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Accuracy of a nomogram to predict the survival benefit of surgical axillary staging in T1 breast cancer patients

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Abstract

T1 breast cancer patients have favorable clinical outcomes, so that whether axillary stating (AS) surgery can be omitted in these patients is still unclear. This retrospective cohort study developed a nomogram to predict the cancer-specific survival (CSS) of T1 breast cancer patients with and without AS and estimate the survival benefit of AS in these patients.

We used surveillance, epidemiology, and end results (SEER) database to identify 232,195 breast cancer patients with T1 tumors diagnosed between 1990 and 2008. In the training cohort, we used the Kaplan–Meier method and the competing risk analysis, with non-CSS as the competing risk, to screen for prognostic factors for CSS. A nomogram to predict the CSS, with receiving AS or not as one of the predictors, was developed and externally validated, using the C-index and calibration plots. The survival benefit of AS can be estimated by the difference of 2 predicted CSS, when the patient was considered as having and not having AS.

With a median follow-up of 109 months, the CSS of the study population were 96.3%, 92.3%, and 88.5% at 5, 10, and 15 years, respectively. Significant predictors for CSS identified in the training cohort were used to develop a nomogram, which was validated internally [C-index = 0.707, 95% confidence interval (95% CI) 0.702–0.712] and externally (C-index = 0.704, 95% CI 0.698–0.710). The nomogram was well calibrated. With this nomogram, AS was predicted to have less than 2% benefit of 5-, 10-, and 15-year CSS in 60.6% (140,599/232,195), 15.5% (36,074/232,195), and 8.6% (20,043/232,195) of the entire study population, respectively.

The new nomogram can accurately predict the CSS of T1 breast cancer patients, and also be able to estimate the survival benefit of AS in these patients. Prospective studies are needed to confirm our findings.

Abbreviations: ALND = axillary lymph node dissection, ALNs = axillary lymph nodes, AS = axillary staging, BCS = breast-conserving surgery, CI = confidence interval, CID = cumulative incidence of breast cancer related death., CSS = cancer-specific survival, ER = estrogen receptor, IDC = invasive ductal carcinoma, PR = progesterone receptor, RT = radiation therapy, SEER = surveillance, epidemiology and end results, SHR = subhazard ratios, SLNB = sentinel lymph node biopsy.

Keywords: axillary staging, breast cancer, nomogram, survival

1. Introduction

Since the description of radical mastectomy, axillary lymph node dissection (ALND) has been the standard axillary staging (AS) method for breast cancer patients.[1] AS is to surgically remove the axillary nodes and assess their status, so as to evaluate the tumor burden and guide the clinical decision-making. As an approach for AS and local control, ALND continued to dominate axillary surgery until the end of the 20th century. ALND carries a high risk of surgical complications, such as upper arm lymphedema, without improving cancer survival, as shown in the NSABP B-04 trial.[2] Sentinel lymph node biopsy (SLNB) was therefore developed for AS. The NSABP B-32 trial demonstrated the safety of SLNB and showed that the regional control, the disease-free survival, and the overall survival were not compromised if ALND was omitted in patients with negative SLNs.[3] Furthermore, studies also showed that the omission of ALND in selected patients with a few positive SLNs is also oncologically sound. The IBCSG-23-01 trial[4] and the ACOSOG Z0011 trial[5] demonstrated that ALND could be omitted in patients with micrometastatic SLNs and 1 to 2 positive SLNs, respectively.

It is now generally believed that the main purpose of axillary surgery for breast cancer is to stage the disease and not to remove all the cancer cells. However, AS only offers therapeutic value for patients with positive nodes.[6] In addition, AS procedures, such as SLNB, can still cause lymphedema or pain in some patients. Patients with small tumors and good biology have a significantly

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reduced chance of having a positive SLN. Bevilacqua et al[7] reported that patients with T1a, T1b, and T1c diseases exhibited a 13.5%, 21.8%, and 35.6% risk of having SLN metastases, respectively. Similarly, Reyal et al[8] reported that 29.6% and 62.6% of patients with T1 and T2 diseases had positive SLNs, respectively. Whether AS can be safely omitted in these patients is unknown.

Both of the SOUND trial[9] (Sentinel node vs Observation after axillary UltraSouND) and the BOOG 2013–08 trial[10] randomized breast cancer patients with clinically negative axilla into SLNB versus observation. Amy Cyr et al initiated a similar study and recently started to recruit patients in the United States (https://clinicaltrials.gov/ct2/show/NCT01821768. 2016). The German INSEMA trial[11] randomized patients into no axillary AS versus SLNB (https://www.clinicaltrials.gov/ct2/show/NCT02466737). For patients with SLNB, those with positive SLNs will be secondly randomized to either observation or completion ALND in cases with <4 positive nodes. Patients with ≥4 positive SLNs should undergo completion ALND. Consistent with the rational of these studies, we hypothesize that surgical AS, whether by SLNB and/or ALND, may not be associated with improved clinical outcomes in selected patients with a small tumor (T1). In this study, we used the surveillance, epidemiology, and end results (SEER) database to investigate the risk factors for long-term clinical outcomes of breast cancer patients with small tumors (≤2 cm). We then developed a nomogram based on these factors to predict the cancer-specific survival (CSS) of these patients with or without AS. The aim of the study was to develop a clinical decision tool that could be used for individualized risk assessment and provide reliable estimation of survival benefit of AS in terms of CSS.

2. Methods

We reported this study based on the STARD statements.[12] The ethical approval from the ethical committee was not necessary as this is an epidemiology study using de-identified data from the SEER registry. We searched for SEER registry data from 18 registries (November 2015 submission, Supplementary File 1, http://links.lww.com/MD/C316). The inclusion and exclusion criteria are listed as follows:

Inclusion criteria included

(1) Female breast cancer patients with pathological diagnosis of malignant disease;
(2) Patients with 0 to 89 axillary nodes examined;
(3) Patients who received breast-conserving surgery, total (simple) mastectomy (breast only) with or without reconstructions, or modified radical mastectomy (may include portion of pectoralis major) with or without reconstructions (Coding detailed in Supplementary File 1, http://links.lww.com/MD/C316);
(4) Diagnosis between 1990 and 2008;
(5) T1mic, T1a, T1b, or T1c patients;
(6) Grade I (well differentiated), grade II (moderately differentiated), grade III (poorly differentiated), or grade IV (undifferentiated; anaplastic) patients.

Exclusion criteria included

(1) Bilateral breast cancer patients;
(2) Patients with previous diagnosis of any malignant tumors;
(3) Patients with unknown laterality, marital status, race, grade, ER or PR status, RT status or follow-up status.

We extracted the following data for each patient: race, age, county type, year of diagnosis, marital status at diagnosis, adjusted AJCC 6th T-stage, tumor size, grade, primary site, histology subtype, estrogen receptor (ER) and progesterone receptor (PR) statuses, radiation therapy (RT), SEER cause-specific death classification, SEER other causes of death classification, and survival month. Patients were categorized into 3 age groups based on their age at diagnosis (<50, 50–69, ≥70 years). Histology was divided into 5 categories (infiltrating ductal carcinoma, lobular carcinoma, infiltrating duct and lobular carcinoma, mucinous adenocarcinoma, and other subtypes). RT was divided into 2 categories (with RT and without RT). Patients with 0 and 1 to 89 axillary lymph nodes (ALNs) examined were classified as the non-AS and AS groups, respectively.

2.1. Statistical analysis

We used the Chi-square test to compare the characteristics of patients with or without AS. The median follow-up was calculated as the median observed survival time of the entire population. CSS was measured as the time from diagnosis to breast cancer related death. Non-CSS was measured as the time from diagnosis to death of any causes other than breast cancer. To study the risk factors for breast cancer death, we used a Kaplan–Meier analysis to estimate the cumulative CSS and non-CSS of patients with different clinicopathological features. To confirm the survival difference of CSS and eliminate the influence of non-CSS as a competing risk, we used a competing-risk analysis (Fine and Gray model)[13] with breast cancer related death and death by causes other than breast cancer (non-CSS events) as the primary endpoint and competing risk events, respectively. In the competing risk analysis, the subhazard ratios (SHRs) and the 95% confidence intervals (95% CIs) were reported.

Patients who were diagnosed in even years (1990, 1992, 1994, etc) and odd years (1991, 1993, 1995, etc) were categorized as training cohort and validation cohort, respectively. In the training cohort, significant variables [not included N-stage, breast surgery, and radiotherapy (RT)] suggested by the competing risk analysis, with an absolute difference of the 10-year CSS ≥2%, were used as predictors for nomogram developments. We used the rms package of R software to develop a nomogram. Interactions between variables were assessed. A final model was selected using a backward step-down process, and the Akaike information criterion was employed as a stopping rule.[14] The nomogram was internally and externally validated in the training and validation cohort, respectively.

To validate the nomogram, we used the Harrell concordance index (C-index)[15] with the 95% CI as the evaluation of the discriminative ability. The C-index ranged between 0.5 and 1.0, with 0.5 indicating a random chance and with 1 indicating perfect discrimination of the model. To assess the accuracy of the nomogram, we used calibration plots to visualize the agreement between the predicted and actual 5-year, 10-year, and 15-year CSSs. For the subgroup analysis, we calculated the corresponding points of each predictor of the nomogram and summed up to a total point for each patient. We used the median total point of the entire study population and stratified patients into high- and low-risk subgroups. We used competing risk analysis to confirm the difference of the clinical outcomes between high- and low-risk subgroups, when patients were stratified by different clinicopathological features.

All *P* values were 2-sided. *P* values of less than .05 were considered statistically significant. The data were obtained using SEER*STAT 8.2.1. The statistical analysis was performed using Stata/MP, version 13.0 (StataCorp LP, College Station, TX) and R.

3. Results

3.1. Clinicopathological features

A total of 232,195 patients were included (Table 1). The median age of this population was 60 years. In total, 23,162 (9.98%), 66,580 (28.7%), and 142,453 (61.4%) patients had T1mic-T1a, T1b, and T1c diseases, respectively. Most of the patients had infiltrating ductal carcinoma (n=179,344, 77.2%). There were 13,844 (6.0%) and 218,351 (94.0%) patients in the non-AS and AS groups, respectively. Patients in the non-AS group tended to be older and more likely to have a smaller sized tumor and lower tumor grade. With a median follow-up of 109 months, the respective 5-year, 10-year, and 15-year CSSs of the study population were 96.3%, 92.3%, and 88.5%, respectively. The 5-year, 10-year, and 15-year non-CSSs were 94.1%, 84.7%, and 73.2%, respectively.

3.2. Predictors of CSS and development of the nomogram

Estimations of the CSS and the non-CSS stratified by patients and tumor characteristics are summarized in Supplementary Table 1, http://links.lww.com/MD/C316. County type and primary site had <2% differences in 10-year CSS and were subsequently not considered as risk factors of CSS. Unadjusted and adjusted competing risk factors suggested that age, marital status, race, T-stage, N-stage, histology, grade, ER, PR, AS, breast surgery, and RT were significant predictors for CSS in the training cohort (Table 2). We used age, race, T-stage, histology, grade, ER, PR, and AS as predictors to develop the nomogram predictive of CSS (Fig. 1).

3.3. Validation of the nomogram

We used the Harrell C-index and calibration plots to assess the discrimination and accuracy of the prediction model. As internal validation, the Harrell C-index of the nomogram for CSS was 0.707 (95% CI 0.702–0.712) in the training cohort, which was higher than that of T-stage (0.589, 95% CI 0.585–0.593), grade (0.648, 95% CI 0.643–0.653), ER (0.589 95% CI 0.584–0.594), and PR (0.591 95% CI 0.585–0.596). As external validation, the Harrell C-index of the nomogram for CSS was 0.704 (95% CI 0.698–0.710) in the validation cohort. Calibration plots (Fig. 2) suggested that the nomogram was well calibrated (predicted probability in agreement with the actual probability) for 5-year, 10-year, and 15-year CSSs, in both of the training and validation cohorts.

The median value of total points of each patient calculated by the nomogram was 20.2. Therefore, we assigned patients into high-risk and low-risk subgroups using the cut-off value of 20 for total points. If the nomogram were accurate, higher-risk group predicted by the nomogram would have increased risk of breast cancer death than the lower-risk group. Competing risk analysis (Supplementary Figure 1 and 2, http://links.lww.com/MD/C316) revealed that patients of the high-risk subgroups had constantly increased risk of breast cancer death than those of the low-risk subgroups, when patients were stratified by tumor stages (T-stage or N-stage), demographical features (age, race), pathological features (grade, ER, PR), and treatment (breast surgery, RT, AS status).

3.4. Survival benefit of AS

We used the nomogram to calculate the predicted CSS for each patient based on whether or not they received AS. The difference of the predicted CSS between these 2 situations was defined as the predicted survival benefit of AS for CSS (ΔCSS). The distribution of the predicted 5-, 10-, and 15-year ΔCSS were similar between the training cohort and the validation cohort (Supplementary Figure 3, http://links.lww.com/MD/C316). In total, AS was predicted to have less than 2% benefit of 5-, 10-, and 15-year CSS in 60.6% (140,599/232,195), 15.5% (36,074/232,195), and 8.6% (20,043/232,195) of the entire study population, respectively.

4. Discussion

In this study, we hypothesized that selected patients with small tumors may not benefit from AS. We used the SEER database to develop a nomogram to predict the CSS of patients with or without AS. The nomogram also provides individualized estimates of potential benefit of AS (See Fig. 1 legend), but further discussions between the surgeon and the patient are required to determine whether to perform the AS. The identification of an optimal cut-off value of the predicted ΔCSS under which AS could exactly be omitted is beyond the scope of this study and can only be investigated through randomized clinical trials. However, in the SOUND trial,[9,16] the margin delta of noninferiority of the 5-year distant disease-free survival (DDFS) was 2.5%. In our study, the nomogram predicted that 60.6% (140,599/232,195) of the study population may have less than 2% benefit of 5-year CSS, suggesting the safety of omitting ALND in these patients. The nomogram also predicted that 15.5% of the study population may have less than 2% benefit of 10-year CSS. These showed the clinical utility of the nomogram. The SOUND trial, Dutch BOOG 2013–08 trial, and German INSEMA trial were all noninferiority design, and therefore required a large number of recruited participants with long-term follow-up, so as to have sufficient events. Therefore, it would be more time-saving if we can use this nomogram, so as we can spare the unnecessary AS much more earlier before the completion of those time-consuming clinical trials.

4.1. Rational of omitting AS

4.1.1. Tumor size. In this study, we only included patients with small-sized tumors (T1-stage) who were expected to have favorable prognosis as the study population.[17–19] Using the SEER database, Hanrahan et al[20] reported that the 10-year CSS and the OS were 96% and 76%, respectively, in patients with T1a and b N0 M0 breast cancer. Vaz-Luis et al[19] showed that the 5-year CSS events were 100%, 99%, 95%, and 95% in T1a and T1b N0 M0 patients classified as HR+/HER2-, HR+/HER2+, HR-/HER2+, and HR-/HER2-, respectively. The long-term outcome is so good in T1a, T1b patients that AS (SLNB and/or ALND) in these patients may not have significant effects on survival. In addition, patients with small tumors, compared with patients with larger tumors, tend to have negative ALNs. Bevilacqua et al[7] reported that patients with T1a, T1b, and T1c diseases exhibited a 13.5%, 21.8%, and 35.6% risk of having

Table 1

Clinicopathological features of study population.

	Training cohort					Validation cohort				
	No AS N = 7261		AS N = 117,079			No AS N = 6583		AS N = 101,272		
	N	%	N	%	*P*	N	%	N	%	*P*
Age group, y										
<50	539	7.42	27,786	23.73	<.001	520	7.90	24,135	23.83	<0.001
50–69	1855	25.55	59,905	51.17		1665	25.29	51,475	50.83	
≥70	4867	67.03	29,388	25.10		4398	66.81	25,662	25.34	
Year of diagnosis										
1990–1999	2378	32.75	26,206	22.38	<.001	2,759	41.91	28,599	28.24	<.001
2000–2007	4883	67.25	90,873	77.62		3824	58.09	72,673	71.76	
County type 2003										
Metropolitan	6457	88.93	104,377	89.15	.008	5868	89.14	89,781	88.65	.012
Non-metropolitan	705	9.71	11,543	9.86		607	9.22	10,152	10.02	
Unknown	99	1.36	1159	0.99		108	1.64	1339	1.32	
Race										
White	6348	87.43	99,607	85.08	<.001	5731	87.06	86,420	85.33	<.001
African–American	544	7.49	8431	7.20		458	6.96	6982	6.89	
Others	369	5.08	9041	7.72		394	5.99	7870	7.77	
Marital status										
Married	3068	42.25	73,200	62.52	<.001	2831	43.00	63,525	62.73	<.001
Single	4193	57.75	43,879	37.48		3752	57.00	37,747	37.27	
Laterality										
Left	3669	50.53	59,258	50.61	.89	3328	50.55	51,490	50.84	.65
Right	3592	49.47	57,821	49.39		3255	49.45	49,782	49.16	
Primary site										
Nipple/Central portion	467	6.43	6415	5.48	<.001	429	6.52	5545	5.48	<.001
UIQ	816	11.24	13,932	11.90		793	12.05	11,990	11.84	
LIQ	548	7.55	7305	6.24		427	6.49	6443	6.36	
UOQ	2579	35.52	44,160	37.72		2318	35.21	38,209	37.73	
LOQ	443	6.10	8660	7.40		445	6.76	7365	7.27	
Overlapping/Unknown	2408	33.16	36,607	31.27		2171	32.98	31,720	31.32	
T-Stage										
T1mic-T1a	1270	17.49	11,243	9.60	<.001	1,119	17.00	9530	9.41	<.001
T1b	2393	32.96	33,133	28.30		2256	34.27	28,798	28.44	
T1c	3598	49.55	72,703	62.10		3208	48.73	62,944	62.15	
N-Stage										
N0			90,198	77.04	N/A		N/A	77,771	76.79	N/A
N1		N/A	21,470	18.34				18,930	18.69	
N2			3938	3.36				3290	3.25	
N3			1473	1.26				1281	1.26	
Nx			0	0				0	0	
Histology										
Infiltrating ductal carcinoma	5319	73.25	90,888	77.63	<.001	4824	73.28	78,313	77.33	<.001
Lobular carcinoma	363	5.00	5687	4.86		302	4.59	4962	4.90	
Infiltrating duct and lobular carcinoma	397	5.47	8879	7.58		382	5.80	7552	7.46	
Mucinous adenocarcinoma	314	4.32	2359	2.01		292	4.44	2052	2.03	
Others	868	11.95	9266	7.91		783	11.89	8393	8.29	
Grade										
Well differentiated; Grade I	2542	35.01	30,462	26.02	<.001	2378	36.12	26,297	25.97	<.001
Moderately differentiated; Grade II	3316	45.67	53,175	45.42		2911	44.22	45,873	45.30	
Poorly differentiated; Grade III	1323	18.22	31,804	27.16		1225	18.61	27,570	27.22	
Undifferentiated; anaplastic; Grade IV	80	1.10	1638	1.40		69	1.05	1532	1.51	
ER										
Negative	944	13.00	20,388	17.41	<.001	788	11.97	17,842	17.62	<.001
Positive	6317	87.00	96,691	82.59		5795	88.03	83,430	82.38	
PR										
Negative	1845	25.41	32,283	27.57	<.001	1612	24.49	28,214	27.86	<.001
Positive	5416	74.59	84,796	72.43		4971	75.51	73,058	72.14	
Breast surgery										
Breast-conserving surgery	6231	85.81	77,756	66.41	<.001	5689	86.42	67,276	66.43	<.001
Mastectomy	1030	14.19	39,323	33.59		894	13.58	33,996	33.57	
Radiation therapy										
No	4074	56.11	48,283	41.24	<.001	3610	54.84	41,388	40.87	<.001
Yes	3187	43.89	68,796	58.76		2973	45.16	59,884	59.13	

ALND = axillary lymph node biopsy, AS = axillary staging; ER = estrogen receptor; LIQ = lower-inner quadrant; LOQ = lower-outer quadrant; PR = progesterone receptor; SLNB = sentinel lymph node biopsy; UIQ = upper-inner quadrant; UOQ = upper-outer quadrant.

Table 2

Competing risk analysis of risk factors for breast cancer death.

Item	Unadjusted		Adjusted	
	SHR (95% CI)	*P*	SHR (95% CI)	*P*
Age, y				
≤50	1.00		1.00	
50–69	0.76 (0.72–0.80)	<.001	0.93 (0.89–0.98)	.01
≥70	0.98 (0.93–01.03)	.465	1.25 (1.18–1.33)	<.001
Race				
White	1.00		1.00	
African–American	1.67 (1.57–1.79)	<.001	1.29 (1.20–1.38)	<.001
Others	0.88 (0.81–0.96)	.002	0.85 (0.79–0.93)	<.001
Marital status				
Married	1.00		1.00	
Divorced/Separated/Single/Widowed	1.24 (1.19–1.29)	<.001	1.16 (1.11–1.21)	<.001
T-Stage				
T1mic-T1a	1.00		1.00	
T1b	1.30 (1.17–1.44)	<.001	1.30 (1.17–1.45)	<.001
T1c	2.60 (2.36–2.86)	<.001	1.90 (1.72–2.09)	<.001
N-Stage				
N0	1.00		1.00	
N1	2.05 (2.96–2.15)	<0.001	1.87 (1.78–1.96)	<.001
N2	4.73 (4.41–5.07)	<.001	3.86 (3.59–4.16)	<.001
N3	8.68 (7.94–9.49)	<.001	6.50 (5.90–7.15)	<.001
Histology				
Infiltrating ductal carcinoma	1.00		1.00	
Lobular carcinoma	0.81 (0.73–0.90)	<.001	0.94 (0.85–1.04)	.26
Infiltrating duct and lobular carcinoma	0.84 (0.78–0.91)	<.001	0.92 (0.85–1.00)	.05
Mucinous adenocarcinoma	0.46 (0.38–0.56)	<.001	0.78 (0.64–0.96)	.02
Others	0.77 (0.71–0.84)	<.001	0.87 (0.80–0.95)	.00
Grade				
Well differentiated; Grade I	1.00		1.00	
Moderately differentiated; Grade II	2.20 (2.05–2.37)	<.001	1.76 (1.64–1.89)	<.001
Poorly differentiated; Grade III	4.33 (4.03–4.65)	<.001	2.59 (2.41–2.79)	<.001
Undifferentiated; anaplastic; Grade IV	4.00 (3.44–4.66)	<.001	2.64 (2.28–3.06)	<.001
ER				
Negative	1.00		1.00	
Positive	0.46 (0.44–0.48)	<.001	0.76 (0.71–0.81)	<.001
PR				
Negative	1.00		1.00	
Positive	0.53 (0.51–0.56)	<.001	0.81 (0.76–0.85)	<.001
Axillary staging				
No	1.00		1.00	
Yes	0.80 (0.74–0.87)	<.001	0.58 (0.54–0.64)	<.001
Breast surgery				
Breast-conserving surgery	1.00		1.00	
Mastectomy	1.49 (1.43–1.56)	<.001	1.10 (1.04–1.17)	<0.001
Radiation therapy				
No	1.00		1.00	
Yes	0.75 (0.72–0.79)	<.001	0.87 (0.82–0.92)	<.001

Ax = axillary treatment; CI = confidence interval; ER = estrogen receptor; LIQ = lower-inner quadrant; LOQ = lower-outer quadrant; PR = progesterone receptor; SHR = subhazard ratio; UIQ = upper-inner quadrant; UOQ = upper-outer quadrant.

SLN metastases, respectively. In addition, positive ALNs may not always compromise clinical outcomes in selected patients. In the Z0011 trial,[5] where patients with 1 to 2 positive SLNs after BCS were randomized into ALND and observation, 27% of the patients in the observation group had positive ALNs untreated in axilla. The local control and disease-free survival rates were similar between the ALND and observation group. Similarly, the AMAROS trial[21] showed that axillary RT had similar axillary control as ALND in T1–2 patients with clinically negative axilla, even when 33% of the patients with positive ALNs were untreated. Taken together, these data suggest that selected patients with small tumors can be spared of AS.

4.1.2. Age. Age is also a critical determinant for the necessities of AS. ALND was typically spared in elderly patients who are more likely to have comorbidities and reduced life expectancy. Chung et al[22] reported that among 140 elderly patients (≥70 years old) with clinically negative axilla who received BCS without SLNB, only 1 patient had axillary relapse, and 4 patients died of breast cancer after a median follow-up of 4.5 years. Similar findings

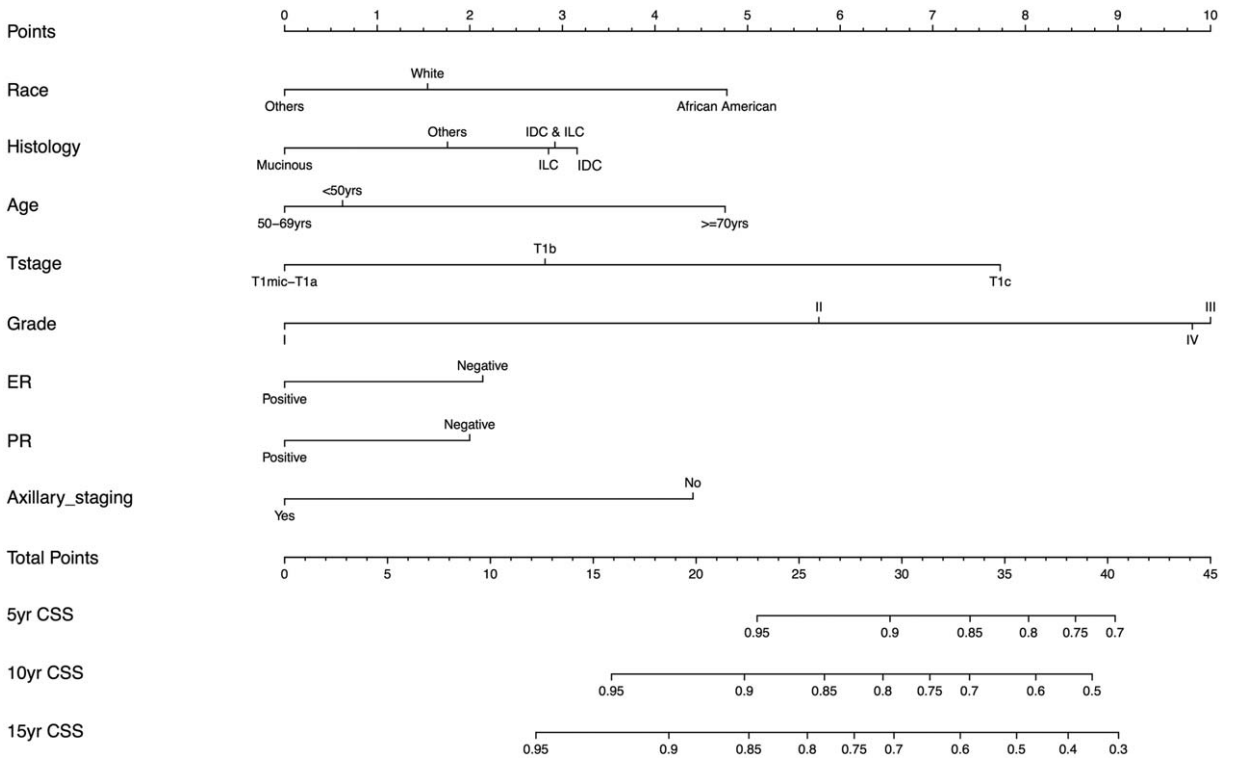

Figure 1. Nomogram to predict the 5-year, 10-year, and 15-year CSS. This nomogram can also estimate the survival benefit of AS on CSS. For example, a 70-year-old (4.75 point) white woman (1.5 point) with T1c (7.75 points) IDC (3.1 points) of the breast and pathologically confirmed grade III (10 points), ER- (2.1 points) and PR- (1.9 points) disease who underwent AS (0 points) had 31.1 total points and an estimated 10-year CSS of 75%. If the same patient had not received AS (4.3 points), she would have 35.4 total points with an estimated 10-year CSS of approximately 63%. Hence, the predicted benefit of 10-year CSS (10-year ΔCSS) by AS for this patient is 12%. On the contrary, an African–American (4.75 points) woman at 60 years of age (0 points) with pathologically confirmed T1b (2.75 points) mucinous carcinoma (0 points) and grade II (5.75 points), ER+ (0 points), and PR+ (0 points) disease would have 13.3 and 17.6 total points if she did or did not receive AS, respectively. The predicted benefit of 15-year CSS was less than 5% for the second patient.

were also reported in the CALGB9343 trial,[23] where axillary relapse occurred in 0% (0/241) and 1.5% (6/395) of elderly breast cancer patients with and without ALND, respectively. Several randomized controlled trials (RCTs)[24–26] confirmed these findings (Supplementary Table 2, http://links.lww.com/MD/C316).

4.1.3. Influence on adjuvant therapy. In the AMAROS trial,[27] the investigators reported no significant difference in the administration of adjuvant systemic therapy between the ALND and RT groups, indicating that the absence of knowledge regarding the extent of nodal involvement (N3 vs N2 vs N1) appears to have no major impact on the clinical decision-making of adjuvant therapy in selected patients with positive SLNs. However, it is possible that positive versus negative ALNs (N1–3 vs N0) may lead to different recommendations of adjuvant therapies. We believe that with the improving quality of different breast imaging technique today, the axillary status could be easily predicted preoperatively. For example, improved magnetic resonance imaging[28–30] and positron emission tomography/computed tomography[31–33] techniques significantly increase the prediction accuracy of ALN status in breast cancer patients when

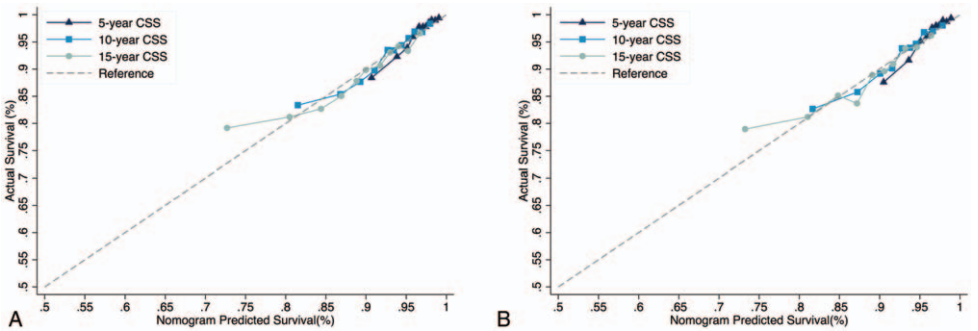

Figure 2. Calibration plots to assess the accuracy of the nomogram for prediction of 5-year, 10-year, and 15-year CSS, in (A) training and (B) validation cohort.

used together with ultrasound and/or mammography. Preoperative ultrasound-guided core-needle biopsy is another effective approach to predict the ALNs status.[34] Thus, omitting AS might not significantly influence clinical decision-making regarding adjuvant therapies.

5. Limitations

The clinical status of the ALNs was unavailable in the SEER database. Although our study population (T1 patients) had a very low risk of positive ALNs (T1a: 8.5%; T1b: 13.0%), and therefore much lower risk of clinically positive axilla, the influence of this limitation was unclear.

The lack of local recurrence and/or distant metastasis in the SEER database is one of the limitations. The meta-analysis by EBCTCG[35] demonstrated that an approximately 20% improvement of the 5-year local control rate should be achieved to improve CSS by 5% over the next 15 years. In the trials with only a 1% reduction of breast cancer related death after 15 years, the corresponding improvement of the 5-year local control rate was 1%. In our study, AS had less than 2% improvement of the 15-year CSS in 8.6% of the study population, suggesting that AS did not reduce the risk of local/distant relapse in these patients.

HER2 status was unavailable in the SEER database. However, for patients with T1a, b tumors, the necessity of using trastuzumab is uncertain, and this population of breast cancer patients was not studied in the current RCTs.[21,36–38] It is unclear how this limitation would impact our study. In addition, information regarding neoadjuvant chemotherapy was not clear in our study. Given that all of the included patients had T1 breast cancer, the proportion of neoadjuvant chemotherapy would not be high. Furthermore, information regarding the systemic therapy was also unknown.

A recent study[39] compared the effects of cancer treatment inferred by randomized trials (EBCTCG meta-analysis) and observational data (SEER database) and showed that nonrandomized comparisons are likely to provide misleading estimates of treatment effects. That study showed that the RT treatment effect is overestimated in observational data compared with RCTs. This notion is reasonable as "treatment by indication" effects typically cause biases that overestimate the therapeutic effects. For example, patients who did not receive RT may have more comorbidities and an increased risk of death compared with those with RT. However, we suggest that this phenomenon may not significantly influence our study, given that our major finding was that there no significant differences in CSS between the AS and non-AS groups in selected patients.

We need another population to externally validate this nomogram in the future.

6. Conclusion

In this study, we developed a nomogram that can be predictive of the survival benefit of AS in breast cancer patients with small tumors. This nomogram will be informative for individualized risk assessment and surgical decision-making in clinical practices.

Author contributions

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Writing – original draft: Yuxia Chen, Yuanqi Zhang, Liling Zhu, Kai Chen, Xiang Chen.
Writing – review & editing: Yuxia Chen, Weixiong Yang, Xiaoping Li, Kai Chen, Xiang Chen.

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