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ORIGINAL SCIENTIFIC REPORT

Surgery of the Primary Tumor Offers Survival Benefits of Breast Cancer with Synchronous Ipsilateral Supraclavicular Lymph Node Metastasis

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Abstract

Background Controversy exists around the locoregional management of the primary tumor for breast cancer associated with synchronous ipsilateral supraclavicular lymph node metastasis (sISLM) due to the rarity of the disease and limited available data. This study aimed to compare outcomes of patients in the Surveillance, Epidemiology, and End Results (SEER) database with sISLM who underwent surgical resection and radiation of the primary tumor with those who did not.
Methods This population-based retrospective study included breast cancer patients with sISLM without distant metastases from 2004 to 2016 in the SEER database. In this study, patients had been stratified by operative management, and propensity score matching (PSM) had been successfully applied.
Results A total of 1172 breast cancer patients with sISLM were included in the study: 863 (73.6%) of patients underwent the primary tumor resection, and 309 (26.4%) patients did not undergo surgery. The median survival time in the surgery group was longer compared to the nonsurgery group in the overall cohort and the PSM cohort. We concluded that the primary tumor resection was associated with improved survival. Subgroup analysis further demonstrated that local surgery was not inferior to radical surgery.
Conclusion For selected breast cancer patients with sISLM, surgery is a promising local intervention which may improve the survival.

Introduction

The incidence of breast cancer with ipsilateral supraclavicular lymph node metastasis (ISLM) without distant metastasis is as low as 1–4% [1–3]. Two types of ISLM can be identified in breast cancer, synchronous ISLM (sISLM) and metachronous ISLM (mISLM) [4]. sISLM is defined as ISLM at the primary diagnosis of breast cancer (T1—4 N3c M0), and mISLM as the occurrence of supraclavicular lymph node metastasis after the initial diagnosis and treatment of breast cancer.

In the 5th edition of the AJCC TNM staging system, breast cancer with the classification of sISLM was modified from N3 to M1 due to its poor outcome and developing distant metastasis within 1 year [5, 6]. Soon after that, in the 6th edition of the AJCC TNM staging system, breast cancer with sISLM, which was no longer regarded as distant metastasis, was reclassified as stage IIIC (N3c) instead of stage IV and it has maintained the IIIC (N3c) classification to date [7–9].

Qi-tong Chen and Li-yun Zeng have contributed equally to this work.

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Despite the low incidence, there has always been significant controversy about the local treatment, especially surgery, of the primary tumor site of breast cancer with sISLM. Fan et al. [4] demonstrated that the primary tumor size and radiotherapy after surgery, not including surgery itself, were independent prognostic factors for sISLM. Chen et al. [10] found that young age and the surgical removal of the primary tumor and supraclavicular nodes after sISLM were associated with a significantly better prognosis and survival. Besides, a retrospective study in Japan showed that local–regional therapy, including surgery and radiation, was incapable of reversing the poor prognosis of sISLM breast cancer patients [11]. Breast surgeons tend to perform the primary tumor and lymph node dissection in patients with newly diagnosed sISLM [12]. Currently, whether breast cancer patients with sISLM can benefit from the primary tumor resection remains debatable.

Hence, our study aimed to evaluate the survival benefit of surgery of the primary lesion in breast cancer patients with sISLM based on the data from the Surveillance, Epidemiology, and End Results (SEER) database. Therefore, we retrospectively analyzed the data of 1172 patients from the SEER database to evaluate the main demographic and clinicopathological characteristics affecting prognosis. Our study provides a more in-depth and comprehensive understanding of the clinical features of breast cancer with sISLM and attempts to obtain more evidence to form a theoretical basis for surgery treatment.

Patients and methods

Data source and cohort selection

Data were acquired from the SEER database between January 1, 2004, and December 31, 2016, because the 6th AJCC TNM staging system was adopted by SEER starting in 2003. We extracted the data for all cases that were initially diagnosed as malignant primary breast cancer, and multiple primary malignant tumors were excluded. A total of 638,902 patients who were diagnosed with the primary breast cancer between January 1, 2004, and December 31, 2016, were used for analysis in this study. Breast cancer patients who did not have N3c stage disease or who had distant metastasis were excluded. After these steps, we excluded patients who were male or for whom data were unavailable for some critical variables. The follow-up time of the patients was from breast cancer diagnosis until death or the end of the follow-up period. Finally, 1172 female patients who were diagnosed with sISLM (stage N3c but not M1) were included in the analysis (S.Fig. 1).

The SEER is a freely available database [13], and the data released by the SEER database do not require informed patient consent, as cancer is a reportable disease in the USA. The original data in this study were downloaded from the SEER Web site server (https://seer.cancer.gov/data/) via the SEER*Stat software version 8.3.5 in the client–server model.

Variables

The following demographic and clinicopathological characteristics of N3c stage patients before and after PSM were included in the analysis process (Table 1): age at diagnosis, race, marital status, laterality, histologic type, tumor differentiation grade, T stage based on the Derived AJCC Stage Group (6th) [14], estrogen receptor (ER) status, progesterone receptor (PR) status, HER2 status, molecular subtype, surgery, radiotherapy, and chemotherapy. Patients were divided into two major subgroups: no surgery and surgery, which could be divided again into the local surgery and radical surgery subgroups (Table 2). The SEER registry provided hormone receptor (HR) information for each patient. Specifically, ER, PR, and HER2 status were included as positive, negative, and undetermined status. A major subset of the patients' HER2 status in this cohort was unavailable because the HER2 status data were collected by SEER starting in 2010. For radiation, due to the data availability of the SEER database, the extent of the radiation fields is not known. Specifically, it is unclear whether the radiation included the sISLM as well.

Propensity score matching (PSM)

This study was a retrospective and observational study, so the surgery assignment was not random. Some significant covariates of the patients in the active treatment and control groups were heterogeneous and possibly affected the outcomes. Therefore, we further compared the survival rate between the surgery and nonsurgery cohorts by using 1:1 nearest-neighbor matching, setting the caliper as 0.02. The PSM process was applied to minimize the selection bias and to approximately balance the baseline covariates with the analytic settings between groups [15].

Statistical analysis

Using the Chi-square test, we compared patient characteristics between the surgery and nonsurgery patients. Overall survival (OS) was defined as the time from diagnosis to death from any cause, and disease-specific survival (DSS) was determined based on the date of initial diagnosis to the date of disease-related death. OS and DSS were the primary endpoints of this study. Kaplan–Meier analysis

Table 1 Baseline characteristics of female patients with sISLM

Category	Before propensity score matching				After propensity score matching			
	No. of patients (%)	Surgery (%)	Nonsurgery (%)	*P* value	No. of patients (%)	Surgery (%)	Nonsurgery (%)	*P* value
Age								
≦35	74 (6.3%)	62 (7.2%)	12 (3.9%)		22 (4.7%)	11 (4.7%)	11 (4.7%)	
36–45	191 (16.3%)	159 (18.4%)	32 (10.4%)		57 (12.3%)	31 (13.4%)	26 (11.2%)	
46–55	336 (28.7%)	262 (30.4%)	74 (23.9%)	**<0.001**	130 (28%)	67 (28.9%)	63 (27.2%)	0.592
56–65	292 (24.9%)	221 (25.6%)	71 (23%)		113 (24.4%)	60 (25.9%)	53 (22.8%)	
>65	279 (23.8%)	159 (18.4%)	120 (38.8%)		142 (30.6%)	63 (27.2%)	79 (34.1%)	
Race								
White	835 (71.2%)	628 (72.8%)	207 (67%)		324 (69.8%)	164 (70.7%)	160 (69%)	
Black	232 (19.8%)	162 (18.8%)	70 (22.7%)	**0.027**	93 (20%)	45 (19.4%)	48 (20.7%)	0.137
Other	96 (8.2%)	70 (8.1%)	26 (8.4%)		42 (9.1%)	23 (9.9%)	19 (8.2%)	
Unknown	9 (0.8%)	3 (0.3%)	6 (1.9%)		5 (1.1%)	0 (0%)	5 (2.2%)	
Marriage								
Single	258 (22%)	183 (21.2%)	75 (24.3%)		110 (23.7%)	55 (23.7%)	55 (23.7%)	
Married	573 (48.9%)	453 (52.5%)	120 (38.8%)	**<0.001**	199 (42.9%)	103 (44.4%)	96 (41.4%)	0.857
DSW	298 (25.4%)	200 (23.2%)	98 (31.7%)		138 (29.7%)	65 (28%)	73 (31.5%)	
Unknown	43 (3.7%)	27 (3.1%)	16 (5.2%)		17 (3.7%)	9 (3.9%)	8 (3.4%)	
Laterality								
Left	658 (56.1%)	490 (56.8%)	168 (54.4%)		249 (53.7%)	124 (53.4%)	125 (53.9%)	
Right	503 (42.9%)	373 (43.2%)	130 (42.1%)	**<0.001**	211 (45.5%)	108 (46.6%)	103 (44.4%)	0.127
Both sides	11 (0.9%)	0 (0%)	11 (3.6%)		4 (0.9%)	0 (0%)	4 (1.7%)	
Histologic type								
Ductal carcinoma	846 (72.2%)	655 (75.9%)	191 (61.8%)		320 (69%)	156 (67.2%)	164 (70.7%)	
Lobular carcinoma	137 (11.7%)	114 (13.2%)	23 (7.4%)	**<0.001**	48 (10.3%)	31 (13.4%)	17 (7.3%)	0.097
Other	189 (16.1%)	94 (10.9%)	95 (30.7%)		96 (20.7%)	45 (19.4%)	51 (22%)	
Grade								
I–II	272 (23.2%)	219 (25.4%)	53 (17.2%)		99 (21.3%)	53 (22.8%)	46 (19.8%)	
III–IV	746 (63.7%)	576 (66.7%)	170 (55%)	**<0.001**	286 (61.6%)	143 (61.6%)	143 (61.6%)	0.573
Unknown	154 (13.1%)	68 (7.9%)	86 (27.8%)		79 (17%)	36 (15.5%)	43 (18.5%)	
T Stage								
T1–T2	505 (43.1%)	414 (48%)	91 (29.4%)		166 (35.8%)	91 (39.2%)	75 (32.3%)	
T3–T4	600 (51.2%)	421 (48.8%)	179 (57.9%)	**<0.001**	265 (57.1%)	124 (53.4%)	141 (60.8%)	0.264
Unknown	67 (5.7%)	28 (3.2%)	39 (12.6%)		33 (7.1%)	17 (7.3%)	16 (6.9%)	
ER								
Positive	578 (49.3%)	428 (49.6%)	150 (48.5%)		227 (48.9%)	114 (49.1%)	113 (48.7%)	
Negative	549 (46.8%)	417 (48.3%)	132 (42.7%)	**<0.001**	217 (46.8%)	107 (46.1%)	110 (47.4%)	0.884
Unknown	45 (3.8%)	18 (2.1%)	27 (8.7%)		20 (4.3%)	11 (4.7%)	9 (3.9%)	
PR								
Positive	428 (36.5%)	320 (37.1%)	108 (35%)		161 (34.7%)	80 (34.5%)	81 (34.9%)	
Negative	702 (59.9%)	529 (61.3%)	173 (56%)	**<0.001**	283 (61%)	142 (61.2%)	141 (60.8%)	0.995
Unknown	42 (3.6%)	14 (1.6%)	28 (9.1%)		20 (4.3%)	10 (4.3%)	10 (4.3%)	
HER-2								
Positive	236 (20.1%)	189 (21.9%)	47 (15.2%)		85 (18.3%)	46 (19.8%)	39 (16.8%)	
Negative	409 (34.9%)	290 (33.6%)	119 (38.5%)	**<0.001**	165 (35.6%)	73 (31.5%)	92 (39.7%)	0.258
Unknown	34 (2.9%)	12 (1.4%)	22 (7.1%)		14 (3%)	6 (2.6%)	8 (3.4%)	
Unavailable	493 (42.1%)	372 (43.1%)	121 (39.2%)		200 (43.1%)	107 (46.1%)	93 (40.1%)	

Table 1 continued

Category	Before propensity score matching				After propensity score matching			
	No. of patients (%)	Surgery (%)	Nonsurgery (%)	*P* value	No. of patients (%)	Surgery (%)	Nonsurgery (%)	*P* value
Molecular subtype								
Luminal A	233 (19.9%)	170 (19.7%)	63 (20.4%)		92 (19.8%)	46 (19.8%)	46 (19.8%)	
Luminal B	134 (11.4%)	109 (12.6%)	25 (8.1%)		51 (11%)	30 (12.9%)	21 (9.1%)	
HER-2-enriched	100 (8.5%)	79 (9.2%)	21 (6.8%)	**0.040**	33 (7.1%)	16 (6.9%)	17 (7.3%)	0.129
TNBC	176 (15%)	120 (13.9%)	56 (18.1%)		73 (15.7%)	27 (11.6%)	46 (19.8%)	
Unknown	529 (45.1%)	385 (44.6%)	144 (46.6%)		215 (46.3%)	113 (48.7%)	102 (44%)	
Radiation								
Radiation	677 (57.8%)	607 (70.3%)	70 (22.7%)	**<0.001**	148 (31.9%)	82 (35.3%)	66 (28.4%)	0.111
Nonradiation	495 (42.2%)	256 (29.7%)	239 (77.3%)		316 (68.1%)	150 (64.7%)	166 (71.6%)	
Chemotherapy								
Chemotherapy	1036 (88.4%)	817 (94.7%)	219 (70.9%)		397 (85.6%)	203 (87.5%)	194 (83.6%)	
Nonchemotherapy	136 (11.6%)	46 (5.3%)	90 (29.1%)	**<0.001**	67 (14.4%)	29 (12.5%)	38 (16.4%)	0.235
Total	1172	863 (73.6%)	309 (26.4%)		464	232 (50.0%)	232 (50.0%)	

sISLM synchronous ipsilateral supraclavicular lymph node metastasis, *DSW* divorced/separated/widowed, *ER* estrogen receptor, *PR* progesterone receptor, *TNBC* triple-negative breast cancer

Table 2 Type of surgery for breast cancer patients with sISLM

Category	No. of patients	Percent
Local surgery	335	38.82
Partial mastectomy[a]	29	3.36
Lumpectomy or excisional biopsy	121	14.02
Reexcision of the biopsy site for gross or microscopic residual disease	30	3.48
Segmental mastectomy	18	2.09
Subcutaneous mastectomy[b]	8	0.93
Total (simple) mastectomy[c]	129	14.95
Radical surgery	528	61.18
Modified radical mastectomy[d]	511	59.21
Radical mastectomy[e]	16	1.85
Extended radical mastectomy[f]	1	0.12
Total	863	100.00

[a]Removal of the gross primary tumor and some of the breast tissue (breast-conserving or breast-preserving surgery)

[b]Removal of breast tissue without the nipple and areolar complex or overlying skin

[c]Removal of all breast tissue, the nipple, and the areolar complex. An axillary dissection is not done

[d]Removal of all breast tissue, the nipple, the areolar complex, and variable amounts of breast skin in continuity with the axilla. The specimen may or may not include a portion of the pectoralis major muscle

[e]Removal of breast tissue, nipple, areolar complex, variable amount of skin, pectoralis minor, and/or pectoralis major, as well as en bloc axillary dissection

[f]Removal of breast tissue, nipple, areolar complex, variable amounts of skin, pectoralis minor, and/or pectoralis major, as well as removal of internal mammary nodes and en bloc axillary dissection

and the log-rank test were used to estimate OS and DSS before and after PSM. Cox proportional hazard regression was used to identify a hazard ratio (HR), and a corresponding 95% confidence interval (CI) was calculated. A forest plot was utilized to conduct a subgroup analysis comparing the survival rate. All data were examined using SPSS statistical software (version 22.0; IBM Corporation). All statistical tests were two-sided, and the statistical significance level was set at $P < 0.05$.

Table 3 A 3-, 5-, and 10-year survival of patients with sISLM

	OS			DSS		
	3 Years (%)	5 Years (%)	10 Years (%)	3 Years (%)	5 Years (%)	10 Years (%)
Nonsurgery	34.7	23.9	14.0	38.8	28.5	17.9
Surgery	61.9	51.2	38.9	64.7	54.8	45.0
Local surgery	63.1	54.8	42.1	65.8	58.3	48.7
Radical surgery	61.1	49.2	37.4	64.0	52.9	43.1

sISLM synchronous ipsilateral supraclavicular lymph node metastasis, *OS* overall survival, *DSS* disease-specific survival

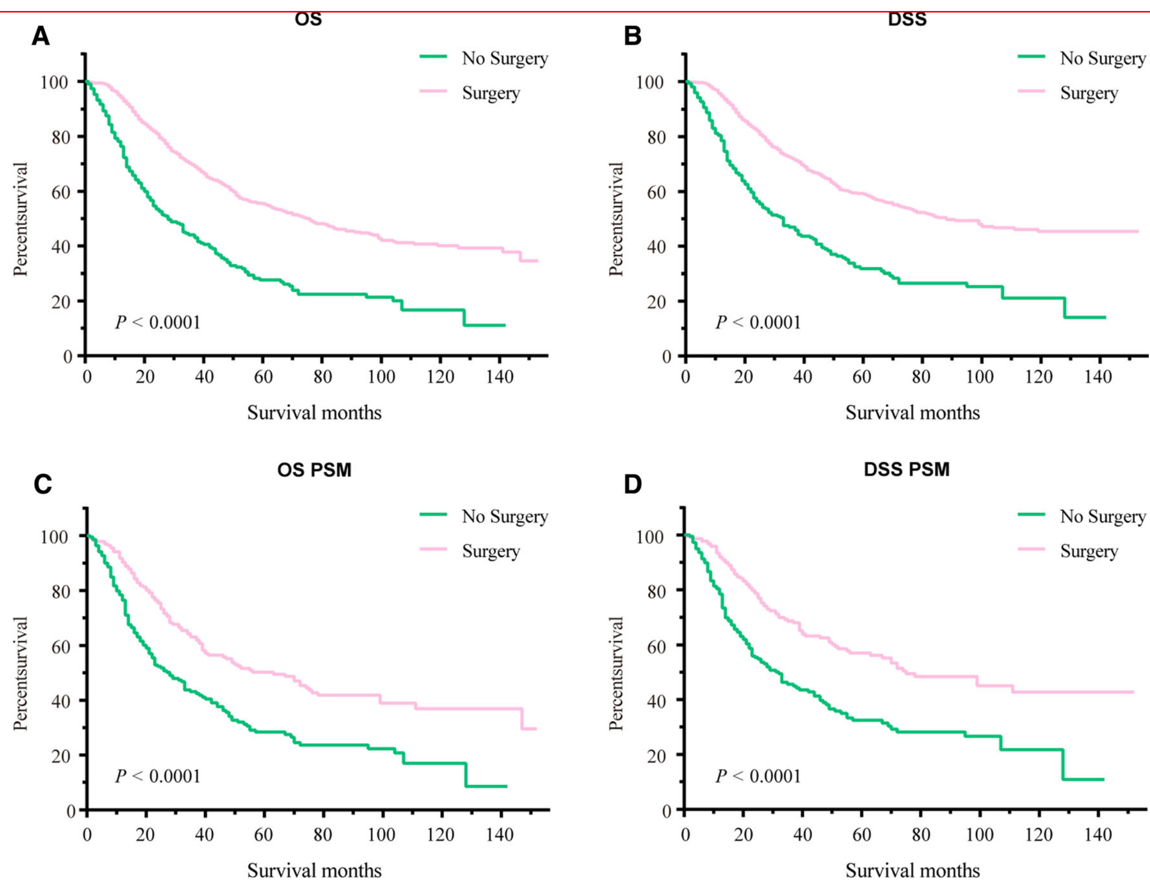


Fig. 1 Kaplan–Meier curves of overall survival (OS) and disease-specific survival (DSS) for patient who underwent surgery and those who did not. **a**, **b** Survival analyses of the surgery and nonsurgery patients in the entire cohort and **c**, **d** PSM cohort for OS and DSS. Univariate log-rank test *P* values are reported

Results

Baseline characteristics of the patients before and after PSM

In the present study, the patient characteristics are presented in Table 1 Based on the eligibility criteria, a cohort of 1172 patients was enrolled in the present study. The median age of the patients was 55 (range 22–98) years. The surgery and nonsurgery cohorts included 863 (73.6%) and 309 (26.4%) patients, respectively. After propensity score matching, a total of 464 patients (surgery 232 (50.0%) versus nonsurgery 232 (50.0%)) were matched. All variables were properly balanced between these two groups. The baseline characteristics of the patients before and after propensity score matching are summarized in Table 1. Patients undergoing surgery could be subdivided into local surgery (n = 335, 38.8%) and radical surgery (n = 528, 61.2%) subgroups, as defined in Table 2.

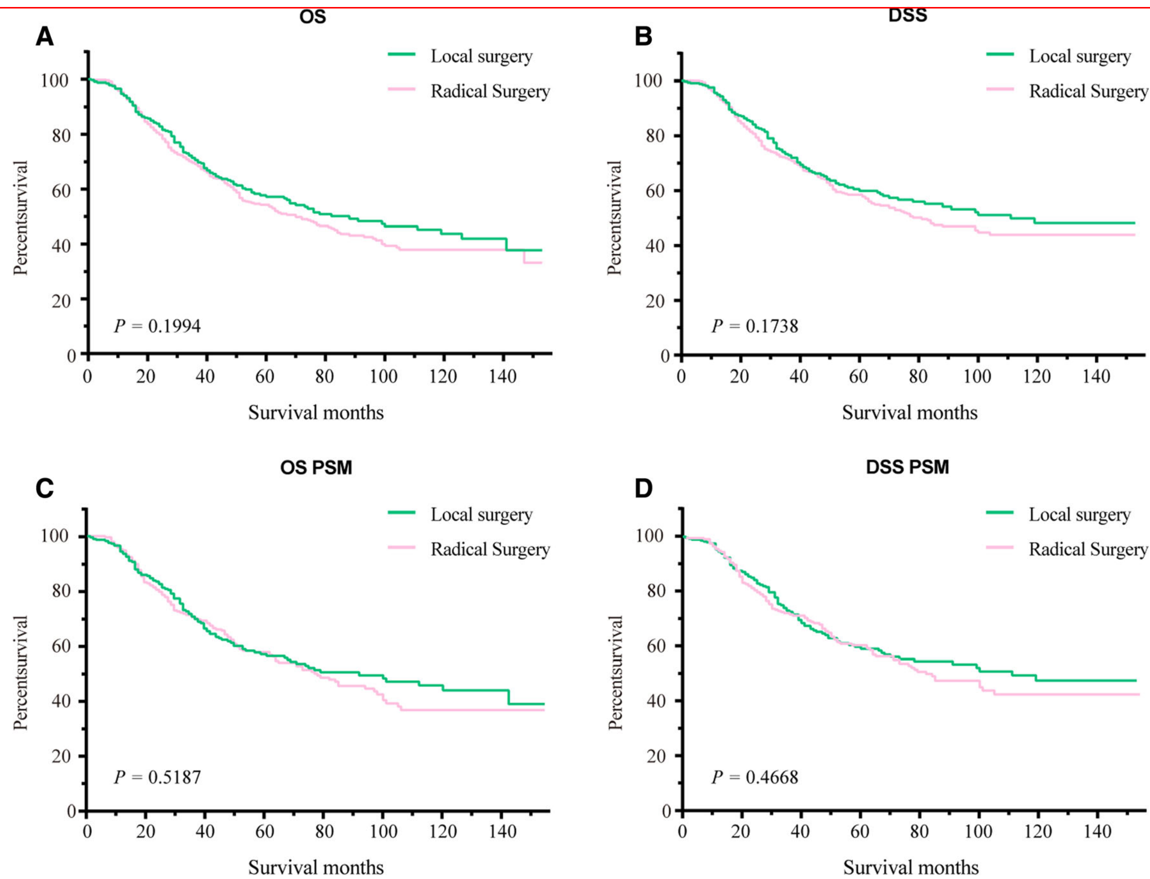


Fig. 2 Kaplan–Meier curves of overall survival (OS) and disease-specific survival (DSS) for patients who underwent local surgery and radical surgery. **a**, **b** Survival analyses of the local surgery and radical surgery patients in the entire cohort and **c**, **d** PSM cohort for OS and DSS. Univariate log-rank test P values are reported

Survival analysis of breast cancer patients with sISLM

OS and DSS of the surgery group were 61.9 and 64.7% at 3 years, 51.2 and 54.8% at 5 years, and 38.9 and 45.0% at 10 years. Comparatively, OS and DSS of nonsurgery group were 34.7 and 38.8% at 3 years, 23.9 and 28.5% at 5 years, and 14.0 and 17.9% at 10 years (Table 3). The median OS for the surgery group and nonsurgery group was 75.27 months and 28.50 months, respectively. Also, the median DSS for the surgery group and nonsurgery group was 90.16 months and 32.31 months, respectively. Kaplan–Meier survival curves with the log-rank test for OS and DSS were performed based on the surgery variables, which are presented in Fig. 1. The survival analyses indicated that the surgery patients had a significantly better OS ($P < 0.0001$) and DSS ($P < 0.0001$) compared with those of nonsurgery patients (Fig. 1a, b). The OS and DSS differences persisted in the PSM cohort (Fig. 1c, d OS $P < 0.0001$, DSS $P < 0.0001$).

Additionally, OS and DSS of the local surgery group were 63.1 and 65.8% at 3 years, 54.8 and 58.3% at 5 years, and 42.1 and 48.7% at 10 years. Comparatively, OS and DSS of the radical surgery group were 61.1 and 64.0% at 3 years, 49.2 and 52.9% at 5 years, and 37.4 and 43.1% at 10 years (Table 3). The median OS for the local surgery group and the radical surgery group was 87.29 months and 69.85 months, respectively. Also, the median DSS for the local surgery group and the radical surgery group was 114.60 months and 79.54 months, respectively. There was no significant difference for the OS ($P = 0.1994$) and DSS ($P = 0.1738$) between the patients who underwent local surgery and those who underwent radical surgery (Fig. 2a, b). PSM between the local surgery group and the radical surgery group was performed (specific data are not shown.) Also, no significant differences were found between these two groups for OS ($P = 0.5187$) and DSS ($P = 0.4668$) after PSM (Fig. 2c, d).

Moreover, Kaplan–Meier curves for OS and DSS were generated based on the surgery and radiation variables, which are presented in Fig. 3. The Kaplan–Meier analyses

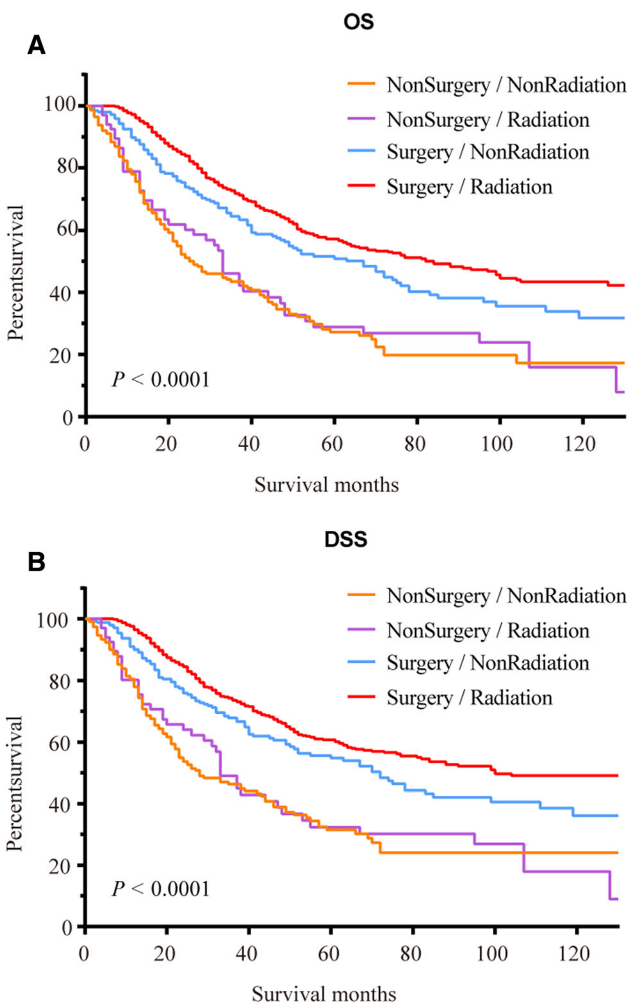


Fig. 3 Kaplan–Meier curves of overall survival (OS) and disease-specific survival (DSS) for patients in different surgery and radiation status. **A** Survival analyses of the combined surgery and radiation for OS; **B** survival analyses of the combined surgery and radiation for DSS. Univariate log-rank test P values are reported

indicated that surgery-treated patients had a remarkably better OS and DSS than nonsurgery group ($P < 0.0001$) (Fig. 3a, b). There was no significant difference in nonsurgery patients for the OS and DSS between the radiation and nonradiation groups (OS $P = 0.5593$, DSS $P = 0.6967$, S.Fig. 2a, b). There was a significant difference for the OS and DSS in surgery patients between the radiation and nonradiation (OS $P = 0.0078$, DSS $P = 0.0101$ S.Fig. 2C & 2D).

Subgroup analyses

To assess whether the distribution of the subject characteristics was consistent, two subgroup analyses of overall survival and disease-specific survival were performed in prespecified subgroups using a forest plot (Figs. 4, 5). The two prespecified stratification factors were the presence or absence of surgical treatment (subgroup analyses A, Fig. 4), and between local surgery and radical surgery (subgroup analyses B, Fig. 5).

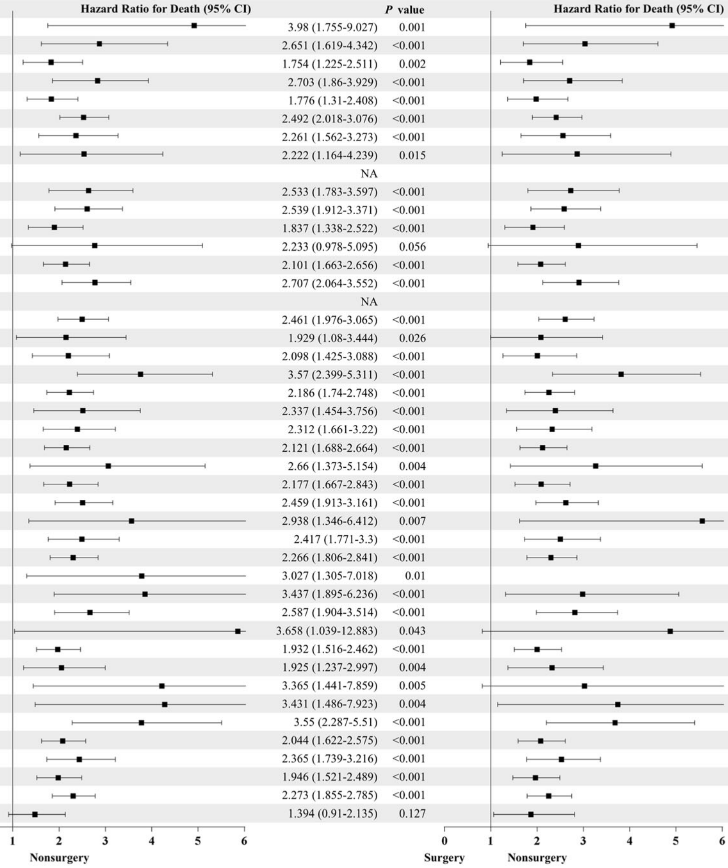
Among the 1172 patients included in subgroup analysis A, for OS, the forest plot indicated that there was a significant difference when the efficacy of surgery to no surgery was compared. Most variables showed that surgery benefited the patients with sISLM compared to no surgery (Fig. 4). Explicitly speaking, no statistical difference was observed in unknown marital status and nonchemotherapy subgroup for OS, unknown marital status, lobular carcinoma, unknown HER-2 status, and luminal B molecular subtype for DSS (Fig. 4).

In the subgroup analysis B involving 863 patients, the forest plot showed that the efficacy of local surgery and radical surgery was similar (Fig. 5). There were statistical differences in the 36–45 age subgroup and ER-positive status subgroup for OS, indicating that local surgery offers less hazard ratio than radical surgery. Similarly, in the 36–45 age subgroup, the unknown marital status subgroup, and ER-positive status subgroup, patients who underwent local surgery have a better prognosis for DSS. Nevertheless, most of the other subgroups did not show statistical differences. It may indicate that, for sISLM patients, compared with radical surgery, local surgery has an equivalent prognostic value (Fig. 5).

Discussion

In recent decades, the classification of patients with sISLM in the AJCC TNM staging system has been revised several times due to the different prognostic conclusions drawn from various studies [5–7, 16, 17]. These findings also raise questions about the most appropriate local treatment for breast cancer patients with sISLM. The most heated debate is whether the implementation of the surgery on the primary lesion affects the patient's prognosis. A meta-analysis published in 2015 suggests that the prognosis for breast cancer patients with ipsilateral ISLM is similar to patients with stages IIIb/c disease and different from patients with stage IV disease. The authors also proposed that radical, instead of palliative therapy, seems more plausible for these patients [18]. Other studies suggested that breast cancer women with sISLM should be considered as a local–regional disease, and aggressive local therapy may indeed improve outcomes [19, 20]. However, studies found that the locoregional surgical therapy after the diagnosis sISLM did not correlate with survival [4, 21].

In our present study, we evaluated 1172 primary breast cancer patients with sISLM from the SEER database between 2004 and 2016. In Kaplan–Meier curve analysis,



Breast cancer patients with sISLM in surgery subgroup analysis (surgery vs. nonsurgery)

Category		No. of patients (%)	OS Hazard Ratio for Death (95% CI)	OS *P* value	DSS Hazard Ratio for Death (95% CI)	DSS *P* value
Age	≤35	74 (6.3%)	3.98 (1.755-9.027)	0.001	3.98 (1.755-9.027)	0.001
	36-45	191 (16.3%)	2.651 (1.619-4.342)	<0.001	2.803 (1.704-4.611)	<0.001
	46-55	336 (28.7%)	1.754 (1.225-2.511)	0.002	1.759 (1.212-2.552)	0.003
	56-65	292 (24.9%)	2.703 (1.86-3.929)	<0.001	2.564 (1.711-3.843)	<0.001
	>65	279 (23.8%)	1.776 (1.31-2.408)	<0.001	1.907 (1.362-2.669)	<0.001
Race	White	835 (71.2%)	2.492 (2.018-3.076)	<0.001	2.373 (1.896-2.971)	<0.001
	Black	232 (19.8%)	2.261 (1.562-3.273)	<0.001	2.434 (1.651-3.589)	<0.001
	Other	96 (8.2%)	2.222 (1.164-4.239)	0.015	2.469 (1.246-4.893)	0.01
	Unknown	9 (0.8%)	NA		NA	
Marriage	Single	258 (22%)	2.533 (1.783-3.597)	<0.001	2.607 (1.801-3.775)	<0.001
	Married	573 (48.9%)	2.539 (1.912-3.371)	<0.001	2.509 (1.865-3.376)	<0.001
	DSW	298 (25.4%)	1.837 (1.338-2.522)	<0.001	1.837 (1.301-2.593)	0.001
	Unknown	43 (3.7%)	2.233 (0.978-5.095)	0.056	2.272 (0.946-5.458)	0.066
Laterality	Left	658 (56.1%)	2.101 (1.663-2.656)	<0.001	2.034 (1.584-2.612)	<0.001
	Right	503 (42.9%)	2.707 (2.064-3.552)	<0.001	2.829 (2.125-3.765)	<0.001
	Both side	11 (0.9%)	NA		NA	
Histologic Type	Ductal Carcinoma	846 (72.2%)	2.461 (1.976-3.065)	<0.001	2.564 (2.035-3.231)	<0.001
	Lobular Carcinoma	137 (11.7%)	1.929 (1.08-3.444)	0.026	1.841 (0.992-3.416)	0.053
	Other	189 (16.1%)	2.098 (1.425-3.088)	<0.001	1.897 (1.26-2.856)	0.002
Grade	I-II	272 (23.2%)	3.57 (2.399-5.311)	<0.001	3.592 (2.332-5.533)	<0.001
	III-IV	746 (63.7%)	2.186 (1.74-2.748)	<0.001	2.213 (1.741-2.812)	<0.001
	Unknown	154 (13.1%)	2.337 (1.454-3.756)	<0.001	2.21 (1.341-3.641)	0.002
T Stage	T1-T2	505 (43.1%)	2.312 (1.661-3.22)	<0.001	2.23 (1.559-3.189)	<0.001
	T3-T4	600 (51.2%)	2.121 (1.688-2.664)	<0.001	2.079 (1.632-2.648)	<0.001
	Unknown	67 (5.7%)	2.66 (1.373-5.154)	0.004	2.812 (1.419-5.572)	0.003
ER	Positive	578 (49.3%)	2.177 (1.667-2.843)	<0.001	2.031 (1.521-2.712)	<0.001
	Negative	549 (46.8%)	2.459 (1.913-3.161)	<0.001	2.562 (1.975-3.324)	<0.001
	Unknown	45 (3.8%)	2.938 (1.346-6.412)	0.007	4.199 (1.619-10.89)	0.003
PR	Positive	428 (36.5%)	2.417 (1.771-3.3)	<0.001	2.415 (1.731-3.37)	<0.001
	Negative	702 (59.9%)	2.266 (1.806-2.841)	<0.001	2.258 (1.781-2.864)	<0.001
	Unknown	42 (3.6%)	3.027 (1.305-7.018)	0.01	4.69 (1.541-14.27)	<0.001
HER-2	Positive	236 (20.1%)	3.437 (1.895-6.236)	<0.001	2.582 (1.317-5.062)	0.006
	Negative	409 (34.9%)	2.587 (1.904-3.514)	<0.001	2.725 (1.985-3.741)	<0.001
	Unknown	34 (2.9%)	3.658 (1.039-12.883)	0.043	2.978 (0.819-10.831)	0.098
	Unavailable	493 (42.1%)	1.932 (1.516-2.462)	<0.001	1.954 (1.509-2.531)	<0.001
Molecular subtype	Luminal A	233 (19.9%)	1.925 (1.237-2.997)	0.004	2.167 (1.368-3.432)	0.001
	Luminal B	134 (11.4%)	3.365 (1.441-7.859)	0.005	2.219 (0.814-6.05)	0.119
	HER-2 riched	100 (8.5%)	3.431 (1.486-7.923)	0.004	2.879 (1.151-7.2)	0.024
	TNBC	176 (15%)	3.55 (2.287-5.51)	<0.001	3.45 (2.2-5.409)	<0.001
	Unknown	529 (45.1%)	2.044 (1.622-2.575)	<0.001	2.035 (1.589-2.608)	<0.001
Radiation	Nonradiation	247 (37.5%)	2.365 (1.739-3.216)	<0.001	2.444 (1.772-3.372)	<0.001
	Radiation	412 (62.5%)	1.946 (1.521-2.489)	<0.001	1.92 (1.477-2.494)	<0.001
Chemotherapy	Chemotherapy	1036 (88.4%)	2.273 (1.855-2.785)	<0.001	2.216 (1.787-2.749)	<0.001
	Nonchemotherapy	136 (11.6%)	1.394 (0.91-2.135)	0.127	1.727 (1.062-2.81)	0.028
Total		1172				

sISLM, synchronous ipsilateral supraclavicular lymph node metastasis; OS, overall survival; DSS, disease-specific survival; CI, confidence interval; DSW, Divorced/Seperated/Widowed; ER, Estrogen Receptor; PR, Progesterone Receptor; TNBC, Triple Negative Breast Cancer

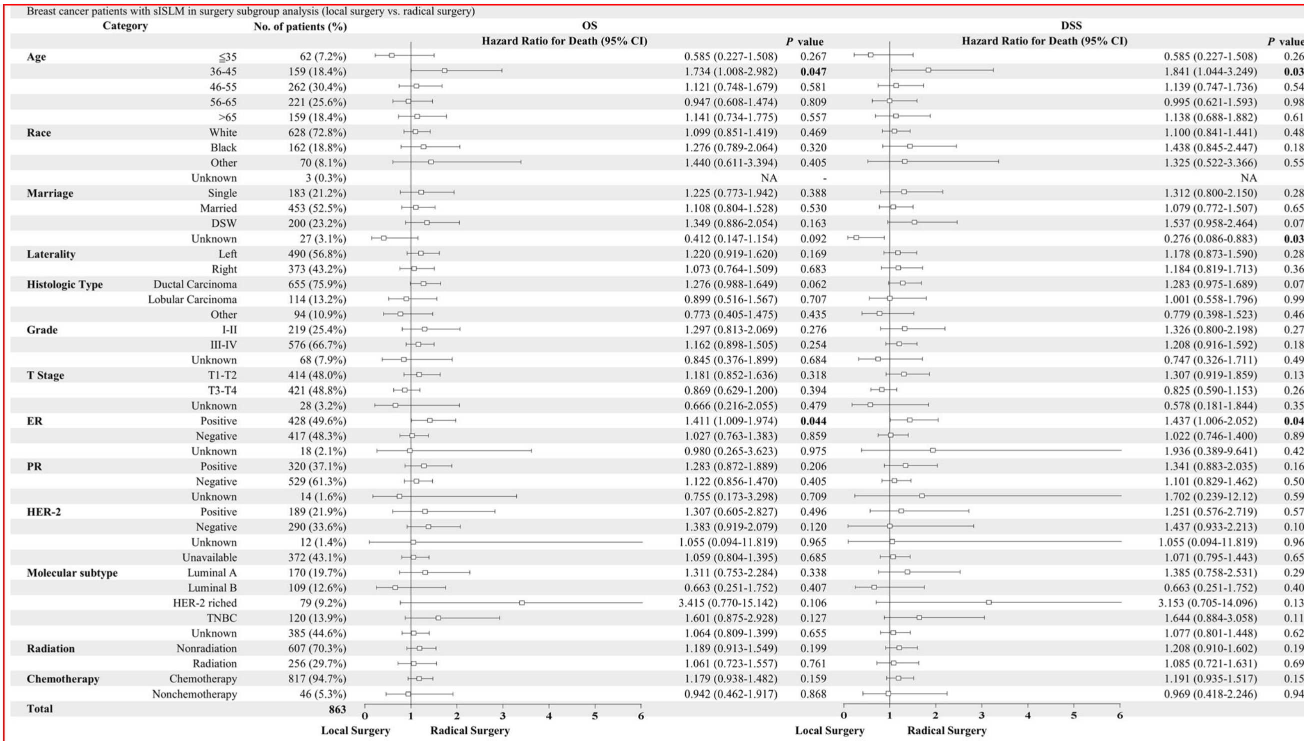
Fig. 4 Forest plot for patients with sISLM in the subgroup analysis A (surgery vs. nonsurgery). Hazard ratio (HR) with 95% confidence interval (CI) for death in the overall survival (OS) and disease-specific survival (DSS) of patients with sISLM who did and did not undergo surgery. P values of the Cox proportional hazard regression are reported

forest plots of subgroup analyses for OS and DSS indicated that surgery was a significant prognostic factor for sISLM patients (Figs. 1, 4). Further, the subgroup analysis showed that both local surgery and radical surgery might have an association with improved prognosis (Fig. 5). Moreover, about enhancing N3c patients' survival, the efficacy of local surgery is not inferior to that of radical surgery (Fig. 5). For radiotherapy, one of the most important means of local treatment, there was a significant difference between the radiation and nonradiation groups in surgery patients but not in nonsurgery patients (Fig. 3). These results suggested to our clinicians that, in the face of this specific type of breast cancer, the surgical approach might significantly improve the patient's quality of life and prognosis. Interestingly, local surgery had a similar prognostic effect as that of radical surgery, suggesting that in the clinical setting, a smaller, local treatment would be a better choice.

Retrospective studies including our study are associated with several limitations, such as inability to control for selection bias and lack of information about the administration of systemic therapy response to therapy and sequencing of treatment in patients who get multimodal therapy. Nevertheless, we tried to perform PSM to reduce the adverse effects of the natural bias and increase the objectivity and scientificity of the research. There was an association with surgery and improved prognosis and that a randomized control trial would be required to demonstrate or explore this further.

Conclusion

In conclusion, for patients with breast cancer with sISLM, surgery is an effective local intervention and the efficacy of local surgery is not inferior to that of radical surgery. The



Breast cancer patients with sISLM in surgery subgroup analysis (local surgery vs. radical surgery)

Category		No. of patients (%)	OS Hazard Ratio for Death (95% CI)	OS *P* value	DSS Hazard Ratio for Death (95% CI)	DSS *P* value
Age	≤35	62 (7.2%)	0.585 (0.227-1.508)	0.267	0.585 (0.227-1.508)	0.267
	36-45	159 (18.4%)	1.734 (1.008-2.982)	**0.047**	1.841 (1.044-3.249)	**0.035**
	46-55	262 (30.4%)	1.121 (0.748-1.679)	0.581	1.139 (0.747-1.736)	0.546
	56-65	221 (25.6%)	0.947 (0.608-1.474)	0.809	0.995 (0.621-1.593)	0.983
	>65	159 (18.4%)	1.141 (0.734-1.775)	0.557	1.138 (0.688-1.882)	0.614
Race	White	628 (72.8%)	1.099 (0.851-1.419)	0.469	1.100 (0.841-1.441)	0.486
	Black	162 (18.8%)	1.276 (0.789-2.064)	0.320	1.438 (0.845-2.447)	0.181
	Other	70 (8.1%)	1.440 (0.611-3.394)	0.405	1.325 (0.522-3.366)	0.554
	Unknown	3 (0.3%)	NA	-	NA	-
Marriage	Single	183 (21.2%)	1.225 (0.773-1.942)	0.388	1.312 (0.800-2.150)	0.282
	Married	453 (52.5%)	1.108 (0.804-1.528)	0.530	1.079 (0.772-1.507)	0.657
	DSW	200 (23.2%)	1.349 (0.886-2.054)	0.163	1.537 (0.958-2.464)	0.074
	Unknown	27 (3.1%)	0.412 (0.147-1.154)	0.092	0.276 (0.086-0.883)	**0.030**
Laterality	Left	490 (56.8%)	1.220 (0.919-1.620)	0.169	1.178 (0.873-1.590)	0.283
	Right	373 (43.2%)	1.073 (0.764-1.509)	0.683	1.184 (0.819-1.713)	0.369
Histologic Type	Ductal Carcinoma	655 (75.9%)	1.276 (0.988-1.649)	0.062	1.283 (0.975-1.689)	0.076
	Lobular Carcinoma	114 (13.2%)	0.899 (0.516-1.567)	0.707	1.001 (0.558-1.796)	0.999
	Other	94 (10.9%)	0.773 (0.405-1.475)	0.435	0.779 (0.398-1.523)	0.465
Grade	I-II	219 (25.4%)	1.297 (0.813-2.069)	0.276	1.326 (0.800-2.198)	0.273
	III-IV	576 (66.7%)	1.162 (0.898-1.505)	0.254	1.208 (0.916-1.592)	0.181
	Unknown	68 (7.9%)	0.845 (0.376-1.899)	0.684	0.747 (0.326-1.711)	0.491
T Stage	T1-T2	414 (48.0%)	1.181 (0.852-1.636)	0.318	1.307 (0.919-1.859)	0.136
	T3-T4	421 (48.8%)	0.869 (0.629-1.200)	0.394	0.825 (0.590-1.153)	0.260
	Unknown	28 (3.2%)	0.666 (0.216-2.055)	0.479	0.578 (0.181-1.844)	0.355
ER	Positive	428 (49.6%)	1.411 (1.009-1.974)	**0.044**	1.437 (1.006-2.052)	**0.046**
	Negative	417 (48.3%)	1.027 (0.763-1.383)	0.859	1.022 (0.746-1.400)	0.893
	Unknown	18 (2.1%)	0.980 (0.265-3.623)	0.975	1.936 (0.389-9.641)	0.420
PR	Positive	320 (37.1%)	1.283 (0.872-1.889)	0.206	1.341 (0.883-2.035)	0.169
	Negative	529 (61.3%)	1.122 (0.856-1.470)	0.405	1.101 (0.829-1.462)	0.507
	Unknown	14 (1.6%)	0.755 (0.173-3.298)	0.709	1.702 (0.239-12.12)	0.595
HER-2	Positive	189 (21.9%)	1.307 (0.605-2.827)	0.496	1.251 (0.576-2.719)	0.571
	Negative	290 (33.6%)	1.383 (0.919-2.079)	0.120	1.437 (0.933-2.213)	0.100
	Unknown	12 (1.4%)	1.055 (0.094-11.819)	0.965	1.055 (0.094-11.819)	0.965
	Unavailable	372 (43.1%)	1.059 (0.804-1.395)	0.685	1.071 (0.795-1.443)	0.652
Molecular subtype	Luminal A	170 (19.7%)	1.311 (0.753-2.284)	0.338	1.385 (0.758-2.531)	0.290
	Luminal B	109 (12.6%)	0.663 (0.251-1.752)	0.407	0.663 (0.251-1.752)	0.407
	HER-2 riched	79 (9.2%)	3.415 (0.770-15.142)	0.106	3.153 (0.705-14.096)	0.133
	TNBC	120 (13.9%)	1.601 (0.875-2.928)	0.127	1.644 (0.884-3.058)	0.116
	Unknown	385 (44.6%)	1.064 (0.809-1.399)	0.655	1.077 (0.801-1.448)	0.622
Radiation	Nonradiation	607 (70.3%)	1.189 (0.913-1.549)	0.199	1.208 (0.910-1.602)	0.191
	Radiation	256 (29.7%)	1.061 (0.723-1.557)	0.761	1.085 (0.721-1.631)	0.696
Chemotherapy	Chemotherapy	817 (94.7%)	1.179 (0.938-1.482)	0.159	1.191 (0.935-1.517)	0.157
	Nonchemotherapy	46 (5.3%)	0.942 (0.462-1.917)	0.868	0.969 (0.418-2.246)	0.941
Total		**863**				

sISLM, synchronous ipsilateral supraclavicular lymph node metastasis; OS, overall survival; DSS, disease-specific survival; CI, confidence interval; DSW, Divorced/Seperated/Widowed; ER, Estrogen Receptor; PR, Progesterone Receptor; TNBC, Triple Negative Breast Cancer

Fig. 5 Forest plot for the patients with sISLM in the subgroup analysis B (local surgery vs. radical surgery). Hazard ratio (HR) with 95% confidence interval (CI) for death in the overall survival (OS) and disease-specific survival (DSS) of patients with sISLM with local surgery compared with radical surgery. P values of the Cox proportional hazard regression are reported

principal clinical value of this study is to demonstrate the effectiveness of local interventions in breast cancer patients with sISLM.

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Author's contribution QC, NL, and D-JO collected the data; LZ, PZ, and QZ performed the statistical analysis; QC, LZ and PL prepare the manuscript; and WY conceived the study. All authors read and approved the final manuscript.

Data availability The authors declare that the data supporting the findings of this study are available within the article.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest

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