area, distance to facility, facility type, year of diagnosis, Charlson comorbidity index (CCI), histology, tumor grade, estrogen and progesterone receptor status, tumor size, number of positive nodes, type of surgery (breast conservation vs. mastectomy), receipt of chemotherapy (for radiotherapy models only), and receipt of radiotherapy (for chemotherapy models only). Because the 21-gene recurrence score (RS) is not available in the NCDB, trends in chemotherapy were assessed during this time frame during which the 21 gene RS was introduced and increasingly utilized. Data on sentinel lymph node biopsy versus axillary lymph node dissection are not included because of inaccuracies with underreporting of sentinel lymph node biopsy before 2012.

Balance between groups was assessed using the Austin criterion for standardized difference.[8] Covariates not achieving balance were adjusted for within the models. Robust standard errors were estimated to account for the correlation between clustered pairs.[9] Using the matched cohort, logistic regression was performed to analyze differences in receipt of chemotherapy and receipt of radiotherapy between SI and non-SI patients. In addition, Cox proportional hazards models were used to analyze overall survival (OS). Interactions between treatment (chemotherapy and radiotherapy) variables and SI status were analyzed to determine if treatment effects differed by SI status. Statistical significance was set at $P = .05$ (2-sided). Analyses were performed by SAS 9.4 (SAS Institute, Cary, NC) and R 3.2.1 (R Foundation for Statistical Computing, Vienna, Austria; http://www.r-project.org/) software.

Results

There were 3485 patients with SI breast cancer and 456,287 patients with non-SI breast cancer fulfilling the inclusion criteria (Figure 1). Median SI and non-SI patient ages were 64 and 59 years ($P < .001$), while median tumor sizes were 5.0 and 1.5 cm ($P < .001$), respectively. A comparison of the SI and non-SI cohorts is shown in Table 1.

Chemotherapy

Chemotherapy was administered to 68.5% and 45.9% of SI and non-SI tumors, respectively ($P < .001$), with 77.2% of SI and 33.4% of non-SI tumors < 2 cm receiving chemotherapy ($P < .001$). After adjusting for patient and tumor characteristics, SI patients overall had a 19.4% increase in the odds of receiving any chemotherapy compared to non-SI patients (odds ratio [OR] = 1.194; 95% confidence interval [CI], 1.069-1.335; $P = .002$) (Table 2). The subset of SI primary lesions < 2 cm was also more likely to receive chemotherapy than non-SI tumors (OR = 1.969; 95% CI, 1.407-2.754).

Predictors of receipt of chemotherapy for SI tumors included younger age, suburban location, lower CCI, increasing tumor grade, tumor size, negative hormone receptor status, number of positive nodes, performance of mastectomy, and receipt of radiotherapy. Predictors of receipt of chemotherapy for non-SI tumors include younger age, race, insurance status, income level, location, distance to a cancer center, lower CCI, increasing tumor grade and tumor size, negative hormone receptor status, increasing number of nodes examined, and number of positive nodes (Table 3).

Neoadjuvant Chemotherapy

Neoadjuvant chemotherapy was also provided more frequently, but not universally, for SI than non-SI tumors; 45.8% versus 8.1% ($P < .0001$). For SI primary lesions (vs. non-SI primary lesions), neoadjuvant chemotherapy was provided more frequently than

Table 2 Receipt of Treatment by SI Status

Outcome	SI Status	N	OR	95% CI		*P*
Chemotherapy	No SI	7560	Ref			
	SI	2520	1.194	1.069	1.335	.002
Chemotherapy in subset of patients with tumor size < 2 cm	No SI	855	Ref			
	SI	285	1.969	1.407	2.754	< .001
Radiotherapy	No SI	8328	Ref			
	SI	2776	1.766	1.609	1.939	< .001

Propensity score matching (3:1) was used to adjust for patient, tumor, and treatment characteristics.
Abbreviations: CI = confidence interval; OR = odds ratio; Ref = referent; SI = skin involvement.

Table 3 Predictors of Treatment

Characteristic	Variable	Chemotherapy				Radiotherapy			
		SI		Non-SI		SI		Non-SI	
		OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
Age		0.883 (0.871, 0.895)	< .0001	0.922 (0.92, 0.923)	< .0001	0.985 (0.976, 0.993)	.001	0.977 (0.976, 0.979)	< .0001
Race	White (Ref)								
	Black	1.226 (0.889, 1.692)	.214	0.967 (0.927, 1.009)	.124	0.93 (0.738, 1.173)	.540	0.96 (0.908, 1.014)	.143
	Other	1.377 (0.827, 2.293)	.219	0.941 (0.895, 0.99)	.019	0.999 (0.677, 1.474)	.995	0.96 (0.901, 1.024)	.215
Hispanic	No (Ref)								
	Yes	1.098 (0.631, 1.912)	.740	1.109 (1.037, 1.185)	.003	1.091 (0.746, 1.596)	.652	0.787 (0.699, 0.885)	< .0001
	Missing	0.794 (0.528, 1.195)	.269	0.97 (0.893, 1.054)	.474	1.536 (1.138, 2.074)	.005	0.966 (0.889, 1.05)	.412
Insurance	Private/managed care (Ref)								
	Medicaid	0.689 (0.435, 1.091)	.112	0.921 (0.877, 0.966)	.001	0.757 (0.576, 0.994)	.045	0.9 (0.854, 0.949)	< .0001
	Medicare	0.908 (0.684, 1.207)	.508	0.777 (0.754, 0.8)	< .0001	0.879 (0.699, 1.105)	.269	0.84 (0.811, 0.87)	< .0001
	Not insured/other	0.624 (0.347, 1.122)	.115	0.901 (0.836, 0.971)	.007	0.882 (0.573, 1.356)	.566	0.81 (0.71, 0.925)	.002
	Government/unknown	2.643 (0.968, 7.216)	.058	0.889 (0.827, 0.956)	.002	0.612 (0.347, 1.079)	.090	0.827 (0.72, 0.95)	.007
Education (% not graduating from high school)	≥ 21% (Ref)								
	13-20.9%	1.336 (0.953, 1.871)	.093	0.989 (0.951, 1.028)	.578	0.886 (0.692, 1.135)	.339	1.006 (0.958, 1.057)	.806
	7-12.9%	1.169 (0.789, 1.731)	.437	1.008 (0.961, 1.056)	.751	1.116 (0.833, 1.495)	.463	1.008 (0.946, 1.073)	.809
	< 7%	1.294 (0.811, 2.064)	.280	0.992 (0.939, 1.049)	.786	1.035 (0.724, 1.478)	.852	1.039 (0.962, 1.122)	.330
	Missing			1.177 (0.739, 1.876)	.492			0.656 (0.37, 1.161)	.148
Income (median household income by zip code)	<$38,000 (Ref)								
	$38,000-$47,999	1.066 (0.754, 1.506)	.718	1.036 (0.999, 1.075)	.055	1.178 (0.921, 1.505)	.192	1.028 (0.98, 1.078)	.251
	$48,000-$62,999	0.885 (0.604, 1.297)	.532	1.044 (1, 1.09)	.049	1.088 (0.819, 1.445)	.562	1.053 (0.992, 1.117)	.091
	$63,000+	1.071 (0.683, 1.681)	.764	1.018 (0.965, 1.074)	.516	1.219 (0.868, 1.712)	.253	1.056 (0.971, 1.149)	.205
	Missing	1.591 (0.005, 531.29)	.876	1.061 (0.746, 1.509)	.741	0.929 (0.023,37.364)	.969	0.928 (0.575, 1.496)	.758
Setting	Large metropolitan (Ref)								
	Small metropolitan	1.057 (0.823, 1.359)	.663	1.083 (1.03, 1.138)	.002	1.125 (0.918, 1.379)	.256	1.143 (1.057, 1.236)	.001
	Suburban	1.643 (1.075, 2.511)	.022	1.08 (1.016, 1.148)	.013	0.924 (0.664, 1.286)	.640	1.363 (1.256, 1.48)	< .0001
	Rural	1.451 (0.85, 2.475)	.172	1.217 (1.105, 1.34)	< .0001	1.264 (0.855, 1.869)	.241	1.379 (1.239, 1.535)	< .0001
	Missing	1.022 (0.497, 2.105)	.952	1.023 (0.95, 1.101)	.551	1.749 (0.86, 3.558)	.123	1.009 (0.881, 1.157)	.894
Distance (miles to reporting facility)	≤ 10 miles (Ref)								
	11-20 miles	1.274 (0.959, 1.692)	.094	1.037 (1.012, 1.064)	.004	0.956 (0.77, 1.187)	.684	0.916 (0.884, 0.949)	< .0001
	21-50 miles	1.14 (0.802, 1.621)	.465	1.004 (0.969, 1.041)	.829	0.934 (0.707, 1.234)	.630	0.808 (0.767, 0.851)	< .0001

Table 3 Continued

Characteristic	Variable	Chemotherapy				Radiotherapy			
		SI		Non-SI		SI		Non-SI	
		OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
	> 50 miles	1.114 (0.683, 1.817)	.664	0.914 (0.856, 0.976)	.007	0.668 (0.439, 1.017)	.060	0.616 (0.561, 0.677)	< .0001
	Missing			0.755 (0.538, 1.061)	.106			1.386 (0.959, 2.004)	.082
Facility location	New England (Ref)								
	Middle Atlantic	1.33 (0.842, 2.1)	.221	1.042 (0.938, 1.158)	.443	1.133 (0.699, 1.836)	.613	0.732 (0.625, 0.857)	.000
	South Atlantic	1.141 (0.713, 1.825)	.584	1.098 (1.004, 1.2)	.040	0.857 (0.532, 1.379)	.524	0.681 (0.587, 0.79)	< .0001
	East North Central	1.697 (1.055, 2.73)	.029	1.208 (1.103, 1.324)	< .0001	0.895 (0.559, 1.433)	.643	0.837 (0.73, 0.96)	.011
	East South Central	1.597 (0.879, 2.901)	.125	1.11 (0.961, 1.283)	.155	0.684 (0.391, 1.196)	.183	0.578 (0.488, 0.684)	< .0001
	West North Central	1.644 (0.931, 2.904)	.087	1.168 (1.047, 1.304)	.006	1.22 (0.707, 2.105)	.476	0.838 (0.719, 0.978)	.025
	West South Central	2.027 (1.131, 3.634)	.018	1.122 (1.008, 1.248)	.036	0.727 (0.436, 1.211)	.220	0.497 (0.399, 0.62)	< .0001
	Mountain	0.808 (0.415, 1.575)	.532	0.981 (0.861, 1.119)	.776	0.878 (0.474, 1.629)	.680	0.679 (0.523, 0.882)	.004
	Pacific	1.05 (0.635, 1.735)	.850	0.799 (0.716, 0.892)	< .0001	0.79 (0.473, 1.318)	.366	0.653 (0.55, 0.775)	< .0001
Facility type	Comprehensive (Ref)								
	Community	0.984 (0.712, 1.359)	.921	0.981 (0.918, 1.049)	.580	0.982 (0.766, 1.259)	.887	1.213 (1.099, 1.339)	.000
	Academic/research	0.988 (0.683, 1.429)	.948	0.941 (0.871, 1.017)	.124	0.989 (0.741, 1.32)	.941	1.107 (0.988, 1.24)	.081
	Other/missing			1.257 (1.151, 1.372)	< .0001			1.693 (1.505, 1.904)	< .0001
Year of diagnosis		1.009 (0.96, 1.061)	.722	.996 (.985,1.006)	.417	1.038 (1,1.077)	.050	1.059 (1.049,1.069)	< .0001
Charlson comorbidity score	0 (Ref)								
	1	0.847 (0.649, 1.106)	.222	0.975 (0.948, 1.003)	.084	0.763 (0.614, 0.949)	.015	0.87 (0.841, 0.9)	< .0001
	2+	0.319 (0.197, 0.515)	< .0001	0.672 (0.632, 0.714)	< .0001	0.887 (0.617, 1.276)	.519	0.707 (0.663, 0.754)	< .0001
Tumor grade/ differentiation	Well (Ref)								
	Moderate	1.493 (1.048, 2.127)	.027	2.273 (2.214, 2.333)	< .0001	0.788 (0.579, 1.072)	.129	0.965 (0.941, 0.989)	.005
	Poor	1.327 (0.925, 1.902)	.124	5.739 (5.52, 5.967)	< .0001	0.86 (0.62, 1.192)	.365	0.862 (0.834, 0.891)	< .0001
	Undifferentiated/anaplastic	4.926 (1.194, 20.318)	.027	4.528 (3.758, 5.455)	< .0001	0.48 (0.22, 1.047)	.065	0.893 (0.745, 1.069)	.218
	Unknown	2.027 (1.129, 3.642)	.018	1.881 (1.774, 1.994)	< .0001	1.069 (0.658, 1.738)	.787	1.012 (0.946, 1.084)	.720
ER	Negative (Ref)								
	Positive/borderline	0.571 (0.411, 0.795)	.001	0.407 (0.393, 0.421)	< .0001	1.424 (1.117, 1.815)	.004	1.183 (1.142, 1.226)	< .0001
	Unknown	0.451 (0.056, 3.633)	.455	0.363 (0.278, 0.472)	< .0001	1.311 (0.343, 5.018)	.692	0.403 (0.318, 0.512)	< .0001
PR	Negative (Ref)								
	Positive/borderline	0.576 (0.428, 0.775)	.000	0.506 (0.491, 0.521)	< .0001	1.192 (0.96, 1.479)	.112	1.043 (1.012, 1.074)	.006
	Unknown	2.227 (0.284, 17.487)	.446	0.402 (0.315, 0.512)	< .0001	0.257 (0.067, 0.99)	.048	1.06 (0.853, 1.318)	.597

Table 3 Continued

		Chemotherapy				Radiotherapy			
		SI		Non-SI		SI		Non-SI	
Characteristic	Variable	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
Histology	Ductal (Ref)								
	Lobular	0.888 (0.621, 1.271)	.517	0.999 (0.969, 1.031)	.960	1.091 (0.785, 1.516)	.604	1.151 (1.113, 1.189)	< .0001
	Other	0.853 (0.515, 1.413)	.537	1.031 (0.971, 1.095)	.322	0.943 (0.671, 1.325)	.734	1.007 (0.945, 1.072)	.832
Tumor size	0-2 cm (Ref)								
	2-5 cm	0.829 (0.557, 1.233)	.353	2.565 (2.503, 2.63)	< .0001	1.139 (0.864, 1.501)	.355	1.13 (1.096, 1.166)	< .0001
	> 5 cm	0.589 (0.399, 0.869)	.008	2.657 (2.497, 2.828)	< .0001	1.182 (0.899, 1.554)	.232	4.418 (4.131, 4.725)	< .0001
No. of nodes examined	1-2 (Ref)								
	3-4	0.983 (0.608, 1.589)	.943	1.055 (1.031, 1.08)	< .0001	1.049 (0.739, 1.487)	.790	0.999 (0.974, 1.024)	.934
	5-10	1.063 (0.698, 1.618)	.776	1.217 (1.185, 1.249)	< .0001	1.291 (0.961, 1.736)	.090	1.012 (0.978, 1.047)	.502
	> 10	1.36 (0.924, 2.003)	.119	1.592 (1.539, 1.647)	< .0001	1.461 (1.091, 1.957)	.011	1.181 (1.132, 1.232)	< .0001
No. of positive nodes	0 (Ref)								
	1-3	1.379 (1.02, 1.864)	.037	5.277 (5.101, 5.459)	< .0001	0.975 (0.795, 1.195)	.805	1.828 (1.738, 1.924)	< .0001
	4-9	1.3 (0.931, 1.815)	.124	7.752 (7.295, 8.238)	< .0001	1.128 (0.9, 1.412)	.296	8.256 (7.66, 8.898)	< .0001
	10+	1.179 (0.803, 1.73)	.400	6.068 (5.595, 6.581)	< .0001	0.921 (0.697, 1.218)	.566	7.973 (7.31, 8.697)	< .0001
Surgery type	Breast-conserving surgery (Ref)								
	Mastectomy	1.939 (1.373, 2.738)	.000	2.086 (2, 2.175)	< .0001	0.261 (0.188, 0.363)	< .0001	0.014 (0.013, 0.015)	< .0001
Radiotherapy	No (Ref)								
	Yes	5.141 (4.162, 6.351)	< .0001	2.9 (2.769, 3.037)	< .0001	NA		NA	
Chemotherapy	No (Ref)								
	Yes	NA		NA		5.452 (4.439, 6.697)	< .0001	2.447 (2.344, 2.555)	< .0001

Abbreviations: CI = confidence interval; NA = not applicable; OR = odds ratio; Ref = referent; SI = skin involved.

Table 4 Survival Models of Treatment Effect by Skin Involvement

Therapy	Neostage[a]	N[b]	Effect	HR	95% CI		P
					Upper	Lower	
Chemotherapy	II	4360	Survival benefit for chemotherapy in SI versus non-SI				.0629
		1090	Chemotherapy versus no chemotherapy in SI	0.2972	0.2302	0.3836	< .001
		3270	Chemotherapy versus no chemotherapy in non-SI	0.3995	0.333	0.4792	< .001
	III	6020	Survival benefit for chemotherapy in SI versus non-SI				.893
		1505	Chemotherapy versus no chemotherapy in SI	0.3879	0.3271	0.46	< .001
		4515	Chemotherapy versus no chemotherapy in non-SI	0.3932	0.3495	0.4423	< .001
Radiotherapy	II	4028	Survival benefit for radiotherapy in SI versus non-SI				< .001
		1007	Radiotherapy versus no radiotherapy in SI	0.3329	0.2585	0.4286	< .001
		3021	Radiotherapy versus no radiotherapy in non-SI	0.6117	0.5019	0.7455	< .001
	III	5744	Survival benefit for radiotherapy in SI versus non-SI				.171
		1436	Radiotherapy versus no radiotherapy in SI	0.4034	0.3381	0.4814	< .001
		4308	Radiotherapy versus no radiotherapy in non-SI	0.4669	0.4164	0.5235	< .001

Abbreviations: CI = confidence interval; HR = hazard ratio; SI = skin involvement.
[a]Neostage was defined as tumor, node, metastasis classification, where T size was used without considering SI for true comparison of outcomes. Neostage I was not analyzed because of sample size.
[b]Number of patients in cohort following 3:1 propensity score (and exact) matching on patient demographics, tumor characteristics, and treatment variables.

adjuvant chemotherapy for tumors that were < 2 cm (46.1% vs. 31.2%), 2 to 5 cm (42.6% vs. 24.8%), and > 5 cm (48.4% vs. 19.3%) ($P < .001$).

For SI tumors and non-SI tumors, chemotherapy provided a significant OS benefit for stage II and III primary lesions (each $P < .001$), but there was no difference in the magnitude of that benefit whether SI was present or not ($P = .0629$ and .893 for stage II and III, respectively) (Table 4). Survival curves are provided in Figure 2. Effects of chemotherapy on OS for stage I cancers could not be assessed because of the small sample size.

Radiotherapy

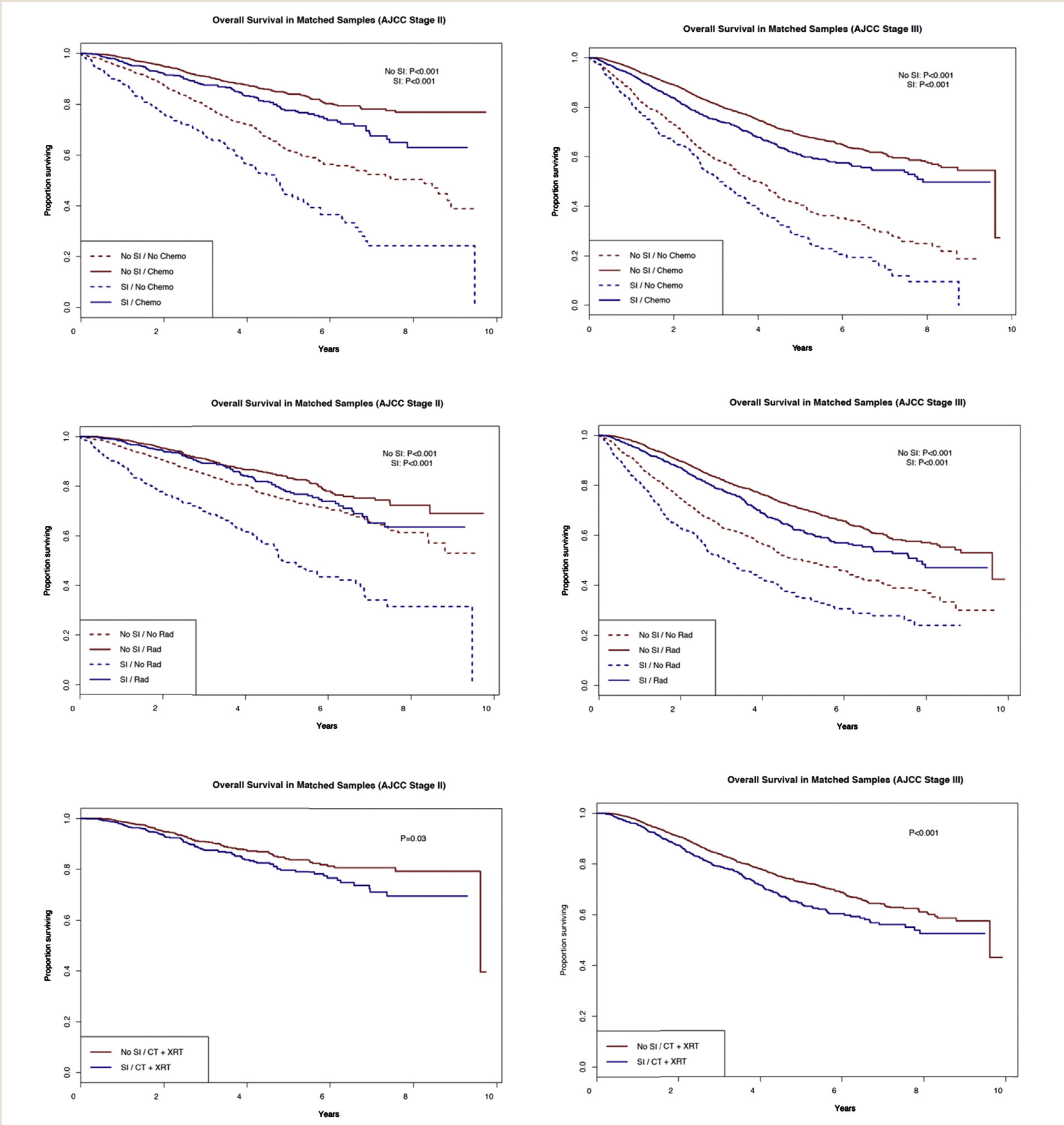
Radiotherapy was administered to 61.1% and 64.3% of SI and non-SI tumors, respectively ($P < .001$), while 65.6% of SI and 66.5% non-SI tumors < 2 cm received radiotherapy ($P = .711$). Adjuvant radiotherapy was more likely to be provided than not for SI tumors < 2 cm (11.4% vs. 9.4%), 2 to 5 cm (39.9% vs. 38.9%), and > 5 cm (48.8% vs. 51.7%). After adjusting for patient and tumor characteristics, SI patients had a 76.6% increase in odds of receiving radiotherapy compared to non-SI patients (OR = 1.766; 95% CI, 1.609, 1.939; $P < .001$) (Table 2).

Predictors of radiotherapy receipt in SI tumors included younger age, insurance status, cancer center distance, lower CCI, positive hormone receptor status, number of nodes examined, performance of breast conservation (vs. mastectomy), and receipt of chemotherapy. Predictors of radiotherapy in non-SI tumors included younger age, non-Hispanic ethnicity, insurance status, location, closer distance to the reporting facility, facility type, lower CCI, lower tumor grade, tumor size, tumor histology, hormone receptor status, number of nodes examined, number of positive nodes, and surgery performed (Table 3). Radiotherapy also provided an OS benefit for stage II and III SI and non-SI tumors (each $P < .001$), with the only differential benefit found to be greater in SI stage II tumors versus their non-SI counterparts (0.3329 vs. 0.6117, $P < .001$) (Table 4). Survival curves are provided in Figure 2. Effects of radiotherapy on OS for stage I cancers could not be assessed because of small sample size.

Discussion

We have found that marked variability exists in treating SI tumors in the United States. Although the paradigms of chemotherapy and radiotherapy are relatively well defined, questions exist regarding SI tumors, which are typically thought to be unresectable regardless of their size, even though many are technically not so. In order to better assess these tumors, we previously evaluated the SEER-Medicare data set where SI and non-SI tumors were reclassified similarly to this study on the basis of tumor size alone using the AJCC 7th edition breast cancer staging system.[5] We observed that the prognosis of SI tumors was related primarily to their size, and we believe that reclassification of SI staging may allow for a stage that is more closely tied to their DSS. When ignoring skin involvement and reclassifying tumors solely on the basis of the size of the primary lesion and numbers of positive nodes, the adjusted 5-year DSS for SI tumors was found to be similar to non-SI tumors

Figure 2 Survival Curves Showing Treatment Effect by SI



Abbreviations: Chemo = chemotherapy; Rad = radiotherapy; SI = skin involvement.

for stages I, IIA, and IIB, but lower than their non-SI counterparts for IIIA and IIIC.[5]

The percentage of tumors presenting with SI are small.[10,11] Although we are aware of no genomic studies evaluating this, their similar prognoses suggest that small, superficial SI tumors are not biologically different than their similarly sized but deeper non-SI counterparts and have simply invaded skin as a result of their random origination closer to skin. To that end, it has remained unknown whether practitioners have deemed smaller SI tumors, such as those < 2 cm, with similar concern to those that are larger solely because of their skin involvement, and whether SI tumors of all sizes have been receiving and benefiting from chemotherapy and radiotherapy.

This study utilized the NCDB to assess patterns of care for adjuvant therapies in these lesions and to determine OS, which includes mortality from those therapies (the NCDB does not provide DSS data).[6,12] In this data set, our evaluation of SI and non-SI breast cancers found that regardless of tumor size and skin involvement, an overwhelming number of patients received chemotherapy and radiotherapy, but the administration of these modalities was not nearly universal, as one might expect based on guidelines,[4] with chemotherapy provided to only 68.5% and 45.9% of SI versus non-SI tumors, respectively. Surprisingly, a larger proportion (77.2%) of those having SI tumors < 2 cm received chemotherapy versus non-SI tumors of equal size (33.3%), even though prior data of ours and others found similar survival between SI and non-SI tumors of those sizes.[5,10,13-16]

While decisions for adjuvant systemic therapy are based on an individual's risk of relapse and sensitivity to treatment based on tumor characteristics, indications for neoadjuvant chemotherapy under the NCCN guidelines are divided into operable versus LABC, which include the T4 tumors seen in our cohort.[4,17-20] Historically, neoadjuvant chemotherapy and radiotherapy were included as an adjunct in the treatment of LABC in order to downstage lesions, improve resectability, eradicate micrometastatic disease, and improve locoregional control.[21] Although this is the standard of care, our study finds that neoadjuvant chemotherapy is also frequently applied to small resectable cancers with or without skin involvement.

There are various definitions for LABC.[22-24] It is important to have uniform agreement of what we define as LABC because often decisions for treatment are tied to this definition. Although smaller SI tumors normally characterized as LABC solely because of their skin involvement have favorable prognoses, LABC may require a more updated and uniform definition. Wolff and Davidson[21] emphasized that there is no standard definition for LABC. Commonly used guidelines have included tumors > 5 cm, skin or chest wall involvement, and fixed ipsilateral axillary nodes or internal mammary lymph node involvement, some of which necessitate a modified radical mastectomy. The SI cancers in our cohort fall into this LABC definition, but while treatment guidelines demand systemic therapy administration, we have found that this is not universally applied.

Deo et al[25] reported a trial evaluating neoadjuvant versus adjuvant therapy in operable LABC. In this study, small T4b tumors were included, suggesting that these should be classified with other SI breast cancers and that chemotherapy remains standard for all such lesions. The treatment patterns observed in our cohort may also reflect trends in chemotherapy and/or radiotherapy seen in guidelines published by Brackstone and colleagues.[26,27] This study found responses to induction chemotherapy followed by radiotherapy in selected patients with LABC who were candidates for breast-conservation therapy. Specifically, adjuvant treatment was equally applied to small tumors, consistent with our findings where many of even the smallest SI primary lesions were provided adjuvant chemotherapy.

Current indications for adjuvant therapy now include assessment via the 21-gene RS assay rather than solely relying on the physical factors used when therapy was first introduced. The introduction of the 21-gene RS has made gene expression profiling standard in clinical practice,[28] and our study is notable because it spans the time period from before the 21-gene RS was used until it became commonplace.[29] Although it is true that for larger SI tumors one would expect chemotherapy administration, obviating the need for the RS assay to be used, we know that during earlier years variability in its use was common. A retrospective study by Panousis et al[30] reviewed 114 breast cancer cases from 2009 to 2015 to evaluate the impact of the RS results on adjuvant treatment decisions applied in this cohort. The application of a 21-gene RS score greatly reduced the chemotherapy recommendations on the cohort, by 39.5%. We believe that inconsistency in its use could contribute to the inconsistency in adjuvant therapy administration seen in our cohort over 7 years, after controlling for patient and tumor characteristics.

We evaluated chemotherapy use over time, and to our surprise, there was no trend seen. Because RS use has increased over the span of our study, this suggests that either decisions for systemic therapy are being made on the basis of skin involvement and size without using the RS, or, less likely, that decisions are not changed by the use of RS.[31] Future studies should attempt to correlate SI and the 21-gene RS to see if there is a biological difference found in tumors that invade skin, regardless of size.

In our data set, administration of chemotherapy or radiotherapy was not uniform when comparing SI and non-SI tumors of similar sizes. Furthermore, within SI lesions, there was no uniform administration of adjuvant therapy within the same tumor size, although neoadjuvant chemotherapy was the predominant timing used for systemic therapy administration in both SI and non-SI tumors of all sizes. The complete omission of adjuvant treatment in some breast cancer cases may have reflected comorbid conditions, 21-gene RS use in later years of the study, the overriding judgment of the practitioner, patient preference, or other factors, which unfortunately cannot be captured in this data set.

Limitations of our study include the retrospective nature of this large national data set, including the inaccuracies that can occur when coding such data. Some patients were excluded who had missing data, including unknown staging, unknown surgery, or no treatment recorded. This can lead to confounding and bias in the data set. It should be noted that neoadjuvant chemotherapy patients required use of clinical T stage, while adjuvant chemotherapy patients required use of pathologic T stage, which are not directly comparable. Because this was not a randomized study, selection and treatment biases can occur affecting outcomes. Furthermore, our data collection spanned more than one AJCC staging edition, although the staging issues related to skin involvement did not change between editions. Future studies should be undertaken to elucidate the reason for exclusion of certain treatment modalities when they remain recommended by guidelines.

Conclusions

Our results demonstrate that the majority of SI tumors are receiving systemic therapy and radiotherapy, regardless of size, although there remains a lack of uniformity. There is a clear OS advantage seen in stage II and III breast cancers receiving adjuvant treatment. Practice patterns indicate that SI tumors < 2 cm are receiving chemotherapy and radiotherapy at levels comparable to larger tumors. Although we could not determine OS on SI tumors < 2 cm as a result of the small sample size, survival advantage of adjuvant therapy in smaller tumors remains important to assess when standardizing treatment recommendations.

Clinical Practice Points

- Although most SI breast cancers are large and have prognosis similar to that of other LABC, small SI primary lesions have prognoses similar to their non-SI counterparts. Unfortunately, their patterns of care and the benefit conferred by radiotherapy and chemotherapy remain unknown. This study was performed to fill these voids.
- There is a clear survival advantage of adjuvant therapy in stage II and III SI and non-SI breast cancer.
- We anticipate that future practice patterns will more uniformly use adjuvant chemotherapy and radiotherapy if guidelines are established. In the interim, this study has shown them to be beneficial.

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Disclosure

The authors have stated that they have no conflict of interest.

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