OPEN

The Extent of Axillary Surgery Is Associated With Breast Cancer-specific Survival in T1−2 Breast Cancer Patients With 1 or 2 Positive Lymph Nodes

A SEER-Population Study

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Abstract: This study aimed to compare the breast cancer-specific survival (BCSS) of a nonclinical trial population of T1−2 breast cancer patients with 1 to 2 positive lymph nodes who received breast-conserving surgery and either sentinel lymph node biopsy (SLNB) or axillary lymph node dissection (ALND).

We used the Surveillance, Epidemiology and End Results (SEER) database to identify 17,028 patients with a median follow-up of 7.1 years. We assigned the patients into a SLNB-cohort (≤5 nodes) and an ALND-cohort (>5 nodes) based on the number of removed lymph nodes. We used Kaplan-Meier analysis to estimate the cumulative BCSS and used Cox-regression analysis to study the risk factors. We also performed subgroup analysis by the patients' age and hormonal receptor (HR) status.

The cumulative BCSS and Overall Survival (OS) of the entire population were 94.4% and 91.4% at 5 years and 88.2% and 79.9% at 10 years, respectively. Axillary surgery (ALND vs SLNB) had no association with BCSS when adjusted for stage, HR status, tumor grade, or other factors. In subgroup analysis by age and HR status, ALND was associated with a significantly improved BCSS relative to SNLB (HR = 0.70, HR = 0.026, 95% confidence interval 0.51–0.96) only in patients younger than 50 years with HR− disease (N = 1281), but not in other subgroup of patients.

In early-stage breast cancer patients with limited lymph node metastasis, ALND had better BCSS than SLNB only in patients younger than 50 years and with HR− disease. More studies are needed to confirm our findings.

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Abbreviations: ALND = axillary lymph node dissection, BCS = breast-conserving surgery, BCSS = breast cancer-specific survival, HR = hormone receptor, IRB = institutional review board, SEER = surveillance epidemiology and end results, SLNB = sentinel lymph node biopsy, WBI = whole-breast irradiation.

INTRODUCTION

Sentinel lymph node biopsy (SLNB) is the standard staging procedure for invasive breast cancer patients with clinically negative axilla. For 10 years, most guidelines have recommended axillary lymph node dissection (ALND) for patients with any positive SLNs. The American College of Surgeons of Oncology Group (ACOSOG) initiated the Z0011 trial,[4] which randomly assigned patients with 1 or 2 positive sentinel lymph nodes to receive either ALND or observation. The trial showed that the use of SLNB alone compared with ALND did not result in poorer survival among patients with limited SLN-metastatic breast cancer. The findings of this study were soon embraced by the surgical oncology community. The American Society of Breast Surgeons[12] and the National Comprehensive Cancer Network (NCCN) guidelines[6] have stated that ALND may no longer be routinely required for patients who meet all of the Z0011 criteria: T1−2 tumors; 1 or 2 positive SLNs without extracapsular extension; breast-conserving surgery (BCS) and whole-breast irradiation (WBI) therapy without extended fields of therapy; and patient acceptance and completion of adjuvant therapy (hormonal, cytotoxic, or both).

We hypothesized that in a nonclinical trial population, SLNB will have equivalent or better long-term breast cancer-specific survival (BCSS) than ALND in patients who received BCS and WBI for T1−2 breast cancer with 1 to 2 positive lymph nodes. In this study, we used the SEER database to compare the BCSS of patients receiving SLNB or ALND. We also

performed subgroup analysis by patient age and hormonal receptor (HR) status.

METHODS

Data Collection

We searched the SEER registry data from 18 registries (Nov. 2013 submission) and identified female patients who had been diagnosed with breast cancer between 1998 and 2008. The following criteria were used to select patients who matched the Z0011 trial population. (The detailed selection criteria used in the SEER*stat 8.1.5 software are provided in Suppl. File 1 for reference, http://links.lww.com/MD/A872):

1   T1−2 tumor (tumor size ≤5 cm).
2   Received BCS (Code: 20−24) with radiation therapy (Beam irradiation).
3   Infiltrating ductal carcinoma (Code: 8500/3).
4   1 to 2 positive lymph nodes (N1 only, not included N0i+ and N1mi).

The following patients were excluded from this analysis:

1   Important prognostic information, such as the race, grade, AJCC stage, T-stage, N-stage, surgery, or radiation unknown or not specified, and estrogen receptor (ER) or progesterone receptor (PR)' unknown.
2   No death events and follow-up time <36 months.
3   Patients with M1 diseases.

The tumor grade, adjusted AJCC 6th stage, adjusted AJCC 6th T-stage and N-stage, surgery of the primary site, radiation, race, number of positive nodes, number of examined nodes, marital status at diagnosis, laterality (left or right breast), ER status, PR status, survival month, county attributes (median family income, county type [metropolitan/non-metropolitan]), SEER cause-specific death classification and SEER other cause of death classification were extracted for each case. The SEER database did not specify the axillary surgery type as SLNB or ALND. Therefore, we used the number of examined nodes as a surrogate in this study. Patients with 1 to 5 or >5 lymph nodes removed were considered to have undergone SLNB or ALND, respectively. We used 5 nodes as the cutoff value for SLNB and ALND based on the definition of ALND by the American Joint Committee on Cancer (AJCC), who argue that a standard ALND should encompass at least 6 lymph nodes.[11,14]

Patients with borderline ER or PR status were considered to be ER- or PR-positive, respectively. A patient was considered to be hormone receptor (HR)-positive if she had ER+ and/or PR+ diseases. The county attribute (median family income) was classified into 4 subgroups by the quartile number/percentage of each index. This study used a national dataset of de-identified patient information and did not meet the criteria for approval by the institutional review board of Sun Yat-sen Memorial Hospital. Hence, this study waived the need for IRB approval.

Statistical Analysis

We conducted a descriptive analysis of the population characteristics. χ^2 tests were used to compare the differences in the demographic and clinicopathological features of patients who received SLNB or ALND. Kaplan-Meier survival analysis was used to calculate the cumulative BCSS.

For the univariate analysis, we used an unadjusted Cox-regression model to screen for potential risk factors for BCSS. Significant risk factors from the univariate analysis (race, family income, marital status, stage, grade and axillary surgery) were incorporated into the multivariate analysis. The multivariate Cox-regression model was used in 4 patient subgroups (age <50 years, HR−; age <50 years, HR+; age ≥50 years, HR−; and age ≥50 years, HR+). All P values are 2-sided, and P values <0.05 were considered to be statistically significant. The SEER data were extracted using SEER*Stat 8.1.5, and the statistical analyses were performed using Stata/SE, version 12.0 (StataCorp LP, College Station, TX).

RESULTS

Population Characteristics

This study included 17,028 patients with a median follow-up of 85 months. The cumulative BCSS and OS were 94.4% and 91.4% at 5 years and 88.2% and 79.9% at 10 years, respectively. As shown in Table 1, the patients who received SLNB (N = 4095) were more likely to be older (≥50 years), white, and divorced and were more likely to live in a metropolitan county and have HR+ diseases with lower stages and lower-grade tumors than those who received ALND (N = 12,571). The tumor burden was imbalanced at baseline, and the SLNB cohort had a lower disease burden.

Risk Factors for BCSS

Unadjusted and adjusted Cox-regression models revealed that race (African-American vs White), lower family income, divorced marital status, higher tumor stage, HR-negative disease (vs positive) and higher tumor grade were associated with poorer BCSS. ALND was associated with shorter BCSS in unadjusted analysis (HR = 1.22, P < 0.01, 95% confidence interval [CI] 1.08−1.39) but not in the multivariate analysis when adjusted for stage, HR status, and tumor grade (Table 2).

ALND Versus SLNB in Breast Cancer Patients Younger Than 50 Years With HR− Disease

Adjusted Cox-regression analyses were further performed in 4 different subpopulations based on their age (<50 years or ≥50 years) and HR status (negative vs positive). In patients younger than 50 years with HR− diseases (N = 1281), ALND was associated with significantly greater BCSS than SLNB (HR = 0.70, HR = 0.026, 95% CI 0.51−0.96) after adjusting for stage, tumor grade, race, family income and marital status (Table 3 and Figure 1). This association was not observed in the other subsets of populations.

DISCUSSION

Major Findings

In this SEER-population study, we selected T1−2 breast cancer patients with 1 or 2 positive lymph nodes who received BCS and radiation therapy. Although the patients in the ALND cohort (>5 lymph nodes removed) had a higher tumor burden (higher stage, higher tumor grade, and more HR-negative diseases) than the SLNB cohort (≤5 lymph nodes removed), there was no difference in BCSS between these groups when adjusted for stage, age, HR status, and tumor grade.

We further divided the populations into 4 different subgroups based on their age (<50 years or ≥50 years) and HR

TABLE 1. Clinicopathological Features of the Patients Included in This Study

	SLNB (N = 4163)		ALND (N = 12,865)		
	n	%	n	%	P*
Age groups, y					
<50	1065	25.58	4255	33.07	<0.001
≥50	3098	74.42	8610	66.93	
Race					
White	3553	85.35	10,539	81.92	<0.001
African-American	332	7.98	1320	10.26	
Others	278	6.68	1006	7.82	
Family income†					
1st (Lowest)	1009	24.24	3280	25.50	0.073
2nd	1021	24.53	3249	25.25	
3rd	1089	26.16	3341	25.97	
4th (Highest)	1044	25.08	2995	23.28	
County type					
Metropolitan	3820	91.76	11,661	90.64	<0.001
Non-Metropolitan	340	8.17	1115	8.67	
Unknown	3	0.07	89	0.69	
Marital status					
Married	2525	60.65	8122	63.13	0.004
Divorced‡	1638	39.35	4743	36.87	
Laterality					
Left, origin of primary	2078	49.92	6564	51.02	NS
Right, origin of primary	2085	50.08	6301	48.98	
Primary site					
Nipple/central portion	215	5.16	608	4.73	NS
UIQ	385	9.25	1222	9.50	
LIQ	205	4.92	723	5.62	
UOQ	1857	44.61	5878	45.69	
LOQ	358	8.60	1085	8.43	
Overlapping/unknown	1143	27.46	3349	26.03	
T-Stage					
Tmic-T1a	127	3.05	250	1.94	<0.001
T1b	705	16.93	1538	11.95	
T1c	2140	51.41	6424	49.93	
T2	1191	28.61	4653	36.17	
AJCC-Stage					
IIa	2972	71.39	8212	63.83	<0.001
IIb	1191	28.61	4653	36.17	
Hormone receptor status					
Negative	577	13.86	2623	20.39	<0.001
Positive	3586	86.14	10,242	79.61	
Grade					
I	862	20.71	1934	15.03	<0.001
II	1901	45.66	5571	43.30	
III	1362	32.72	5201	40.43	
IV§	38	0.91	159	1.24	

ALND = axillary lymph node dissection, LIQ = lower-inner quadrant, LOQ = lower-outer quadrant, SLNB = sentinel lymph node biopsy, UIQ = UPPER-inner quadrant; UOQ = Upper-outer quadrant.
*Chi-square test was used.
†Family income was categorized into 4 quartiles.
‡Separated, single, and widowed women and those with unknown marital status were included in the divorced category.
§In SEER database, Grade IV indicates undifferentiated or anaplastic.

status (negative or positive), considering the endocrine therapy approach may be significantly different among these subgroups. We noticed that the ALND group had a significantly better BCSS than the SLNB group in patients younger than 50 years with HR− diseases, after adjusting for tumor stage, grade, and race (Table 3). Although the tumor T-stage, stage, and grade were all similar between groups in HR− patients younger than 50 years (Supplementary Table 1, http://links.lww.com/MD/A872), the influence of ''confounding by indication'' cannot be excluded. For example, patients who are younger than 50 years with HR− disease are more likely to have metastatic disease. Therefore, it is possible that surgeons tend to perform less-extensive surgeries in patients with metastatic disease, which in turn serves as a marker for worse BCSS. In our study, we had excluded the metastatic patients from the analysis. However, this is unlikely to completely address this question because of the inaccuracies in the recorded information.[8] Supporting these concerns, we noticed that the BCSS curves diverge very early in this subgroup of patients. Taken together, we suggest prospective, randomized study to eliminate the influence of ''confounding by indication'' in our study.

Clinical Implications

Patients with 1 to 2 positive SLNs who received BCS and radiotherapy were randomized into SLNB alone or ALND group in the Z0011 study. With a median follow-up of 6.3 years, the local-regional recurrence-free survival, disease-free survival (DFS), and overall survival were similar between the 2 groups.[4] Only 16% (n = 134) of the Z0011 population was HR-negative. As the median age was 55 years, we estimated that there were about <8% (n = 67) of the Z0011 population who were younger than 50 years and had HR-negative disease. Therefore, the safety of omitting ALND in these patients cannot be guaranteed because of the small sample size.[4,10] In our study, there were 1281 (7.3%) patients who were younger than 50 years and had HR-negative disease. The association between the extent of axillary surgery and BCSS was observed only in these patients, suggesting more attention should be given when applying Z0011 conclusions this subgroup of patients.

In the Z0011 study, there were 27% of the patients in the ALND group who had additional metastatic lymph nodes, indicating that similar proportion of patients in the SLNB alone group may have metastatic lymph nodes untreated in the axilla. However, the likelihoods of having additional metastatic lymph nodes after positive SLNs were generally higher (30%–50%) in the other studies,[1–3,5,7,9,13] when different inclusion criteria were used. If the patients younger than 50 years with HR-negative disease in the Z0011 had relatively higher likelihood of having additional metastatic lymph nodes, then omitting ALND would be unsafe in these patients.

Without further evidence, however, our study is unable to suggest that the Z0011 conclusions cannot be generalized in patients younger than 50 years with HR-negative disease. Our study is different from the Z0011 in the following aspects: the information of local-regional relapse and distant metastasis is not available in our study; all of the patients in the Z0011 studies received standard adjuvant therapies, which is not clear in our study population; the retrospective design of our study caused inherent bias that cannot be eliminated; the information of the axillary radiotherapy was not available in our study.

In addition, we suggested that the benefit of more extensive axillary treatment on BCSS only lies in the high-risk breast cancer patients, rather than low-risk patients. In the Z0011 study, patients

TABLE 2. Risk Factors for Breast Cancer-specific Survival

Variable	Unadjusted Cox				Adjusted Cox			
	HR	P	LL	UL	HR	*P*	LL	UL
Age groups, y								
<50	1.00				1.00			
≥50	0.78	<0.01	0.71	0.87	0.99	0.89	0.89	1.10
Race								
White	1.00				1.00			
African-American	1.88	<0.01	1.64	2.16	1.30	<0.01	1.13	1.51
Others	0.9	0.34	0.74	1.11	0.84	0.10	0.68	1.04
Family income*								
1st (lowest)	1.00				1.00			
2nd	0.84	0.02	0.73	0.97	0.85	0.02	0.74	0.98
3rd	0.84	0.02	0.73	0.97	0.91	0.16	0.79	1.04
4th (highest)	0.76	<0.01	0.66	0.88	0.80	<0.01	0.69	0.92
County type								
Metropolitan	1.00				Not included			
Non-metropolitan	0.95	0.56	0.78	1.14				
Unknown	0.94	0.85	0.52	1.71				
Marital status								
Married	1.00				1.00			
Divorced†	1.18	<0.01	1.06	1.3	1.15	0.01	1.03	1.28
Laterality								
Left, origin of primary	1.00				Not included			
Right, origin of primary	1.07	0.22	0.96	1.18				
Primary site								
Nipple/central portion	1.00				1.00			
UIQ	1.37	0.03	1.03	1.83	1.17	0.28	0.88	1.57
LIQ	1.55	0.01	1.14	2.11	1.37	0.05	1.01	1.87
UOQ	1.06	0.64	0.82	1.37	0.88	0.33	0.68	1.14
LOQ	1.15	0.35	0.85	1.56	1.02	0.92	0.75	1.37
Overlap/unknown	1.17	0.25	0.9	1.52	1.03	0.84	0.79	1.34
T-stage								
Tmic-T1a	1.00				Not included‡			
T1b	0.82	0.50	0.45	1.48				
T1c	2.04	0.01	1.18	3.53				
T2	4.55	<0.01	2.63	7.88				
Breast - Adjusted AJCC 6th Stage (1988+)								
IIA	1.00				1.00			
IIB	2.59	<0.01	2.34	2.87	1.95	<0.01	1.76	2.17
Hormone receptor status								
Negative	1.00				1.00			
Positive	0.36	<0.01	0.32	0.4	0.57	<0.01	0.51	0.65
Grade								
I	1.00				1.00			
II	2.89	<0.01	2.22	3.76	2.49	<0.01	1.91	3.24
III	6.76	<0.01	5.24	8.73	4.14	<0.01	3.18	5.39
IV	5.25	<0.01	3.28	8.41	3.07	<0.01	1.90	4.94
Axillary surgery								
SLNB	1.00				1.00			
ALND	1.22	<0.01	1.08	1.39	1.02	0.76	0.90	1.16

ALND = axillary lymph node dissection, HR = hazard ratio, LIQ = lower-inner quadrant, LL and UL = lower limits and upper limits of the 95% of the confidence interval, LOQ = lower-outer quadrant, SLNB = sentinel lymph node biopsy, UIQ = upper-inner quadrant; UOQ = upper-outer quadrant.

*Family income was categorized into 4 quartiles.

†Separated, single, and widowed women and those with unknown marital status were included in the divorced category.

‡T-stage was not included as it was highly associated the stage.

TABLE 3. Multivariate Analysis of Risk Factors for Breast Cancer-specific Survival

Variable	Age <50 y and HR− (N = 1281)				Age <50 y and H+ (N = 4039)				Age ≥50 y and HR− (N = 1919)				Age ≥50 y and HR+ (N = 9789)			
	HR	*P*	LL	UL	HR	*P*	LL	UL	HR	*P*	LL	UL	HR	*P*	LL	UL
Race																
White	1.00				1.00				1.00				1.00			
African-American	1.29	0.101	0.95	1.74	1.35	0.066	0.98	1.85	1.17	0.296	0.87	1.57	1.43	0.008	1.10	1.85
Others	1.13	0.622	0.70	1.80	0.72	0.134	0.47	1.11	0.83	0.456	0.50	1.36	0.86	0.405	0.61	1.22
Family income*																
1st (Lowest)	1.00				1.00				1.00				1.00			
2nd	0.93	0.667	0.67	1.29	0.80	0.172	0.59	1.10	0.87	0.391	0.64	1.19	0.87	0.199	0.70	1.08
3rd	0.77	0.130	0.54	1.08	0.90	0.501	0.67	1.22	1.09	0.567	0.81	1.48	0.90	0.352	0.73	1.12
4th (Highest)	0.73	0.084	0.51	1.04	0.69	0.018	0.50	0.94	0.96	0.801	0.69	1.33	0.85	0.153	0.68	1.06
Marital status																
Married	1.00				1.00				1.00				1.00			
Divorced†	1.02	0.898	0.78	1.33	1.27	0.042	1.01	1.60	1.11	0.379	0.88	1.41	1.16	0.069	0.99	1.36
Stage																
IIa	1.00				1.00				1.00				1.00			
IIb	1.52	0.001	1.18	1.98	1.82	<0.001	1.46	2.29	2.16	<0.001	1.71	2.73	2.09	<0.001	1.78	2.46
Grade																
I	1.00				1.00				1.00				1.00			
II	1.13	0.865	0.27	4.77	3.31	<0.001	1.74	6.32	2.13	0.296	0.52	8.80	2.27	<0.001	1.68	3.08
III	1.22	0.784	0.30	4.91	6.07	<0.001	3.19	11.53	2.73	0.157	0.68	11.02	4.08	<0.001	3.00	5.56
IV	1.02	0.985	0.20	5.05	4.48	0.012	1.40	14.36	1.50	0.630	0.29	7.74	3.73	<0.001	1.82	7.63
Axillary surgery																
SLNB	1.00				1.00				1.00				1.00			
ALND	0.70	0.026	0.51	0.96	0.91	0.528	0.69	1.21	1.14	0.389	0.84	1.54	1.14	0.169	0.94	1.39

ALND = Axillary lymph node dissection, HR = hazard ratio, LIQ = lower-inner quadrant, LL and UL = lower limits and upper limits of the 95% of the confidence interval, LOQ = lower-outer quadrant, SLNB = sentinel lymph node biopsy, UIQ = upper-inner quadrant, UOQ = upper-outer quadrant.
*Family income was categorized into 4 quartiles.
†Separated, single, and widowed women and those with unknown marital status were included in the divorced category.

were randomized into SLNB or ALND, whereas in the AMAROS study, patients were randomized into radiation or ALND. Neither of these studies showed a significant improvement of 5-year DFS in the more extensive surgical treatment (ALND) group (Supplementary Table 2, http://links.lww.com/MD/A872). In the MA.20 study, which had more patients with T2, ER-negative, and grade 3 disease, patients who received WBI+ regional nodal irradiation (RNI) had improved distant DFS (92.4% vs 87.0%, *P* = 0.002) and a trend toward improved overall survival (92.3% vs 90.7, *P* = 0.07)[10] when compared to the WBI-only group. Our study population (age <50 years and HR−) had more T2 and grade 3 disease than the MA.20 study (Supplementary Table 2, http://links.lww.com/MD/A872), and we showed that ALND (vs SLNB) was associated with BCSS in this subgroup of patients.

Limitations

Therefore, this study should be interpreted cautiously. A major limitation of this study is the lack of information in the SEER database. The HER-2 status, margin status, extracapsular extension of positive nodes, adjuvant/neoadjuvant chemotherapy, and the radiation field (whole/partial breast radiation or nodal irradiation) are all unavailable in the SEER database, and these omissions may lead to a certain number of patients in our study who do not actually fit the Z0011 criteria.

1 Systemic therapy: It is possible that patients with larger tumor burden and higher grade (associated more with ALND) may have had higher rate of chemotherapy use. Hence, the survival benefit of ALND may come from chemotherapy, which had not been adjusted in this study.
2 Nodal burden: The SEER database did not contain detailed information of nodal burden, such as macrometastasis or micrometastasis in SLNs. ALND may have been done for patients with macroscopic nodal involvement (eg, detected clinically/preoperatively), whereas the SLNB-cohort (<6 nodes removed) may have had micrometastatic nodes only. This would cause significant bias for analysis. Additionally, there were nearly 27% of patients who had >2 positive nodes in Z0011 trial, whereas in the ALND-cohort of our study, all of those patients had 1 to 2 positive nodes. The population of our study may have less axillary nodal burden than that of the Z0011 study.
3 Her-2 status: No data about HER-2 status were available in SEER. The HER-2 status and the use of trastuzumab may also contribute to surgeon' decision in axillary surgery treatment.
4 SLNB/ALND: The use of SLNB and ALND is not clearly recorded in the SEER database. We defined the SLNB and ALND groups in this study based on the number of excised lymph nodes.
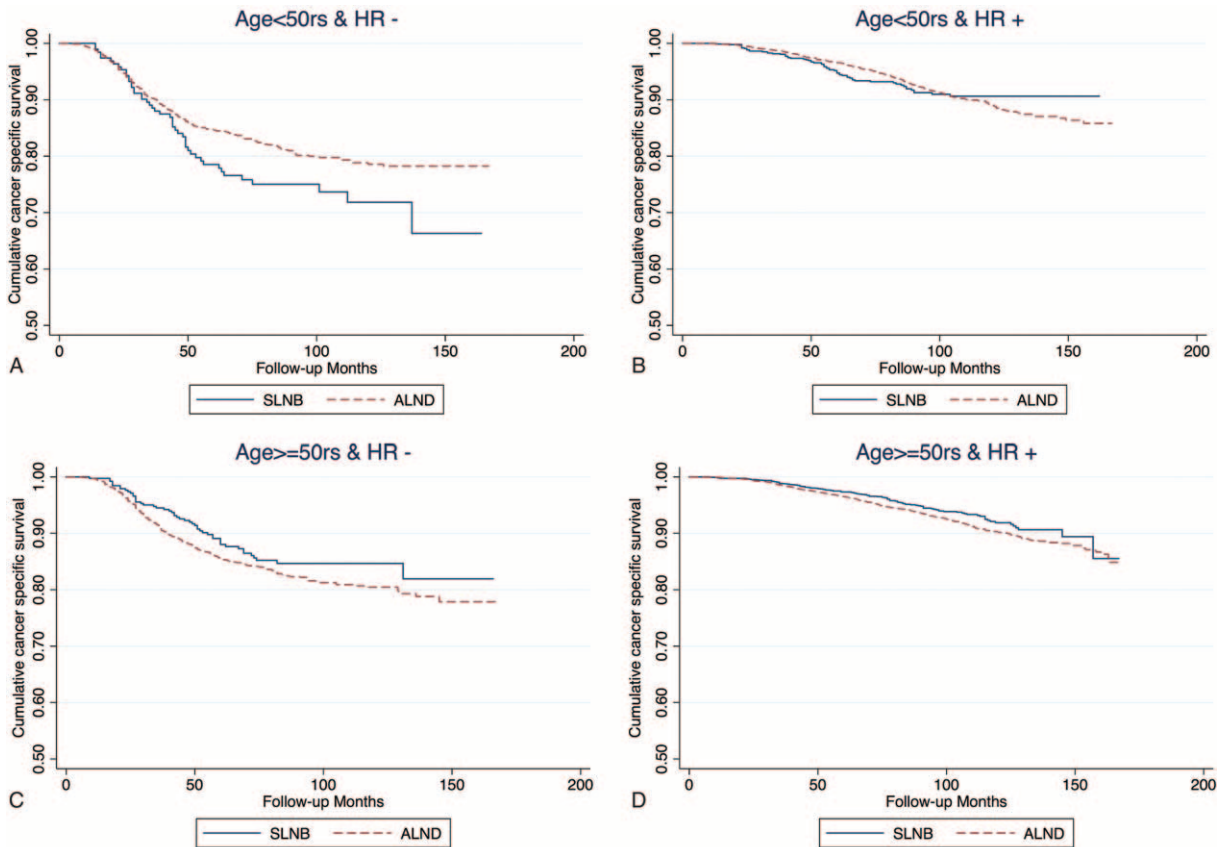
FIGURE 1. Differences in BCSS between the SLNB and ALND cohorts in different subgroups of patients. ALND = axillary lymph node dissection, HR = hormonal receptor; SLNB = sentinel lymph node biopsy.

5   Historical limitation: In 1998–1999, when the sentinel lymph nodes biopsy had not been widely adopted, patients most likely had less than 5 nodes removed for reasons other than those advocated by the ACOSOG Z0011 trial.

6   Lack of information about local/distant relapse: The endpoint used in our study was BCSS, which did not provide any information regarding the risk of local or distant relapses. Therefore, it is unclear whether the survival benefit shown by the difference of BCSS was determined by the effect of ALND, or by the poor tumor biology in patients younger than 50 years with HR− diseases.

However, we are going to argue that the limitations here may have similar influence on all subgroups. We noticed that ALND was associated with improved BCSS only in one subgroup (age <50 years and HR−), but not in the others, suggesting that this subgroup of patients needs more attention when considering axillary treatment.

Summary

This study included T1−2 breast cancer patients who received BCS + RT, with only 1 or 2 positive lymph nodes from the SEER database. In the entire study population, axillary surgery (SLNB vs ALND) was not associated with BCSS when adjusted for tumor stage, age, HR status, or other factors. In subgroup analysis by age and HR status, we noticed a significant difference in BCSS between the SLNB and ALND cohorts in patients younger than 50 years with HR− diseases. We concluded that in early-stage breast cancer patients with limited lymph node metastasis, ALND had better BCSS than SLNB in patients younger than 50 years and with HR− disease. More studies are needed to confirm our findings.

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