Received: 6 October 2022 | Revised: 30 January 2023 | Accepted: 1 February 2023

DOI: 10.1002/cncr.34708

ORIGINAL ARTICLE

Is repeat sentinel lymph node biopsy possible for surgical axillary staging among patients with ipsilateral breast tumor recurrence?

Xunxi Lu MD[1] | Mengting He MD[2] | Luoting Yu PhD[3] | Zongchao Gou MD[2,3]

[1]Department of Pathology, West China Hospital, West China School of Medicine, Sichuan University, Chengdu, China

[2]Department of Breast Surgery, West China Hospital, West China School of Medicine, Sichuan University, Chengdu, China

[3]State Key Laboratory of Biotherapy and Cancer Center, West China Hospital, West China School of Medicine, Sichuan University, Chengdu, China

Correspondence

Zongchao Gou, Department of Breast Surgery, West China Hospital, West China School of Medicine, Sichuan University, Chengdu, China.
Email: fdchao@126.com

Funding information

Natural Science Foundation of Sichuan Province, Grant/Award Number: 2022NSFSC1385; West China Hospital, Grant/Award Number: 2021HXBH080; West China Hospital, Sichuan University

Abstract

Background: There is a lack of studies assessing the survival of repeat sentinel lymph node biopsy (rSLNB) versus axillary lymph node dissection (ALND) for surgical axillary staging among patients with ipsilateral breast tumor recurrence (IBTR).

Methods: We retrospectively identified patients with IBTR from the Surveillance, Epidemiology, and End Results database from 2000 to 2017. The primary outcome was overall survival (OS) between the rSLNB and ALND groups.

Results: Of the 2141 women with IBTR after lumpectomy and SLNB, 524 did not receive surgical axillary staging (nonsurgery group) and 1617 patients who did undergo axilla surgery received either rSLNB or ALND as axillary staging (1268 with rSLNB and 349 with ALND). The 10-year OS rates were 61.9% for the nonsurgery and 73.8% for axilla surgery groups (p = .001). In the 1:1 matched cohorts, the 10-year OS rates were 61.4% for the nonsurgery and 69.1% for axilla surgery groups (p = .072). After adjusting for other factors, axillary surgery treatment of IBTR was an independent favorable factor for OS (hazard ratio [HR], 0.71; 95% CI, 0.56–0.90; p = .004). Within the axilla surgery group, rSLNB presented a comparable 10-year OS to the ALND cohort (log-rank test p = .054). Multivariate Cox analysis, as well as subgroup analysis, showed that rSLNB had a similar benefit to ALND (10-year OS; HR, 1.18; 95% CI, 0.88–1.58; p = .268).

Conclusions: The results of this cohort study suggested that receiving surgical axillary staging was associated with better survival of IBTR patients, and rSLNB had a similar long-term survival outcome as ALND. rSLNB might be considered for surgical axillary staging among patients with IBTR after lumpectomy and initial SLNB.

KEYWORDS

axillary surgery, breast cancer-specific survival, ipsilateral breast tumor recurrence, overall survival, repeat sentinel lymph node biopsy

The first and last authors contributed equally to this work.

INTRODUCTION

Breast cancer has become the most common malignancy worldwide.[1] Axillary lymph node dissection (ALND) is an effective treatment for maintaining regional lymph node control, but it is correlated with complications, such as axillary web syndrome, lymphedema, and decreased upper extremity mobility.[2] The sentinel lymph node, by definition, is the first node or nodes that directly drains the lymph from the breast carcinoma area. Sentinel lymph node biopsy (SLNB) has been gradually performed on patients with early-stage breast cancer since 1994 and has been demonstrated as the standard staging method for patients with breast cancer and clinically negative axillae.[3,4] The Z0011 trial further validated the safety of SLNB in patients with one to two positive sentinel lymph nodes; therefore, SLNB was applied in more cases than ALND.[5,6]

In recent decades, lumpectomy plus radiation and SLNB have been used as surgical approaches for those with primary early-stage breast cancer.[7,8] Nevertheless, approximately 14.3% to 20% will develop local recurrences that necessitate reoperation.[9,10] For patients with early breast cancer who received (neo)adjuvant chemotherapy, the local recurrence rates were 15.9% (receiving adjuvant chemotherapy) and 21.4% (receiving neoadjuvant chemotherapy) within 15 years of lumpectomy.[11] Updated National Comprehensive Cancer Network guidelines suggested that, for patients with local recurrence after lumpectomy and SLNB, repeat SLNB (rSLNB) may be an option.[12] For patients with ipsilateral breast tumor recurrences (IBTR) after initial lumpectomy and SLNB, concerns were reported that initial breast or axillary surgery can temporarily or partially disrupt the lymphatic flow, making recognition of the sentinel lymph node more difficult.[13] Several studies have supported the hypothesis that the breast tumor area drains through several common afferent lymphatic channels to the sentinel lymph nodes regardless of the tumor location and that an alternative pathway to the sentinel lymph nodes may be exploited successfully for the SLNB tracer if one or more trunks are disrupted.[14,15]

ALND is still commonly conducted as the standard treatment for IBTR after earlier lumpectomy and negative SLNB,[16] although more than one-half of patients with IBTR have no axillary metastases.[17,18] Port et al. reported that either previous partial dissection or lymph node biopsy did not affect the success rate of rSLNB.[19] Similarly, Intra et al. reported that the success rate for rSLNB was 92.5% within a 212 IBTR-patient cohort.[20] However, controversy still exists regarding whether rSLNB is safe and efficient. Confronted with the clinically arguable question, the panel of the 2021 St Gallen Consensus Conference attempted for the first time to address the challenges in IBTR treatment. The 74 panelists narrowly supported rSLNB in the case of IBTR after previous treatment with lumpectomy and SLNB (35% for SLN with frozen section, 33% SLN without frozen section, 12% ALND, 20% no axillary surgery).[21]

To assess the necessity and long-term survival of rSLNB for axillary staging among patients with IBTR, we extracted data from the population-based Surveillance, Epidemiology, and End Results (SEER) database and obtained the nonsurgery group (IBTR without surgical axillary staging) and axilla surgery group (IBTR with surgical axillary staging). Within the axilla surgery group, IBTR received either rSLNB or ALND as axillary staging. The 10-year overall survival (OS) and breast cancer–specific survival were evaluated between the rSLNB and ALND groups, as well as between the nonsurgery and axilla surgery groups.

MATERIALS AND METHODS

Database

We used the SEER database (November 2021 submission), a National Cancer Institute–supported program. The data were obtained from 17 population-based registries with SEER*Stat software, version 8.4.0 (http://seer.cancer.gov/about/). SEER 17 includes data from Alaska, Connecticut, Atlanta, Greater Georgia, Rural Georgia, San Francisco, San Jose, California, Hawaii, Iowa, Kentucky, Los Angeles, Louisiana, New Mexico, New Jersey, Seattle, and Utah. The study was approved by the ethics board of West China Hospital, Sichuan University, and deemed exempt from ethical approval. The data released by the SEER database were publicly available and deidentified and did not require the patient's informed consent.

Study population

The SEER database did not clearly define the type of axillary surgery. Previous studies have shown that SLNB usually involves one to three axillary lymph nodes (ALNs) and does not surpass five ALNs,[22,23] and a standard ALND should contain at least six lymph nodes.[23,24] Therefore, we in practice specified the type of axillary surgery according to the number of examined ALNs, as described by previous studies[25]: (1) patients with zero examined ALNs did not receive any axillary surgery; (2) patients with one to five examined ALNs underwent SLNB; and (3) patients with ≥6 examined ALNs underwent ALND. Namely, we used five ALNs as the cutoff value between SLNB and ALND. Consistent with the classification of SLNB, rSLNB was also categorized as a removed ALN number between 1 and 5 in IBTR axillary surgery.

The selection of the study cohort was described as follows, and the flow diagram is presented in Figure 1. Our study derived a cohort of female patients with breast cancer diagnosed from 2000 to 2017. The inclusion criteria were as follows: aged greater than 18 years; unilaterality breast cancer; known T stage, N0 stage; breast cancer as the first cancer diagnosis; receiving lumpectomy and SLNB in the initial treatment; histologically confirmed IBTR; and known ALN surgery of IBTR. Exclusion criteria included IBTR in situ disease, metastatic disease, skin/muscle infiltration, and ALN metastasis. Between January 1, 2000, and December 31, 2017, 998,361 patients who were older than 18 years were diagnosed with breast cancer. We excluded patients after 2017 to ensure a follow-up time of at least 24 months. Of these patients, 243,747 with unilateral invasive

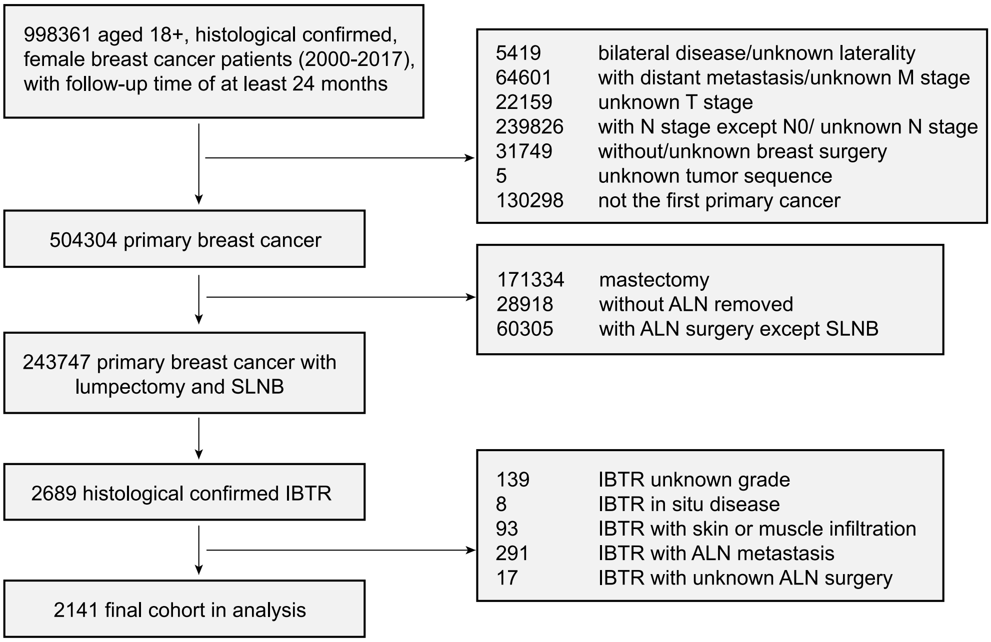

FIGURE 1 Flow diagram for selection of the study cohort. A total of 2141 patients were enrolled in this study.

breast cancer who underwent lumpectomy and initial SLNB were included. After matching patient-unique identification numbers, patients with IBTR could be extracted as described in the articles.[26,27] Then, 2689 patients with IBTR after primary lumpectomy and SLNB were identified. Patients with IBTR were excluded if they had in situ disease or if they had an unknown grade, skin, or chest wall infiltration, ALN metastasis, or unknown ALN surgery. Finally, we enrolled 2141 patients for further research, including 524 patients (nonsurgery group) who did not receive any axillary surgery (24.47%) and 1617 for the axilla surgery group (75.53%, including 1268 patients with rSLNB and 349 patients with ALND).

Assembly of key variables

Using the case listing sessions within SEER*Stat software, we obtained a data table including individual cancer entries and patient characteristics (year of diagnosis, age at the diagnosis of IBTR, race, patient-unique identification number, tumor sequence number, first malignant primary indicator), initial and recurrent tumor characteristics (laterality, International Classification of Diseases for Oncology, third edition histology, histological grade, estrogen receptor (ER), progesterone receptor (PR), adjusted American Joint Committee on Cancer tumor node metastasis staging classification, human epidermal growth factor receptor 2), treatment data (breast surgery type, number of surgically removed lymph nodes, number of pathological positive lymph nodes, chemotherapy, radiation therapy) and survival information (vital status, cause-specific death classification, and survival month). Patient ER and PR information has been recorded in the SEER database since 1990. The ER and PR data were combined as the hormone receptor (HoR) status. The National Comprehensive Cancer Network guidelines and some studies have suggested that breast cancers with at least 1% cells positive for ER staining should be considered ER positive. Therefore, patients with borderline HoR are defined as HoR positive. The IBTR interval time was measured from the year of diagnosis of the initial breast cancer to the year of diagnosis of IBTR.

Outcome measure

The primary outcome was S between the rSLNB and ALND cohorts and was defined as the survival time from the diagnosis of IBTR to the date of death from any cause. The second outcome was OS between nonsurgery and axilla surgery cohorts. Breast cancer–specific survival (BCSS) was also evaluated between cohorts and was defined as the survival time from the diagnosis of IBTR to the date of death caused by breast cancer. The main object of our study was the survival comparison between the rSLNB and ALND groups.

Sensitivity analysis

Sensitivity analyses were performed to assess the possibility of unintentional bias from our practical definitions of SLNB and ALND. In the IBTR treatment, rSLNB was redefined as one, two, three, four, or five axillary lymph nodes removed, and ALND was redefined as >5 or >9 axillary lymph nodes removed. Multivariate Cox proportional hazards analysis (including the factors significant in the univariate analysis) was used to evaluate whether the criteria of rSLNB/ALND would make a difference in the 10-year OS survival analysis between the rSLNB and ALND groups.

Statistical analysis

The demographic and clinicopathological variables were compared across two groups using the Pearson χ^2 test or Fisher exact test, if appropriate. Kaplan–Meier curves and log-rank tests were generated to measure differences in the survival analyses. Ten-year univariate and multivariate Cox proportional hazards models were applied to estimate the factors associated with OS and BCSS. In addition, a 1:1 paired match, generated by caliper matching without replacement, was conducted to balance the biased baseline. Subgroup analyses represented the hazard ratios (HRs) of rSLNB versus ALND in the specific subgroups. All statistical analyses were implemented using Stata statistical software, version 14.0 (StataCorp, College Station, TX, USA). Two-sided $p < 0.05$ was considered significant.

RESULTS

Patient description and the 1:1 matched cohort

We summarized the baseline IBTR characteristics of all 2141 patients with at least a 2-year follow-up in Table 1 (initial tumor characteristics in Table S1). The median follow-up time from the initial tumor was 164 months. The subsequent survival data of patients were followed from the IBTR onward. The median follow-up time from IBTR was more than 5 years (61 months). There were 524 patients in the nonsurgery group who did not receive any axillary surgery in IBTR treatment and 1617 patients in the axilla surgery group who received either rSLNB (1268 patients) or ALND (349 patients) in IBTR treatment.

Compared with the nonsurgery patients, the axilla surgery patients were more likely to be younger (aged older than 65 years: 46.2% vs 56.1%, $p < .001$), have earlier recurrence (18.1% vs 8.8% for interval times within 2 years, $p < .001$), have more mastectomy (73.5% vs 56.9%, $p < .001$), have more radiation therapy (14.9% vs 10.3%, $p = .008$), and have more chemotherapy (25.7% vs 19.3%, $p = .003$). Within the axilla surgery group, patients with rSLNB had more recurrent tumors in the same quadrant (30.9% vs 24.1%, $p = .013$), better histological grade (71.9% vs 56.2% for well-differentiated tumors, $p < .001$), a higher HoR + rate (HoR+: 78.8% vs 70.5%, $p = .001$), and smaller recurrent tumors (81.5% vs 73.4% for T1, $p = .003$) than those in the ALND group. In addition, the patients in the rSLNB cohort were also associated with earlier recurrence (21.1% vs 6.9% for interval times within 2 years, $p < 0.001$), less mastectomy (68.3% vs 92.6%, $p < 0.001$), more radiation therapy (18.4% vs 2.3%, $p < .001$) and less chemotherapy (23.7% vs 33.0%, $p < .001$) than patients with ALND.

Furthermore, a 1:1 matched case–control analysis was performed by caliper matching without replacement. Five and 11 factors of unbalanced baseline were included in the calipmatch model, between the nonsurgery group and axilla surgery group or between the rSLNB group and ALND group, respectively. After the matching procedure, 934 patients (467 patients in the nonsurgery group and 467 patients in axilla surgery group) and 514 patients (257 patients in the rSLNB group and 257 patients in the ALND group) were obtained with known HoR status. Imbalance across the paired cohorts was avoided for all characteristics (Table S2).

Survival analysis

Kaplan–Meier plots were used to assess the OS and BCSS between the groups (OS in Figure 2; BCSS in Figure S1). Patients in the nonsurgery group had a worse 10-year OS than those in the axilla surgery group (61.9% vs 73.8%; log-rank test $p = .001$). Within the axilla surgery group, rSLNB presented a comparable 10-year OS to the ALND cohort (76.0% vs 67.6%; log-rank test $p = .054$). Similar to the entire cohort, the survival analysis of the 1:1 paired cohorts showed that the axilla surgery group presented a trend toward better OS outcomes (61.4% vs 69.1%; log-rank test $p = .072$). There was no significant difference in the 10-year OS between the matched rSLNB and ALND groups (78.2% vs 74.5%, log-rank test $p = .927$).

There was no significant difference in 10-year BCSS between the nonsurgery and axilla surgery groups (84.3% vs 90.9%; log-rank test $p = .129$). Within the axilla surgery group, rSLNB presented a better 10-year BCSS than ALND (92.2% vs 86.7%; log-rank test $p = .008$). Furthermore, the survival analysis of the 1:1 paired cohorts showed that the axilla surgery group presented better BCSS outcomes (93.7% vs 85.1%; log-rank test $p = .037$), and the rSLNB and ALND groups had similar 10-year BCSS rates (92.1% vs 87.8%, log-rank test $p = .261$).

Multivariate analysis

Then, univariate and multivariate Cox proportional hazards models were conducted to balance the effect of other factors. All the variables in Table 1 were included in the univariate analysis regarding OS or BCSS (Tables S3 and S4), and the features that were significant in the univariate analysis were included in the subsequent multivariate analysis (Table 2, Table S5), such as age, tumor T stage and HoR status. After adjusting for other factors, axilla surgery treatment of IBTR was confirmed as an independent favorable factor over the nonsurgery group in 10-year OS (HR, 0.71; 95% CI, 0.56–0.90; $p = .004$) and 10-year BCSS (HR, 0.68; 95% CI, 0.47–0.98; $p = .041$). Univariate analysis showed that rSLNB seemed to have a trend toward favorable survival compared with ALND (10-year OS HR, 1.32; 95% CI, 0.99–1.76; $p = .055$). Interestingly, after balancing the effect of biased baseline, rSLNB presented no statistical significance for survival benefit over ALND regardless of OS or BCSS (10-year OS HR, 1.18; 95% CI, 0.88-1.58; $p = = .268$; 10-year BCSS HR, 1.27; 95% CI, 0.82–1.97; $p = .278$).

Subgroup analysis

To clarify the potential effect of rSLNB compared with ALND in IBTR treatment, we repeated the previous multivariable Cox regression

TABLE 1 Baseline characteristics of 2141 patients diagnosed with IBTR from the SEER database 2000–2017.

Characteristics	Total (*n* = 2141) No. (%)	Nonsurgery (*n* = 524) No. (%)	Axilla surgery (*n* = 1617) No. (%)	*p*	rSLNB (*n* = 1268) No. (%)	ALND (*n* = 349) No. (%)	*p*
Year				.348			.005
2000–2009	389 (18.17)	88 (16.79)	301 (18.61)		218 (17.19)	83 (23.78)	
2010–2017	1752 (81.83)	436 (83.21)	1316 (81.39)		1050 (82.81)	266 (76.22)	
Age, years				<.001			.233
≤50	287 (13.40)	62 (11.83)	225 (13.91)		179 (14.12)	46 (13.18)	
51–65	813 (37.97)	168 (32.06)	645 (39.89)		492 (38.80)	153 (43.84)	
≥66	1041 (48.62)	294 (56.11)	747 (46.20)		597 (47.08)	150 (42.98)	
Race				.548			.039
White	1774 (82.86)	440 (83.97)	1334 (82.50)		1062 (83.75)	272 (77.94)	
Black	209 (9.76)	51 (9.73)	158 (9.77)		116 (9.15)	42 (12.03)	
Others	158 (7.38)	33 (6.30)	125 (7.73)		90 (7.10)	35 (10.03)	
Laterality				.293			.239
Left	1101 (51.42)	259 (49.53)	842 (52.07)		670 (52.84)	172 (49.28)	
Right	1040 (48.58)	265 (50.57)	775 (47.93)		598 (47.16)	177 (50.72)	
IBTR interval time				<.001			<.001
Within 2 years	338 (15.79)	46 (8.78)	292 (18.06)		268 (21.14)	24 (6.88)	
More than 2 years	1803 (84.21)	478 (91.22)	1325 (81.94)		1000 (78.86)	325 (93.12)	
IBTR subregion				.267			.013
Same quadrant	617 (28.82)	141 (26.91)	476 (29.44)		392 (30.91)	84 (24.07)	
Different quadrant	1524 (71.18)	383 (73.09)	1141 (70.56)		876 (69.09)	265 (75.93)	
Histology				.508			<.001
IDC	1487 (69.45)	370 (70.61)	1117 (69.08)		847 (66.80)	270 (77.36)	
ILC and others	654 (30.55)	154 (29.39)	500 (30.92)		421 (33.20)	79 (22.64)	
Grade				.133			<.001
1, 2	1484 (69.31)	377 (71.95)	1107 (68.46)		911 (71.85)	196 (56.16)	
3, 4	657 (30.69)	147 (28.05)	510 (31.54)		357 (28.15)	153 (43.84)	
T				.088			.003
T1	1729 (80.76)	440 (83.97)	1289 (79.72)		1033 (81.47)	256 (73.35)	
T2	374 (17.47)	75 (14.31)	299 (18.49)		216 (17.03)	83 (23.78)	
T3	38 (1.77)	9 (1.72)	29 (1.79)		19 (1.50)	10 (2.87)	
N							
N0	2141 (100)	524 (100)	1617 (100)		1268 (100)	349 (100)	
HoR				.586			.001
Negative	420 (19.62)	95 (18.13)	325 (20.10)		231 (18.22)	94 (26.93)	
Positive	1657 (77.39)	412 (78.63)	1245 (76.99)		999 (78.79)	246 (70.49)	
Unknown	64 (2.99)	17 (3.24)	47 (2.91)		38 (3.00)	9 (2.58)	
HER2				.182			.095
Negative	1461 (68.24)	374 (71.37)	1087 (67.22)		868 (68.45)	219 (62.75)	
Positive	193 (9.01)	40 (7.63)	153 (9.46)		119 (9.38)	34 (9.74)	
Unknown	487 (22.75)	110 (20.99)	377 (23.31)		281 (22.16)	96 (27.51)	

(Continues)

TABLE 1 (Continued)

Characteristics	Total (n = 2141) No. (%)	Nonsurgery (n = 524) No. (%)	Axilla surgery (n = 1617) No. (%)	*p*	rSLNB (n = 1268) No. (%)	ALND (n = 349) No. (%)	*p*
Breast surgery				<.001			<.001
Lumpectomy	654 (30.55)	226 (43.13)	428 (26.47)		402 (31.70)	26 (7.45)	
Mastectomy	1487 (69.45)	298 (56.87)	1189 (73.53)		866 (68.30)	323 (92.55)	
Radiation				.008			<.001
Yes	295 (13.78)	54 (10.31)	241 (14.90)		233 (18.38)	8 (2.29)	
No/unknown	1846 (86.22)	470 (89.69)	1376 (85.10)		1035 (81.62)	314 (97.71)	
Chemotherapy				.003			<.001
Yes	516 (24.10)	101 (19.27)	415 (25.66)		300 (23.66)	115 (32.95)	
No/unknown	1625 (75.90)	423 (80.73)	1202 (74.34)		968 (76.34)	234 (67.05)	

Abbreviations: ALND, axillary lymph node dissection; HoR, hormone receptor; IBTR, ipsilateral breast tumor recurrence; IDC, invasive lobular carcinoma; ILC, invasive ductal carcinoma; rSLNB, repeat sentinel lymph node biopsy; SEER, Surveillance, Epidemiology, and End Results.

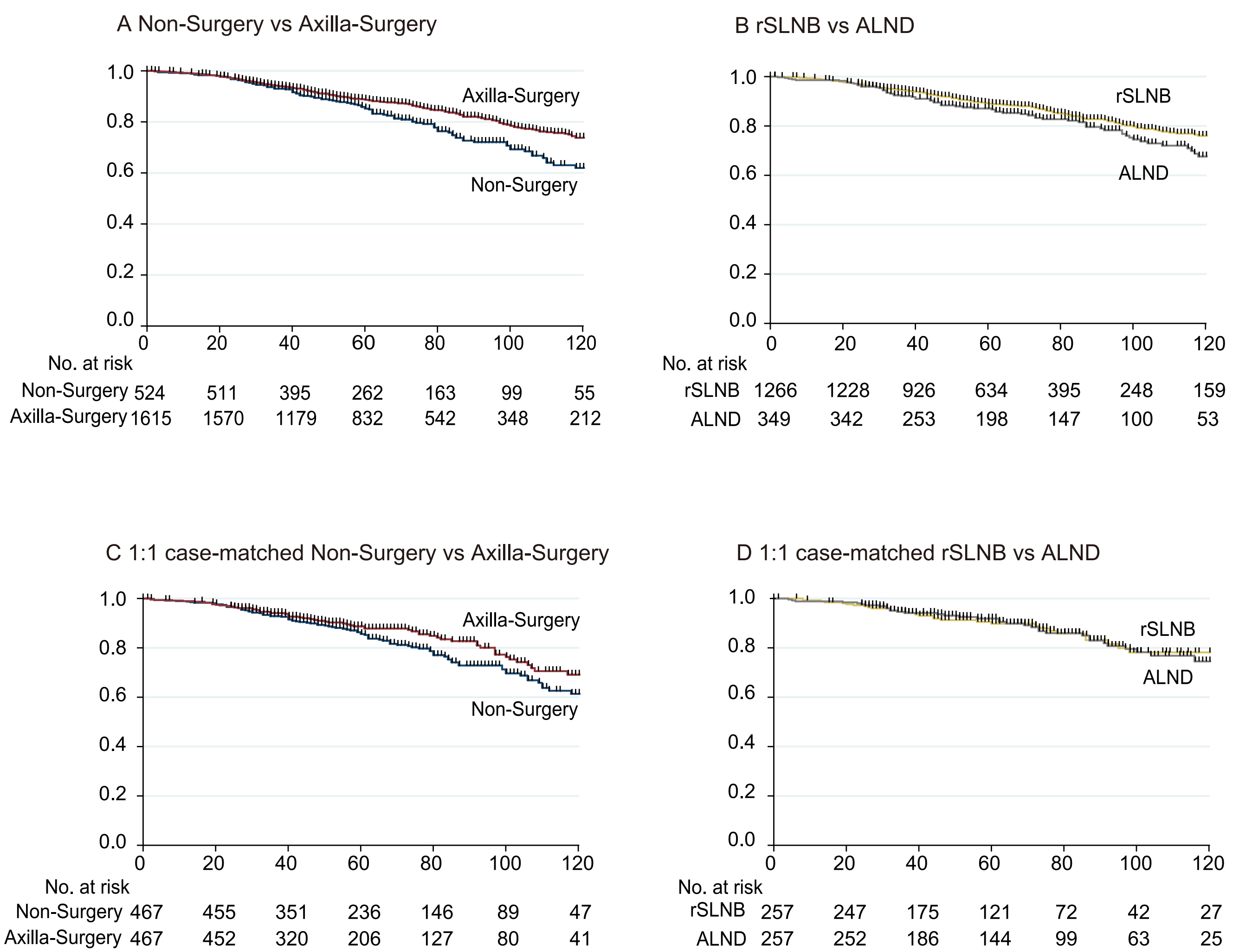

FIGURE 2 Kaplan–Meier plots of the 10-year OS for overall survival among patients with IBTR. (A) The OS comparison of the nonsurgery versus axilla surgery groups. (B) rSLNB vs ALND. (C) 1:1 paired nonsurgery versus axilla surgery. (D) 1:1 paired rSLNB versus ALND. ALND indicates axillary lymph node dissection; IBTR, ipsilateral breast tumor recurrence; OS, overall survival; rSLNB, repeat sentinel lymph node biopsy.

TABLE 2 Multivariate Cox regression model analysis of 10-year OS.

	Nonsurgery vs axilla surgery			rSLNB vs ALND	
Characteristics	**HR (95% CI)**	***p***	**Characteristics**	**HR (95% CI)**	***p***
Age, years			**Age, years**		
≤50	Reference		≤50	Reference	
51–65	1.29 (0.82–2.03)	.265	51–65	1.62 (0.92–2.86)	.097
≥66	3.92 (2.57–5.97)	<.001	≥66	4.62 (2.70–7.92)	<.001
Race			**Race**		
White	Reference		White	Reference	
Black	1.51 (1.09–2.08)	.013	Black	1.39 (0.94–2.05)	.101
Others	1.04 (0.66–1.65)	.869	Others	1.27 (0.76–2.13)	.364
IBTR subregion					
Same quadrant	Reference				
Different quadrant	1.27 (0.99–1.63)	.063			
Grade			**Grade**		
1, 2	Reference		1, 2	Reference	
3, 4	1.60 (1.22–2.09)	.001	3, 4	1.63 (1.18–2.25)	.003
T			**T**		
T1	Reference		T1	Reference	
T2	1.86 (1.43–2.41)	<.001	T2	1.73 (1.26–2.37)	.001
T3	4.42 (2.56–7.66)	<.001	T3	3.53 (1.85–6.76)	<.001
HoR			**HoR**		
Negative	Reference		Negative	Reference	
Positive	0.85 (0.63–1.15)	.297	Positive	0.77 (0.55–1.09)	.142
Unknown	0.53 (0.27–1.05)	.070	Unknown	0.71 (0.32–1.60)	.412
HER2					
Negative	Reference				
Positive	0.64 (0.38–1.07)	.089			
Unknown	1.17 (0.91–1.50)	.227			
ALND surgery			**ALND surgery**		
Nonsurgery	Reference		rSLNB	Reference	
Axilla surgery	0.71 (0.56–0.90)	.004	ALND	1.18 (0.88–1.58)	.268
Chemotherapy			**Chemotherapy**		
Yes	Reference		Yes	Reference	
No/unknown	1.64 (1.20–2.24)	.002	No/unknown	1.80 (1.25–2.58)	.002

Abbreviations: ALND, axillary lymph node dissection; HoR, hormone receptor; HR, hazard ratio; IBTR, ipsilateral breast tumor recurrence; OS, overall survival; rSLNB, repeat sentinel lymph node biopsy.

analysis within the subgroups. The patients were divided based on 4 key variables (IBTR histology, IBTR histological grade, IBTR HoR status, and IBTR T stage). Consistent with the overall analysis, rSLNB presented similar OS HRs in the subgroups with ALND (Table 3).

Sensitivity analysis

Sensitivity analyses were conducted to evaluate the possibility of unintentional bias from our practical definition of SLNB and ALND. Multivariable Cox analysis demonstrated that none of the axillary

TABLE 3 Subgroup analysis of 10-year OS for rSLNB vs ALND among patients with IBTR.

	rSLNB		ALND		
Characteristics	*n*	HR (95% CI)	*n*	HR (95% CI)	*p*
Overall	1268	Reference	349	1.18 (0.88–1.58)	.268
Subgroups					
IBTR histology					
IDC	847	Reference	270	1.09 (0.77–1.53)	.634
ILC and others	421	Reference	79	1.56 (0.89–2.74)	.123
IBTR histological grade					
1, 2	911	Reference	196	1.19 (0.79–1.78)	.412
3, 4	357	Reference	153	1.08 (0.71–1.65)	.704
IBTR HoR					
Negative	231	Reference	94	1.27 (0.76–2.12)	.370
Positive	999	Reference	246	1.03 (0.71–1.49)	.865
IBTR T stage					
T1	1033	Reference	256	1.09 (0.76–1.58)	.640
T2	216	Reference	83	1.45 (0.86–2.45)	.163

Abbreviations: ALND, axillary lymph node dissection; HoR, hormone receptor; HR, hazard ratio; IBTR, ipsilateral breast tumor recurrence; IDC, invasive lobular carcinoma; ILC, invasive ductal carcinoma; OS, overall survival; rSLNB, repeat sentinel lymph node biopsy.

surgery criteria made a difference in the survival outcomes between the rSLNB and ALND groups (Table S6).

DISCUSSION

We analyzed the data of 2141 patients from 2000 to 2017, and the median follow-up time from IBTR was more than 5 years. Our investigation suggested that receiving surgical axillary staging was associated with lower overall mortality, whereas the choice of ALND or rSLNB did not affect the 10-year survival. rSLNB might be considered for surgical axillary staging among IBTR.

Our research showed that the significant independent factors for both OS and BCSS in patients with IBTR included age, IBTR histological grade, and IBTR tumor size. Consistent with the research of Li et al., breast surgery (lumpectomy and mastectomy) for IBTR had no statistically significant differences in the long-term follow-up.[28] Repeat lumpectomy might be considered with caution for IBTR patients. It is worth noting that Su et al. found that repeat lumpectomy plus radiation reflected better survival than lumpectomy alone.[26]

IBTR tumor size was an important factor when surgical axillary staging was considered. Tumor size was not the only independent factor for both OS and BCSS of IBTR, as our data showed. Tumor size also has a close relationship with the prevalence of lymph node metastases. There was a positive correlation between lymph node status and tumor size if tumors were between 11 and 50 mm in size.[29] Concern might exist that rSLNB would decrease the survival of larger IBTR because of omission of possible positive lymph nodes. Therefore, we further conducted a subgroup analysis based on IBTR T stage. In both the T1 and T2 subgroups, rSLNB presented HRs similar to those of ALND. This finding inferred that rSLNB might be a safe method of surgical axillary staging for both T1 and T2 IBTR.

Previous studies have shown that rSLNB has an acceptable identification rate and low false-negative rate in terms of feasibility. A representative study by Intra et al. included 212 patients with IBTR and rSLNB, and the identification rate for rSLNB was 92.5% if the rational tracing or mapping technique was used.[20] This reported identification rate is acceptable in terms of the identification rate of initial SLNB, ranging from 92% to 98%.[30,31] Additionally, Port et al. reported that either partial dissection of level I/II or a previous lymph node biopsy did not affect the identification rate of rSLNB, especially when fewer than 10 nodes were removed during the initial procedure.[19] Chang et al. reported on 464 patients in a systematic review and demonstrated that the false-negative rate was lower than 10%, indicating that rSLNB was a reliable axillary surgery in patients with IBTR.[32]

Our report showed 10-year OS data and that rSLNB had no statistically significant differences from ALND. Selection bias should be considered because patients with smaller recurrent tumors and better histological grades were prone to rSLNB. We conducted 1:1 paired cohort analysis and multivariable Cox analysis. Both methods verified the results that rSLNB had a similar survival benefit as ALND. Ingrid et al. showed the follow-up data of an unsuccessful rSLNB and identified 239 patients with unsuccessful rSLNB. The 5-year follow-up showed that regional recurrence in patients with IBTR and unsuccessful rSLNB seemed to be negligible, regardless of the use of ALND.[33] Ugras et al. questioned whether nodal restaging was worthwhile after analyzing the subsequent events of local recurrence from the institutional database.[34] Confronted with the clinical controversy and limited publication, 78% of panelists of the 2021 St Gallen Consensus Conference chose rSLNB in the case of IBTR after previous treatment with lumpectomy and SLNB.[21] Interestingly, the settings of the St Gallen questionnaire were in keeping with the inclusion of our study.

Surgical axillary staging might not be suggested for all patients with IBTR, especially those who are elderly. Our multivariate analysis showed that older age (>65 years) was an independent risk factor for 10-year OS (HR, 3.92; 95% CI, 2.57–5.97; $p < .001$) and 10-year BCSS (HR, 1.91; 95% CI, 1.15–3.17; $p = .012$). Elder age seemed to be a more important factor than axillary staging in terms of HR value. Guidelines for management of the axilla in early breast cancer by Ontario Health and the American Society of Clinical Oncology suggested that SLNB is not suggested for those patients aged more than 70 years with cT1N0 HoR + human epidermal growth factor receptor 2.[35] The retrospective study verified this conclusion.[36] Therefore, surgical axillary staging might be suggested individually for elderly patients with IBTR based on age, tumor characteristics, physical performance, and life expectancy.

Conventional SLNB was thought to require one to five sentinel nodes to be removed and that four or five lymph nodes might be an optimal threshold number to evaluate the axillary stage.[37,38] In addition, opinions about the minimum number of ALND lymph nodes ranged from six to 10.[23-25] In terms of the initial completed SLNB, we defined the initial lymph nodes removed from one to five as SLNB and used the five lymph nodes as the cutoff to define rSLNB and ALND in the IBTR treatment. To avoid possible unintentional misleading by our practical definition of SLNB and ALND, sensitivity analyses of axillary surgery redefinition were performed to demonstrate that axillary surgery criteria did not make a difference in the survival outcomes between the rSLNB and ALND groups.

Two of the major strengths of our research were the large sample size and long-term follow-up based on the SEER database. We would like to acknowledge some limitations of our study that may induce unintentional bias. First, the baseline characteristics of the cohorts were not totally comparable. We performed multivariate Cox analysis and subgroup analysis and tried to compensate for the bias, whereas the retrospective design analysis could not completely achieve the goal. Second, some important clinical and treatment-level information, including detailed adjuvant treatment, physical status, and local/regional/distant events, was unknown. Because of a lack of definite information about recurrence, we retrieved IBTR information with two registered entries of ipsilateral breast cancer as described by previous research.[26,39] Third, factors such as failure of SLNB or rSLNB were not analyzed. According to previous studies, the success rate of SLNB is high, ranging between 92% and 98%,[30,31] and the success rate for rSLNB is 92.5%.[20] Fourth, information on failed SLNB is not reported in the SEER database. Previous studies have shown that the success rate of SLNB or rSLNB is higher than 92%.[19,30,31] For patients with attempted SLNB, ALND was suggested according to the guidelines. Failed SLNB might be negligible in our research. In addition, the SEER database has other limitations, such as the lack of indications for specific axillary surgery and the type of sentinel mapping performed. The subjects with “no/unknown” radiation or chemotherapy were also not guaranteed to have not received these treatments or just have missing information. Moreover, we did not quantify or analyze the minimum interval necessary between the first and repeat SLNB, and the time of the restoration of lymphatic drainage was still inconclusive. Therefore, further prospective trials are needed to validate the safety and accuracy of rSLNB.

CONCLUSIONS

This research supported that receiving surgical axillary staging was associated with better survival of patients with IBTR and that rSLNB had a similar long-term survival outcome as ALND. In terms of the comparable long-term survival, our findings suggest that rSLNB might be considered for surgical axillary staging among patients with IBTR after lumpectomy and initial SLNB.

AUTHOR CONTRIBUTIONS

Xunxi Lu: Data curation, formal analysis, investigation and methodology, and writing – original draft. **Mengting He:** Formal analysis. **Luoting Yu:** Investigation and methodology. **Zongchao Gou:** Conceptualization, formal analysis, investigation and methodology, and funding acquisition. All authors: Writing – review and editing.

ACKNOWLEDGMENTS

This study was supported by Post-Doctor Research Project, West China Hospital, Sichuan University (2021HXBH080), and Natural Science Foundation of Sichuan Province (2022NSFSC1385).

CONFLICTS OF INTEREST STATEMENT

All authors made no disclosures.

ORCID

Zongchao Gou https://orcid.org/0000-0002-9264-7586

REFERENCES

1. Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2021;71(3):209-249. doi:10.3322/caac.21660
2. Lucci A, McCall LM, Beitsch PD, et al. Surgical complications associated with sentinel lymph node dissection (SLND) plus axillary lymph node dissection compared with SLND alone in the American College of Surgeons Oncology Group Trial Z0011. *Am Soc Clin Oncol*. 2016;25(24):3657-3663. doi:10.1200/jco.2006.07.4062
3. Canavese G, Catturich A, Vecchio C, et al. Sentinel node biopsy compared with complete axillary dissection for staging early breast cancer with clinically negative lymph nodes: results of randomized trial. *Ann Oncol*. 2009;20(6):1001-1007. doi:10.1093/annonc/mdn746
4. Giuliano AE, Kirgan DM, Guenther JM, Morton DL. Lymphatic mapping and sentinel lymphadenectomy for breast cancer. *Ann Surg*. 1994;220(3):391-401. doi:10.1097/00000658-199409000-00015
5. Giuliano AE, Ballman KV, McCall L, et al. Effect of axillary dissection vs no axillary dissection on 10-year overall survival among women with invasive breast cancer and sentinel node metastasis: the ACOSOG Z0011 (Alliance) randomized clinical trial. *JAMA*. 2017;318(10):918-926. doi:10.1001/jama.2017.11470
6. Gou Z, Lu X, He M, Yu L. Trends in axillary surgery and clinical outcomes among breast cancer patients with sentinel node metastasis. *Breast*. 2022;63:9-15. doi:10.1016/j.breast.2022.02.014
7. Kummerow KL, Du L, Penson DF, Shyr Y, Hooks MA. Nationwide trends in mastectomy for early-stage breast cancer. *JAMA Surg*. 2015;150(1):9-16. doi:10.1001/jamasurg.2014.2895
8. Rescigno J, Zampell JC, Axelrod D. Patterns of axillary surgical care for breast cancer in the era of sentinel lymph node biopsy. *Ann Surg Oncol*. 2009;16(3):687-696. doi:10.1245/s10434-008-0195-5
9. Fisher B, Anderson S, Bryant J, et al. Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. *N Engl J Med*. 2002;347(16):1233-1241. doi:10.1056/nejmoa022152
10. van Dongen JA, Voogd AC, Fentiman IS, et al. Long-term results of a randomized trial comparing breast-conserving therapy with mastectomy: European Organization for Research and Treatment of Cancer 10801 Trial. *JNCI J Natl Cancer Inst*. 2000;92(14):1143-1150. doi:10.1093/jnci/92.14.1143

11. Asselain B, Barlow W, Bartlett J, et al. Long-term outcomes for neoadjuvant versus adjuvant chemotherapy in early breast cancer: meta-analysis of individual patient data from ten randomised trials. *Lancet Oncol*. 2018;19:27-39.
12. National Comprehensive Cancer Network. Breast cancer (version 4.2022). 2022. Accessed August 10, 2022. https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf
13. Intra M, Trifirò G, Galimberti V, Gentilini O, Rotmensz N, Veronesi P. Second axillary sentinel node biopsy for ipsilateral breast tumour recurrence. *Br J Surg*. 2007;94(10):1216-1219. doi:10.1002/bjs.5813
14. Goyal A, Mansel RE. Multifocality and sentinel node biopsy in breast cancer. *Eur J Surg Oncol*. 2004;30(1):3-4. doi:10.1016/j.ejso.2003.10.022
15. Kumar R, Potenta S, Alavi A. Sentinel lymph node biopsy in multifocal and multicentric breast cancer. *J Am Coll Surg*. 2004;198(4):674-676. doi:10.1016/j.jamcollsurg.2004.01.015
16. Burger AE, Pain SJ, Peley G. Treatment of recurrent breast cancer following breast conserving surgery. *Breast J*. 2013;19(3):310-318. doi:10.1111/tbj.12105
17. Maaskant-Braat AJ, Voogd AC, Roumen RM, Nieuwenhuijzen GA. Repeat sentinel node biopsy in patients with locally recurrent breast cancer: a systematic review and meta-analysis of the literature. *Breast Cancer Res Treat*. 2013;138(1):13-20. doi:10.1007/s10549-013-2409-1
18. Poodt IGM, Vugts G, Schipper RJ, Nieuwenhuijzen GAP. Repeat sentinel lymph node biopsy for ipsilateral breast tumor recurrence: a systematic review of the results and impact on prognosis. *Ann Surg Oncol*. 2018;25(5):1329-1339. doi:10.1245/s10434-018-6358-0
19. Port ER, Fey J, Gemignani ML, et al. Reoperative sentinel lymph node biopsy: a new option for patients with primary or locally recurrent breast carcinoma. *J Am Coll Surg*. 2002;195(2):167-172. doi:10.1016/s1072-7515(02)01268-1
20. Intra M, Viale G, Vila J, et al. Second axillary sentinel lymph node biopsy for breast tumor recurrence: experience of the European Institute of Oncology. *Ann Surg Oncol*. 2015;22:2372-2377. doi:10.1245/s10434-014-4282-5
21. Thomssen C, Balic M, Harbeck N, Gnant M. St. Gallen/Vienna 2021: a brief summary of the consensus discussion on customizing therapies for women with early breast cancer. *Breast Care*. 2021;16(2):135-143. doi:10.1159/000516114
22. Wang J, Mittendorf EA, Sahin AA, et al. Outcomes of sentinel lymph node dissection alone vs. axillary lymph node dissection in early stage invasive lobular carcinoma: a retrospective study of the Surveillance, Epidemiology and End Results (SEER) database. *PLoS One*. 2014;9(2):1-7. doi:10.1371/journal.pone.0089778
23. Li S, Liu F, Chen K, et al. 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. *Medicine (Baltimore)*. 2016;95(14):e3254. doi:10.1097/md.0000000000003254
24. Edge SBB DR, Compton CC, Fritz AG, Greene FLTA. *AJCC Cancer Staging Manual*. 7th ed. Springer; 2011.
25. Jung J, Kim BH, Kim J, et al. Validating the ACOSOG Z0011 trial result: a population-based study using the SEER database. *Cancers (Basel)*. 2020;12(4):9-12. doi:10.3390/cancers12040950
26. Su Y, Guo R, Xue J, et al. Increased mortality with repeat lumpectomy alone after ipsilateral breast tumor recurrence. *Oncologist*. 2019;24(9):818-827. doi:10.1634/theoncologist.2018-0606
27. Wang C, Hu K, Luo C, et al. Cardiovascular mortality among cancer survivors who developed breast cancer as a second primary malignancy. *Br J Cancer*. 2021;125(10):1450-1458. doi:10.1038/s41416-021-01549-w
28. Li Y, wen LW, Yuan L, Xu B. Is repeat breast conservation possible for small ipsilateral breast cancer recurrence? *Cancer*. 2022;128(22):3919-3928. doi:10.1002/cncr.34468
29. Sopik V, Narod SA. The relationship between tumour size, nodal status and distant metastases: on the origins of breast cancer. *Breast Cancer Res Treat*. 2018;170(3):647-656. doi:10.1007/s10549-018-4796-9
30. Albertini JJ, Lyman GH, Cox C, et al. Lymphatic mapping and sentinel node biopsy in the patient with breast cancer. *JAMA*. 1996;276:1818-1822. doi:10.1001/jama.1996.03540220042028
31. Veronesi U, Paganelli G, Galimberti V, et al. Sentinel-node biopsy to avoid axillary dissection in breast cancer with clinically negative lymph-nodes. *Lancet*. 1997;349(1):1864-1867. doi:10.1046/j.1524-4741.1998.4100633.x
32. Yoon CI, Ahn SG, Kim D, et al. Repeat sentinel lymph node biopsy for ipsilateral breast tumor recurrence after breast conserving surgery with sentinel lymph node biopsy: pooled analysis using data from a systematic review and two institutions. *Front Oncol*. 2020;10:1-8. doi:10.3389/fonc.2020.518568
33. Poodt IGM, Walstra CJEF, Vugts G, et al. Low risk of development of a regional recurrence after an unsuccessful repeat sentinel lymph node biopsy in patients with ipsilateral breast tumor recurrence. *Ann Surg Oncol*. 2019;26(8):2417-2427. doi:10.1245/s10434-019-07272-4
34. Ugras S, Matsen C, Eaton A, Stempel M, Morrow M, Cody HS. Reoperative sentinel lymph node biopsy is feasible for locally recurrent breast cancer, but is it worthwhile? *Ann Surg Oncol*. 2016;23(3):744-748. doi:10.1245/s10434-015-5003-4
35. Brackstone M, Baldassarre FG, Perera FE, et al. Management of the axilla in early-stage breast cancer: Ontario Health (Cancer Care Ontario) and ASCO Guideline. *J Clin Oncol*. 2021;39(27):3056-3082. doi:10.1200/jco.21.00934
36. Cha C, Jeong J, Kim H-K, et al. Survival benefit from axillary surgery in patients aged 70 years or older with clinically node-negative breast cancer: a population-based propensity-score matched analysis. *Eur J Surg Oncol*. 2022;48(12):2385-2392. doi:10.1016/j.ejso.2022.07.005
37. Ban EJ, Lee JS, Koo JS, Park S, Kim SI, Park BW. How many sentinel lymph nodes are enough for accurate axillary staging in t1-2 breast cancer? *J Breast Cancer*. 2011;14(4):296-300. doi:10.4048/jbc.2011.14.4.296
38. Yi M, Meric-Bernstam F, Ross MI, et al. How many sentinel lymph nodes are enough during sentinel lymph node dissection for breast cancer? Cancer. 2008;113(1):30-37. doi:10.1002/cncr.23514
39. Poleszczuk J, Luddy K, Chen L, et al. Neoadjuvant radiotherapy of early-stage breast cancer and long-term disease-free survival. *Breast Cancer Res*. 2017;19(1):75. doi:10.1186/s13058-017-0870-1

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Lu X, He M, Yu L, Gou Z. Is repeat sentinel lymph node biopsy possible for surgical axillary staging among patients with ipsilateral breast tumor recurrence? *Cancer*. 2023;1-10. doi:10.1002/cncr.34708