UPDATE OF CURRENT EVIDENCES IN BREAST CANCER SURGERY

EDITED BY: Gianluca Franceschini, Giuseppe Visconti, Akitatsu Hayashi and Riccardo Masetti

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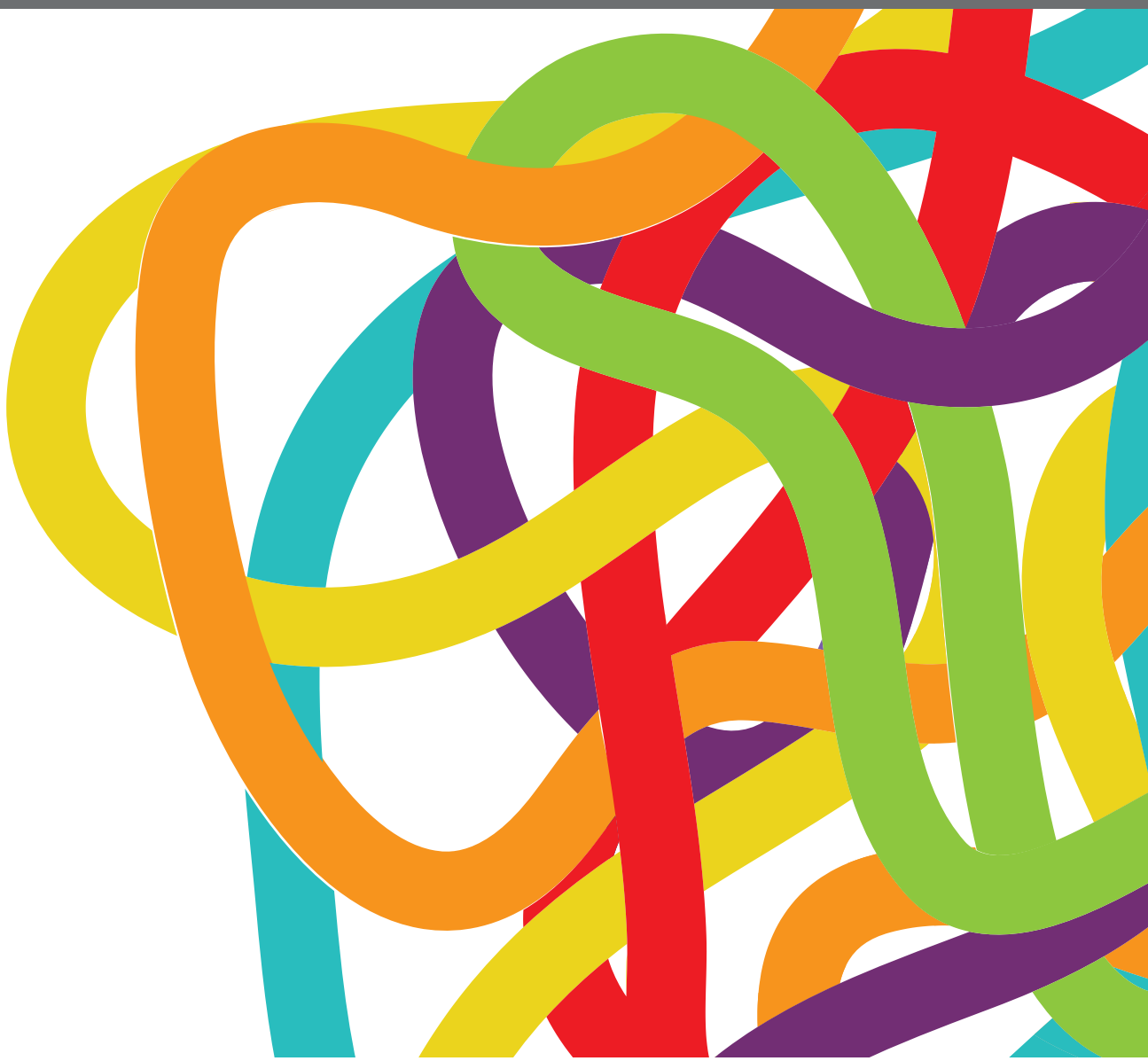

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UPDATE OF CURRENT EVIDENCES IN BREAST CANCER SURGERY

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EDITORIAL
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Editorial: Update of Current Evidences in Breast Cancer Surgery

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Keywords: breast cancer, surgical treatment, breast-conserving surgery, mastectomy, breast reconstruction, sentinel lymph node biopsy, axillary surgery

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Editorial on the Research Topic

Update of Current Evidences in Breast Cancer Surgery

Breast cancer is acknowledged as an international priority in health care; it is currently the most common cancer in women worldwide with demographic trends indicating a continuous increase in incidence (Keelan et al.). Significant efforts and resources have been dedicated in order to develop optimal strategies in breast cancer diagnosis and treatment over the last decades; increased population based screening and improved adjuvant therapies have been able to progressively reduce breast cancer mortality rates.

Early diagnosis is increasing in many developed countries thanks to the diffusion of screening programs and improvement of radiological devices despite the negative impact of COVID-19 pandemic (Buonomo et al.) (1).

Nowadays, the therapeutic strategies against breast cancer are increasingly customized for each patient and modulated according to clinical features, staging, biologic factors such as hormone receptor status, Ki67, HER2 overexpression; an accurate discussion with each patient about the advantages and issues associated with the chosen treatment should always be performed in a correct decision-making process.

However, a multidisciplinary management, involving surgical, medical and radiation oncology, is crucial to define optimal strategy, improve oncological and aesthetic results, increase patient's quality of life and prolong survival (2, 3).

Early-stage breast cancer should usually be treated by primary surgery to the breast and axillary lymph nodes; breast-conserving treatment (breast-conserving surgery (BCS) plus radiotherapy) or mastectomy are the possible surgical options; in both cases, oncological radicality and patient aesthetic satisfaction should always be ensured.

The modern breast surgeon should perform the choice of breast-conserving treatment versus mastectomy based on breast volume to cancer volume ratio, multicentricity, presence of mammographic microcalcifications, ability to achieve clear surgical margins and patient wishes; a careful evaluation of the disease by clinical and radiological examination is crucial to select the optimal local treatment.

BCS combined with adjuvant radiotherapy is now deemed the gold standard approach for early-stage breast cancer because it permits to preserve the breast without affecting oncologic results;

various prospective randomized studies have shown no significant differences in disease-free and overall survival rates when comparing breast-conserving treatment with mastectomy for early-stage breast cancer.

BCS should always ensure the complete surgical removal of the tumor with negative surgical margins and an adequate aesthetic outcome followed by adjuvant radiotherapy to eradicate any residual disease. The role of BCS has been also expanded to include some patients who would otherwise require mastectomy to obtain appropriate tumor clearance thanks to the use of oncoplastic techniques (4–6); these innovative procedures combine the principles of surgical oncology and plastic surgery to remove larger amounts of breast tissue with safer margins while improving aesthetic outcomes also with the use of filler biomaterials (7–9).

Mastectomy should be considered when a conservative treatment is unable to ensure appropriate local control and adequate aesthetic outcomes; common indications to mastectomy include extensive or multicentric disease, large cancer size in relation to the breast size that cannot be incorporated by local excision with a satisfactory cosmetic result; persistent positive margins despite multiple re-excisions; inability to perform adjuvant radiotherapy after BCS due to active connective tissue disease involving the skin or previous radiation therapy to the breast or chest wall; presence of BRCA pathogenic variants; patient preference (Yang et al., Li et al.,) (10).

The conservative mastectomies (skin-sparing and nipple-sparing mastectomies) are accepted new techniques that allow to improve aesthetic results and patient quality of life; these mastectomies combine the oncological advantage of the complete glandular excision with the optimal cosmetic result of the conservation of the skin envelope and, wherever possible, the nipple areola complex.

Immediate breast reconstruction with prosthesis or autologous tissue should always be performed after mastectomy as it can enhance the patient quality of life and positively affect their psychological health, sexuality, body image, and self-esteem (Zheng et al.).

Traditionally, reconstruction with prosthesis has been performed by placement of the implant in a submuscular pocket created beneath the pectoralis major muscle; in recent years, the placement of the prosthesis in a prepectoral plane, using polytech prothesis with micropolyurethane foam coated shell surface (microthane), has been increasingly employed (10); prepectoral approach is a safe, reliable and effective alternative to traditional technique while offering better aesthetic outcomes and patient quality life. The increasing demand for further aesthetic result improvement in breast reconstruction after mastectomy has also led to search innovative solutions by endoscopic and robotic approaches in order to limit scar visibility (Lee et al.).

As regards the surgical treatment of the axillary nodes, sentinel lymph node biopsy (SLNB) is deemed the gold standard for nodal staging in patients with early breast cancer and clinically negative nodes (Yoon et al., Wang et al., Xu et al.); axillary dissection remains the standard of care for patients with clinically positive nodes even if new therapeutic strategies are emerging in patients with a pathological positivity in sentinel lymph node (Luo et al., Al-Masri et al.).

Neoadjuvant chemotherapy (NAC) is being used with increasing frequency in the multidisciplinary treatment of patients with operable breast cancer (11). Several clinical trials have proved that NAC permits to achieve essential benefits such as assessment *in vivo* tumor's chemosensitivity by monitoring response to therapy; downstaging of tumor favoring BCS over mastectomy; reduction of excision volumes in patients with cancer who are already candidates for BCS; downstaging of the axilla in order to avoid complete axillary dissection (Lee et al.,) (12).

The locoregional treatment of metastatic breast cancer is largely reserved for palliation in patients with significant symptoms from primary tumor (13). The efficacy of this surgery is still controversial and the debate about resection of primary tumor in metastatic breast cancer patients persists (Zheng et al., Wang et al.). Surgical treatment of primary breast cancer in metastatic setting could be an option after systemic therapies. Randomized prospective trials for each immunophenotype are necessary in order to confirm this evidence (Zhang et al., Zhou et al.).

In conclusion, this Research Topic offers a set of evidence-based practice articles useful to optimize the surgical treatment of breast cancer patient by a multidisciplinary and personalized approach.

AUTHOR CONTRIBUTIONS

Contribution Author(s) Manuscript preparation: LS, GF Manuscript editing: LS, GF Manuscript review: RM, GF. All authors contributed to the article and approved the submitted version.

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ORIGINAL RESEARCH
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A Risk Stratification Model for Predicting Overall Survival and Surgical Benefit in Triple-Negative Breast Cancer Patients With *de novo* Distant Metastasis

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Background and Aims: This research aimed to construct a novel model for predicting overall survival (OS) and surgical benefit in triple-negative breast cancer (TNBC) patients with *de novo* distant metastasis.

Methods: We collected data from the Surveillance, Epidemiology, and End Results (SEER) database for TNBC patients with distant metastasis between 2010 and 2016. Patients were excluded if the data regarding metastatic status, follow-up time, or clinicopathological information were incomplete. Univariate and multivariate analyses were applied to identify significant prognostic parameters. By integrating these variables, a predictive nomogram and risk stratification model were constructed and assessed with C-indexes and calibration curves.

Results: A total of 1,737 patients were finally identified. Patients enrolled from 2010 to 2014 were randomly assigned to two cohorts, 918 patients in the training cohort and 306 patients in the validation cohort I, and 513 patients enrolled from 2015 to 2016 were assigned to validation cohort II. Seven clinicopathological factors were included as prognostic variables in the nomogram: age, marital status, T stage, bone metastasis, brain metastasis, liver metastasis, and lung metastasis. The C-indexes were 0.72 [95% confidence interval [CI] 0.68–0.76] in the training cohort, 0.71 (95% CI 0.68–0.74) in validation cohort I and 0.71 (95% CI 0.67–0.75) in validation cohort II. Calibration plots indicated that the nomogram-based predictive outcome had good consistency with the recoded prognosis. A risk stratification model was further generated to accurately differentiate patients into three prognostic groups. In all cohorts, the median overall survival time in the low-, intermediate- and high-risk groups was 17.0 months (95% CI 15.6–18.4), 11.0 months (95% CI 10.0–12.0), and 6.0 months (95% CI 4.7–7.3), respectively. Locoregional surgery improved prognosis in both the low-risk [hazard ratio [HR] 0.49, 95% CI 0.41–0.60, $P < 0.0001$] and intermediate-risk groups (HR 0.55, 95% CI 0.46–0.67, $P < 0.0001$), but not in high-risk group (HR 0.73, 95% CI 0.52–1.03, $P = 0.068$). All stratified groups could prognostically benefit from chemotherapy (low-risk group: HR 0.50, 95% CI 0.35–0.69, $P < 0.0001$; intermediate-risk group: HR 0.34,

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95% CI 0.26–0.44, $P < 0.0001$; and high-risk group: HR 0.16, 95% CI 0.10–0.25, $P < 0.0001$).

Conclusion: A predictive nomogram and risk stratification model were constructed to assess prognosis in TNBC patients with *de novo* distant metastasis; these methods may provide additional introspection, integration and improvement for therapeutic decisions and further studies.

Keywords: triple-negative breast cancer, metastasis, nomogram, overall survival, therapeutic decision

INTRODUCTION

Triple-negative breast cancer (TNBC) is a biologically invasive disease that accounts for ∼15% of breast malignancies (1). Despite the rapid development of treatment methods such as surgery, chemotherapy and immunotherapy, TNBC is still the common cause for cancer-related deaths, mainly due to distant metastasis (2).

Cancer metastasis is a complicated process, involving several stages such as invasion of the extracellular matrix, epithelial-mesenchymal transition, angiogenesis, immune invasion, and distal colonization (3). Usually during the process of distant metastasis, cancer cells (seed) escape from the primary site and adapt to the distant microenvironment (soil), which can be mediated by the "seed and soil" interaction (4). Furthermore, distant target organs can be changed and prepared for the arrest and colonization of circulating cancer cells (5, 6). In terms of triple-negative breast cancer, several studies have indicated that different genes mediate tumor cell metastasis to either bone, lung, brain or liver tissues, resulting in organ-specific metastatic heterogeneity (7–10).

In the real world, metastatic TNBC is a heterogeneous neoplasm with diverse prognostic endings and can be influenced by demographic features, including age, race and marital status, as well as clinicopathological parameters (for example, tumor size, grade, and clinical treatment) (11–14). Different metastatic sites can also influence the survival outcomes of TNBC. For instance, visceral metastasis results in a poorer prognosis than bone metastasis (15). Thus, in consideration of these clinicopathological factors that may influence patient survival, it is vital to construct a comprehensive analytic model to accurately estimate the prognostic outcome of every patient. This predictive model can help physicians make therapeutic decisions and perform clinical trials.

In recent years, the nomogram has been considered a commonly viable predictive model for assessing prognostic outcome, especially in cancer patients (16–20). Several nomograms have been established for predicting the risk of recurrence, the benefit of radiation or the response to neoadjuvant chemotherapy in breast cancer (21–23). However, no nomogram has been developed for predicting the survival outcomes of TNBC patients diagnosed with *de novo* distant metastasis. Thus, in the present research, we intended to establish and validate a nomogram for the general distantly metastatic TNBC set.

Abbreviations: TNBC, Triple-Negative Breast Cancer; OS, Overall Survival; BCSS, Breast Cancer-Specific Survival; HR, Hazard Ratio; CI, Confidence Interval; SEER, Surveillance, Epidemiology, and End Results; ECOG, Eastern Cooperative Oncology Group.

MATERIALS AND METHODS

Cohort Population and Data Processing

This was a retrospective study based on data from the Surveillance, Epidemiology, and End Results (SEER) database. In this study, case selection was conducted on the basis of the following inclusion and exclusion criteria.

Inclusion criteria: (1) pathological diagnosis was made between 2010 and 2016; (2) molecular subtype of triple-negative breast cancer; and (3) at least one distant site of *de novo* metastasis.

Exclusion criteria: (1) male breast cancer; (2) unknown metastatic status; (3) missing follow-up data; (4) incomplete clinicopathological information including race, marital status, grade, T/N stage and therapy.

Statistical Analysis

We randomly assigned the patients enrolled from 2010 to 2014 into two cohorts, the training cohort and the validation cohort I, at a ratio of three to one, and we assigned the patients enrolled from 2015 to 2016 into the validation cohort II. Descriptive statistics were applied to summarize the clinicopathological features of the three cohorts. Overall survival (OS) was compared among different subgroups with Kaplan-Meier methods and log-rank tests. Further multivariate modeling was conducted to assess the independent predictive variables for survival. In consideration of potential competitive risk factors, breast cancer-specific survival (BCSS) was further analyzed with univariate and multivariate models. Cumulative mortality curves were generated to assess the impact of competitive mortality. Statistical significance was determined with a two-sided $P < 0.05$. We executed statistical analyses with SPSS 22.0.

Based on the data of the multivariate model, a nomogram was constructed with RMS and the SURVIVAL package in R software. We used 2-, 3-, and 5-years OS for analysis in the nomogram. One thousand bootstrap resamples were used to calculate C-indexes and generate calibration plots, which assessed the predictive accuracy of the nomogram. Furthermore, a risk stratification model was developed on the basis of each patient's total scores in the nomogram to divide all cases into three prognostic groups.

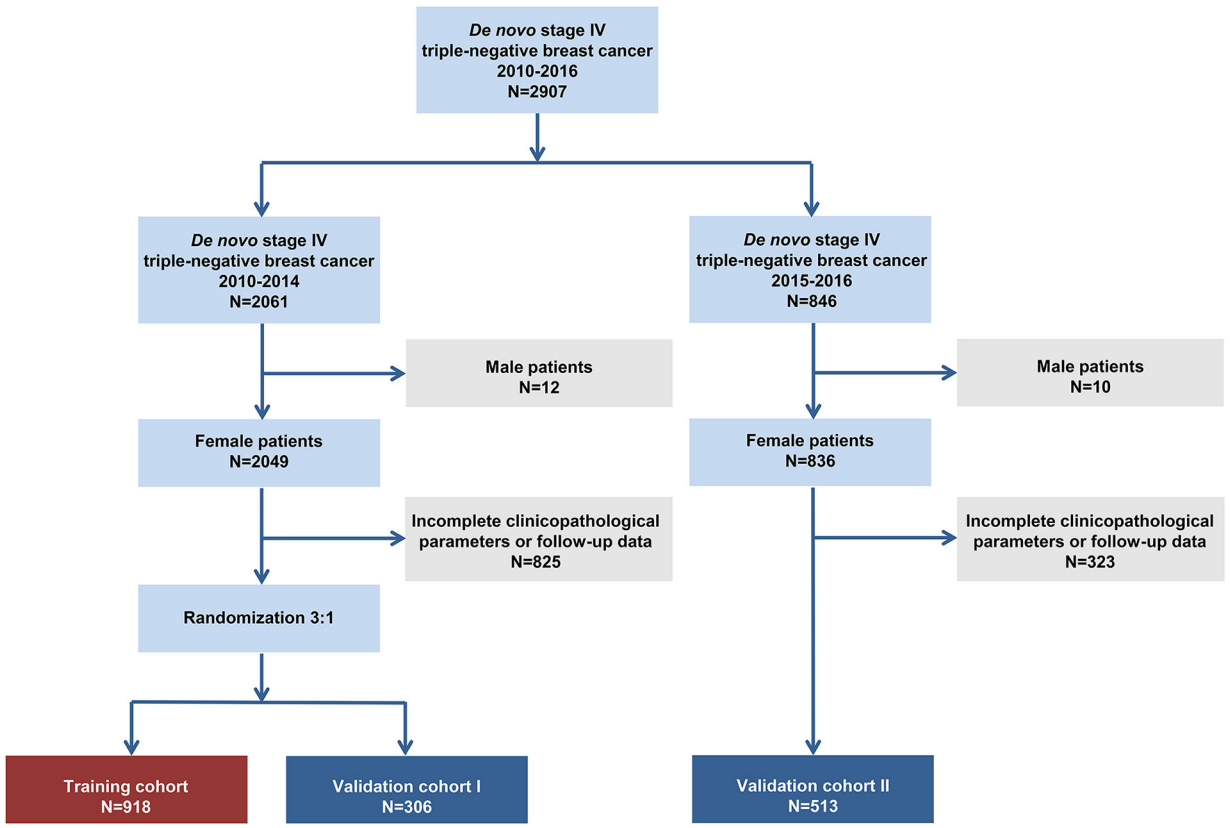

FIGURE 1 | Patient selection flowchart.

RESULTS

Patient Characteristics

The flowchart of the patient selection process is shown in **Figure 1**. In total, we included 1,737 patients based on the following criteria: 918 patients in the training set, 306 patients in validation set I and 513 patients in validation set II. The patients' baseline clinicopathological features and OS data within each subgroup are shown in **Table 1**. In the training set, 24.5% (225/918), 52.8% (485/918), and 22.7% (208/918) of the patients aged <50, 50–69, and ≥70, respectively. In addition, 9.9% (91/918), 29.5% (271/918), 19.6% (180/918), and 41.0% (376/918) of the patients had stage T1, T2 T3, and T4 tumors, respectively. Furthermore, 22.0% (202/918) of the patients had negative N stage and 78.0% (716/918) had positive N stage.

In terms of the different metastatic sites, 41.4% (380/918), 9.0% (83/918), 28.8% (264/918), and 41.9% (385/918) of the patients had metastasis to the bone, brain, liver and lung, respectively, in the training set. The median overall survival time was 11.0 (95% CI 9.6–12.4), 6.0 (95% CI 3.5–8.5), 9.0 (95% CI 7.3–10.7), and 12.0 (95% CI 10.6–13.4) months for patients with bone, brain, liver and lung metastasis, respectively.

Univariate and Multivariate Analyses for Prognosis

The following clinicopathological variables were found to be statistically significant factors for overall survival: age (<50: HR 0.671, 95% CI 0.546–0.824; 50–69: HR 0.765, 95% CI 0.641–0.913; ≥70 as a reference), marital status (married: HR 0.810, 95% CI 0.702–0.936; unmarried as a reference), T stage (T1: HR 0.664, 95% 0.513–0.859; T2: HR 0.689, 95% CI 0.581–0.818; T3: HR 0.705, 95% CI 0.583–0.853; T4 as a reference), bone metastasis (metastasis: HR 1.432, 95% CI 1.239–1.655; no metastasis as a reference), brain metastasis (metastasis: HR 1.769, 95% CI 1.394–2.246; no metastasis as a reference), liver metastasis (metastasis: HR 1.769, 95% CI 1.518–2.060; no metastasis as a reference), lung metastasis (metastasis: HR 1.313, 95% CI 1.135–1.519; no metastasis as a reference) (**Table 2**, **Figure 2**). Furthermore, univariate and multivariate analyses identified the same prognostic factors for breast cancer-specific survival (**Supplementary Table 1**, **Supplementary Figure 1**). Thus, we included all these prognostic factors for nomogram construction.

Nomogram Construction and Validation

A predictive nomogram integrating seven independent risk factors for prognosis was constructed (**Figure 3**) and scores were assigned for the clinical variables in each subgroup (**Table 3**). Among all included variables, brain metastasis had a score of 100, followed by liver metastasis (score 99), T stage (T4: score 72; T3: score 11; T2: score 7), age (≥70: score 70; 50–69: score 23), bone metastasis (score 63), lung metastasis (score 47), and marital status (unmarried: score 36). The total score of an individual patient was obtained by adding all scores based on the patient's clinical variables. The likelihood of 2-, 3-, and 5-years OS could

TABLE 1 | Baseline clinicopathological characteristics of the included patients with initially diagnosed metastatic triple-negative breast cancer.

Clinicopathological characteristics	Training set (*N* = 918)		Validation set I (*N* = 306)		Validation set II (*N* = 513)	
	No. of patients (%)	Median OS (95% CI)	No. of patients (%)	Median OS (95% CI)	No. of patients (%)	Median OS (95% CI)
Race						
White	630 (68.6)	13.0 (11.9–14.1)	194 (63.4)	12.0 (10.0–14.0)	343 (66.9)	14.0 (12.4–15.6)
Black	236 (25.7)	12.0 (10.5–13.5)	88 (28.8)	12.0 (9.7–14.3)	125 (24.4)	11.0 (10.0–12.0)
OthersΔ	52 (5.7)	13.0 (8.0–18.0)	24 (7.8)	14.0 (11.1–16.9)	45 (8.8)	14.0 (11.3–16.7)
Age						
<50	225 (24.5)	15.0 (13.2–16.8)	74 (24.2)	14.0 (12.3–15.7)	120 (23.4)	15.0 (12.7–17.3)
50–69	485 (52.8)	13.0 (11.4–14.6)	164 (53.6)	13.0 (11.3–1.47)	257 (50.1)	14.0 (10.8–17.2)
≥70	208 (22.7)	8.0 (5.6–10.4)	68 (22.2)	9.0 (5.0–13.0)	136 (26.5)	10.0 (7.8–12.2)
Marriage						
Married	383 (41.7)	15.0 (13.4–16.6)	126 (41.2)	14.0 (12.1–15.9)	241 (47.0)	16.0 (12.9–19.1)
Unmarried	535 (58.3)	11.0 (9.8–12.2)	180 (58.8)	12.0 (10.3–13.7)	272 (53.0)	11.0 (9.9–12.1)
Grade						
I	12 (1.3)	13.0 (7.9–18.1)	1 (0.3)	/	7 (1.4)	/
II	155 (16.9)	13.0 (12.0–14.0)	50 (16.3)	13.0 (11.4–14.6)	96 (18.7)	13.0 (11.5–14.5)
III	751 (81.8)	11.0 (7.8–14.2)	255 (83.3)	12.0 (9.4–14.6)	410 (79.9)	13.0 (11.2–14.8)
T stage						
T1	91 (9.9)	16.0 (10.3–21.7)	30 (9.8)	14.0 (10.0–18.0)	52 (10.1)	17.0 (10.8–23.2)
T2	271 (29.5)	15.0 (13.0–17.0)	94 (30.7)	14.0 (12.0–16.0)	149 (29.0)	14.0 (10.3–17.7)
T3	180 (19.6)	14.0 (11.8–16.2)	57 (18.6)	13.0 (10.3–15.7)	104 (20.3)	13.0 (10.2–15.8)
T4	376 (41.0)	9.0 (7.6–10.4)	125 (40.8)	11.0 (9.1–12.9)	208 (40.5)	12.0 (9.8–14.2)
N stage						
Negative	202 (22.0)	13.0 (12.0–14.0)	47 (15.4)	13.0 (11.6–14.4)	105 (20.5)	14.0 (11.1–16.9)
Positive	716 (78.0)	11.0 (8.7–13.3)	259 (84.6)	11.0 (7.0–15.0)	408 (79.5)	13.0 (11.1–14.9)
Bone metastasis						
No	538 (58.6)	15.0 (13.4–16.6)	173 (56.5)	14.0 (12.5–15.5)	284 (55.4)	15.0 (13.4–16.6)
Yes	380 (41.4)	11.0 (9.6–12.4)	133 (43.5)	10.0 (7.7–12.3)	229 (44.6)	11.0 (8.8–13.2)
Brain metastasis						
No	835 (91.0)	13.0 (12.1–13.9)	271 (88.6)	13.0 (11.5–14.5)	460 (89.7)	14.0 (12.3–15.7)
Yes	83 (9.0)	6.0 (3.5–8.5)	35 (11.4)	7.0 (2.4–11.6)	53 (10.3)	6.0 (4.0–8.0)
Liver metastasis						
No	654 (71.2)	15.0 (13.6–16.4)	220 (71.9)	13.0 (11.6–14.4)	375 (73.1)	14.0 (12.1–15.9)
Yes	264 (28.8)	9.0 (7.3–10.7)	86 (28.1)	8.0 (4.2–11.8)	138 (26.9)	11.0 (6.5–15.5)
Lung metastasis						
No	533 (58.1)	13.0 (11.7–14.3)	199 (65.0)	14.0 (12.8–15.2)	306 (59.6)	14.0 (11.8–16.2)
Yes	385 (41.9)	12.0 (10.6–13.4)	107 (35.0)	10.0 (7.1–12.9)	207 (40.4)	12.0 (9.4–14.6)
Chemotherapy						
No	203 (22.1)	3.0 (2.2–3.8)	65 (21.2)	2.0 (1.4–2.6)	105 (20.5)	3.0 (1.7–4.3)
Yes	715 (77.9)	15.0 (13.8–16.2)	241 (78.8)	15.0 (13.8–16.2)	408 (79.5)	15.0 (13.4–16.6)
Surgery						
No	465 (50.7)	8.0 (6.9–9.1)	160 (52.3)	10.0 (7.8–12.2)	333 (64.9)	10.0 (8.5–11.5)
Yes	453 (49.3)	18.0 (16.5–19.5)	146 (47.7)	16.0 (12.7–19.3)	180 (35.1)	18.0 (14.3–21.7)

ΔOthers include American Indian, AK Native, Asian, and Pacific Islander.
OS, Overall Survival; CI, Confidence Interval.

be obtained by drawing a straight line on the "total points" axis (**Figure 3**).

The C-indexes in the training (0.72, 95% CI 0.68–0.76), validation I (0.71, 95% CI 0.68–0.74), and validation II (0.71, 95% CI 0.67–0.75) cohorts suggested acceptable predictive accuracy of the model. The calibration plots in the training set suggested that the predictive outcome had good agreement with the recorded survival results (**Figures 4A,B**). The calibration curves

TABLE 2 | Univariate and multivariate analyses for overall survival.

Clinicopathological characteristics	Univariable analysis *P*	Multivariable analysis	
		Hazard ratio (95% CI)	*P*
Race	0.810		
White			
Black			
Others			
Age	0.001		0.001
<50		0.671 (0.546–0.824)	<0.001
50–69		0.765 (0.641–0.913)	0.003
≥70		Reference	
Marriage	<0.001		0.004
Married		0.810 (0.702–0.936)	0.004
Unmarried		Reference	
Grade	0.441		
I			
II			
III			
T stage	<0.001		<0.001
T1		0.664 (0.513–0.859)	0.002
T2		0.689 (0.581–0.818)	<0.001
T3		0.705 (0.583–0.853)	<0.001
T4		Reference	
N stage	0.249		
Negative			
Positive			
Bone metastasis	<0.001		<0.001
Yes		1.432 (1.239–1.655)	<0.001
No		Reference	
Brain metastasis	<0.001		<0.001
Yes		1.769 (1.394–2.246)	<0.001
No		Reference	
Liver metastasis	<0.001		<0.001
Yes		1.769 (1.518–2.060)	<0.001
No		Reference	
Lung metastasis	<0.001		<0.001
Yes		1.313 (1.135–1.519)	<0.001
No		Reference	

in validation sets I and II also showed that the nomogram-based predictive outcome had good consistency with the recoded prognosis results (**Figures 4C–F**).

Risk Stratification Model

Moreover, a risk stratification model was generated on the basis of each patient's total scores from the nomogram to divide all patients into three prognostic groups. According to the risk stratification model, all the patients were stratified into three groups: low-risk group (792/1,737, 45.6%; total score<150), intermediate-risk group (692/1,737, 39.8%; total score 150–249), and high-risk group (253/1,737, 14.6%; total score ≥ 250) (**Figure 3**). In all cohorts, the median overall survival time in the low-, intermediate- and high-risk groups was 17.0 months (95% CI 15.6–18.4), 11.0 months (95% CI 10.0–12.0), and 6.0 months (95% CI 4.7–7.3), respectively. The Kaplan-Meier methods indicated that the risk stratification model could accurately differentiate survival in the three prognostic groups (**Figures 5A–C**). Cumulative mortality curves were generated to assess the impact of competitive events. There was no significant difference with regard to competitive mortality in all cohorts ($P > 0.05$) (**Figures 5D–F**), indicating that the primary outcome in this research was not affected by the potential competitive risk factors.

Survival Benefit of Surgery and Systemic Therapy in Stratified Risk Groups

To further assess the survival benefit of surgery, Kaplan-Meier curves were generated in the stratified risk groups. The results showed that surgery could prolong overall survival in both the low- and intermediate-risk groups (low-risk group: HR 0.49, 95% CI 0.41–0.60, $P < 0.0001$; intermediate-risk group: HR 0.55, 95% CI 0.46–0.67, $P < 0.0001$) (**Figures 6A,B**). However, surgery did not significantly improve prognosis in the high-risk group (HR 0.73, 95% CI 0.52–1.03, $P = 0.068$) (**Figure 6C**). In terms of systemic therapy, all stratified groups could prognostically benefit from chemotherapy (low-risk group: HR 0.50, 95% CI 0.35–0.69, $P < 0.0001$; intermediate-risk group: HR 0.34, 95% CI 0.26–0.44, $P < 0.0001$; high-risk group: HR 0.16, 95% CI 0.10–0.25, $P < 0.0001$) (**Figures 7A–C**).

DISCUSSION

In the present study, a nomogram was conducted and validated for predicting survival outcomes in distantly metastatic TNBC patients. We finally included 1,737 patients and identified seven demographic and clinicopathological features as prognostic factors including age, marital status, T stage, and bone/brain/liver/lung metastasis. Further C-index assessment and calibration curves suggested that the nomogram had optimal predictive accuracy. Moreover, a risk stratification model was generated on the basis of each patient's total scores from the nomogram and the survival benefits of therapeutic choices were analyzed in the classified risk groups.

To the best of knowledge, this is the first large-cohort, comprehensive retrospective study that has developed a predictive nomogram for the prognosis of TNBC patients with distant organ metastasis. Our prognostic model can be feasibly applied in clinical practice to predict the survival probability of each individual patient, and remind doctors of the expected benefits of different treatments. Furthermore, the newly established risk stratification system recognizes high-risk patients who need additional adjuvant therapies. Follow-up period can be narrowed for timely adjustment of treatment protocols in the high-risk subgroups. In the meantime, these high-risk patients can also be encouraged to take part in ongoing clinical trials for novel drugs. Moreover, this predictive tool is useful for the guidance of controlling confounding bias in research design, especially in those regarding overall survival as primary endpoints. In brief, we believe that patients enrolled for nomogram construction

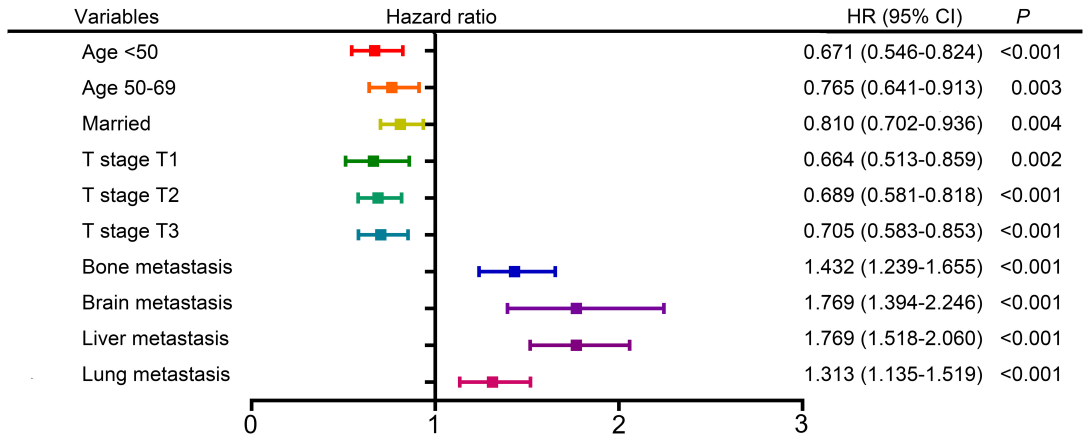

FIGURE 2 | Forest plot showing the results of multivariate analysis for overall survival.

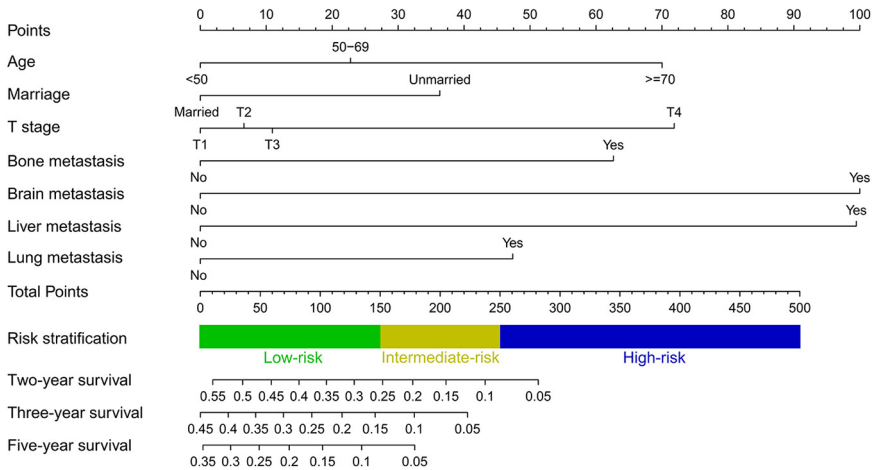

FIGURE 3 | Nomogram for predicting 2-, 3- and 5-years overall survival in TNBC patients with *de novo* distant metastasis.

TABLE 3 | Scores of clinical variables in each subgroup.

Variables	Points	Variables	Points
Age		Bone metastasis	
<50	0	No	0
50–69	23	Yes	63
≥70	70	Lung metastasis	
Marriage		No	0
Married	0	Yes	47
Unmarried	36	Liver metastasis	
T stage		No	0
T1	0	Yes	99
T2	7	Brain metastasis	
T3	11	No	0
T4	72	Yes	100

represent the majority of metastatic TNBC patients, which guarantees the translational value of this predictive model in real situations.

In our findings, demographic features (age and marital status) and clinicopathological variables (T stage and bone/brain/liver/lung metastasis) were independent prognostic factors, results that were consistent with previous publications (11, 24, 25). Among all these distal metastatic sites, brain metastasis was the key factor with the poorest prognosis, followed by liver, lung and bone metastasis. A previous large-cohort study considered breast cancer patients as a whole population and showed a similar trend in terms of the influence of different distant metastatic sites on patient survival (13).

The standard treatment for TNBC patients with *de novo* distant metastasis usually consists of palliative systemic therapies such as chemotherapy. The survival benefit of locoregional resection remains controversial. A multicenter, phase III, randomized, controlled trial MF07-01 indicated that locoregional treatment could improve 5-years survival in *de novo* stage IV breast cancer patients (26). A recently published multicentric retrospective study in France indicated that locoregional treatment improved overall survival in breast cancer patients

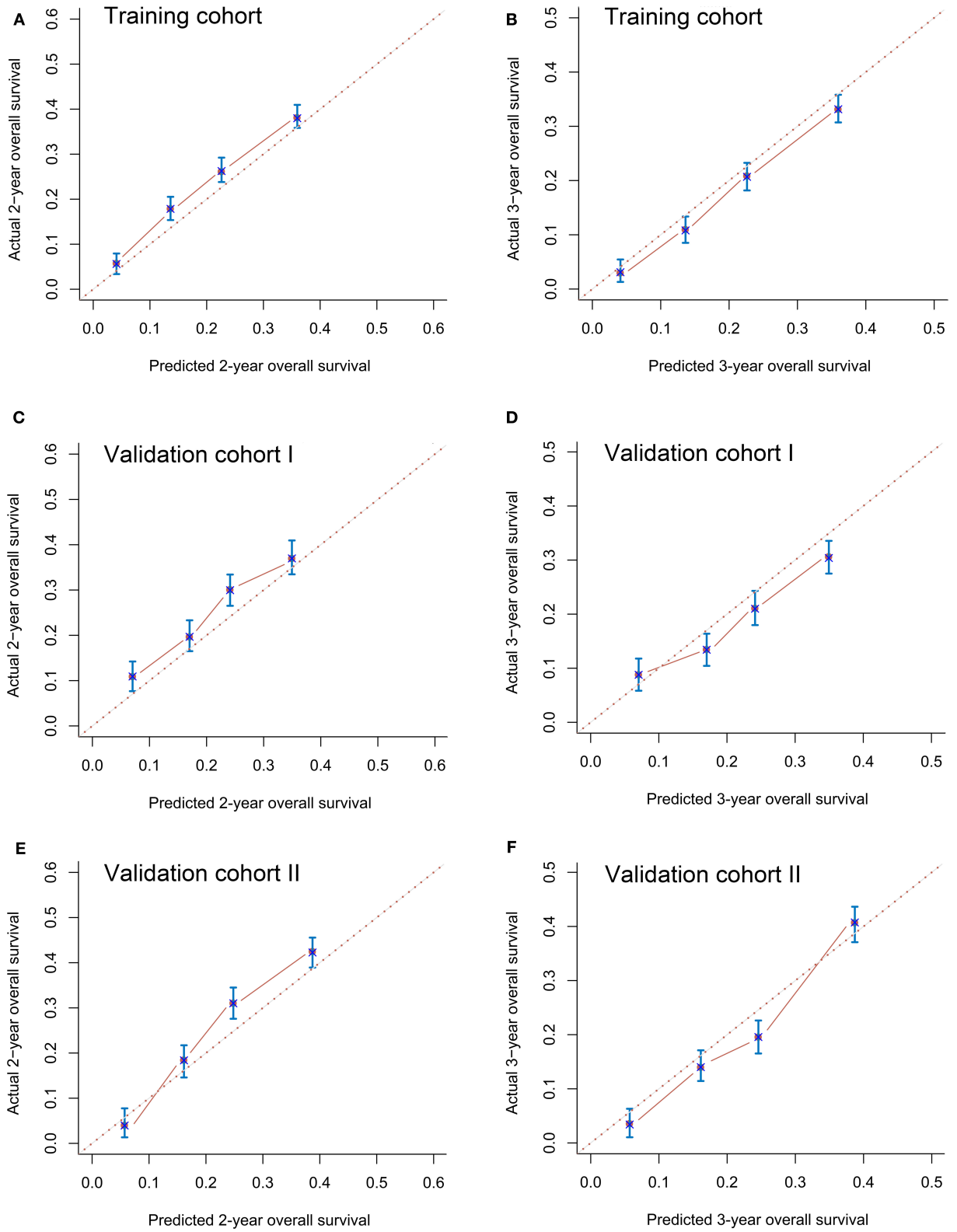

FIGURE 4 | Calibration curves for predicting 2-years **(A)** and 3-years **(B)** overall survival in the training cohort, 2-years **(C)** and 3-years **(D)** overall survival in validation cohort I and 2-years **(E)** and 3-years **(F)** overall survival in validation cohort II.

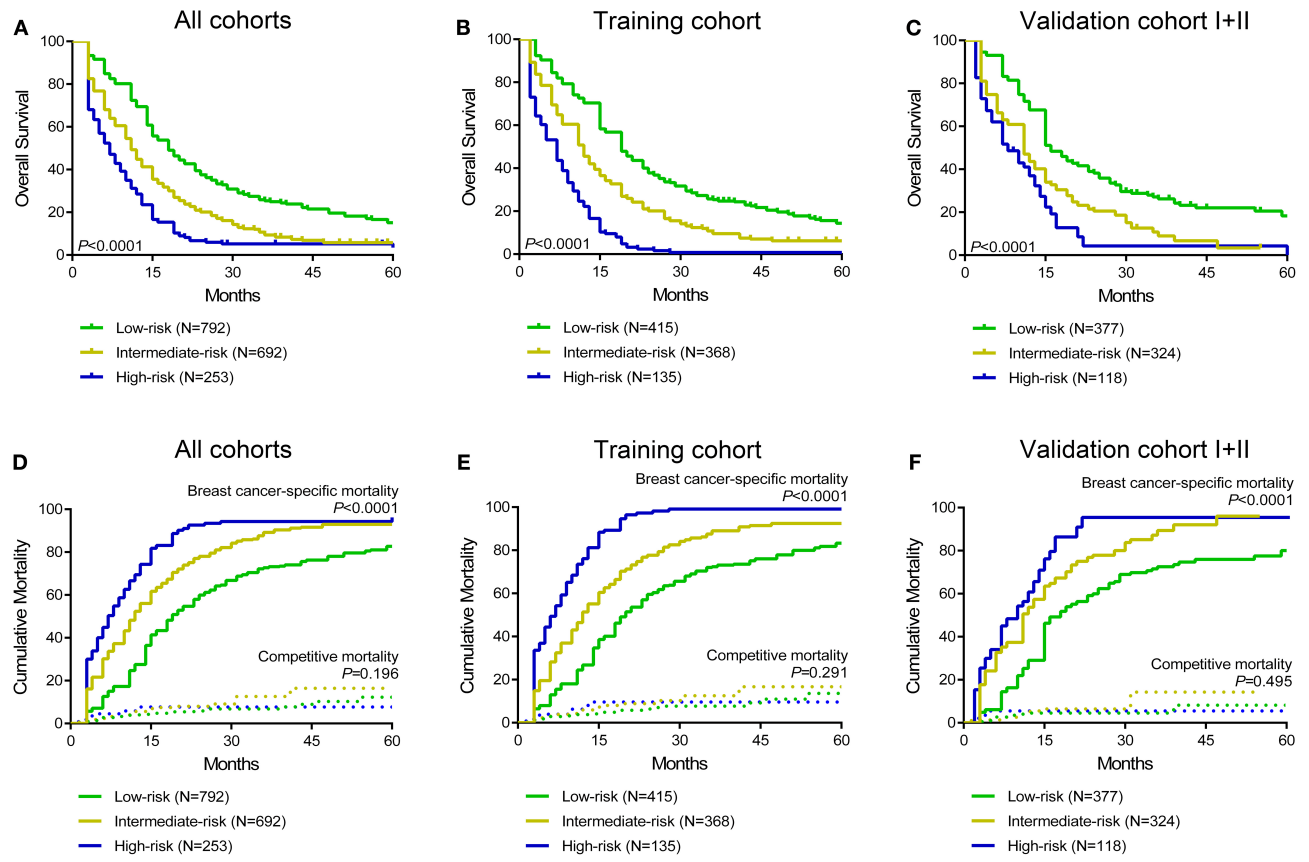

FIGURE 5 | Kaplan curves of low-, intermediate- and high-risk groups in all cohorts **(A)**, the training cohort **(B)**, and validation cohort I+II **(C)**. Cumulative breast cancer-specific and competitive mortality curves stratified by risk groups in all cohorts **(D)**, the training cohort **(E)**, and validation cohort I+II **(F)**.

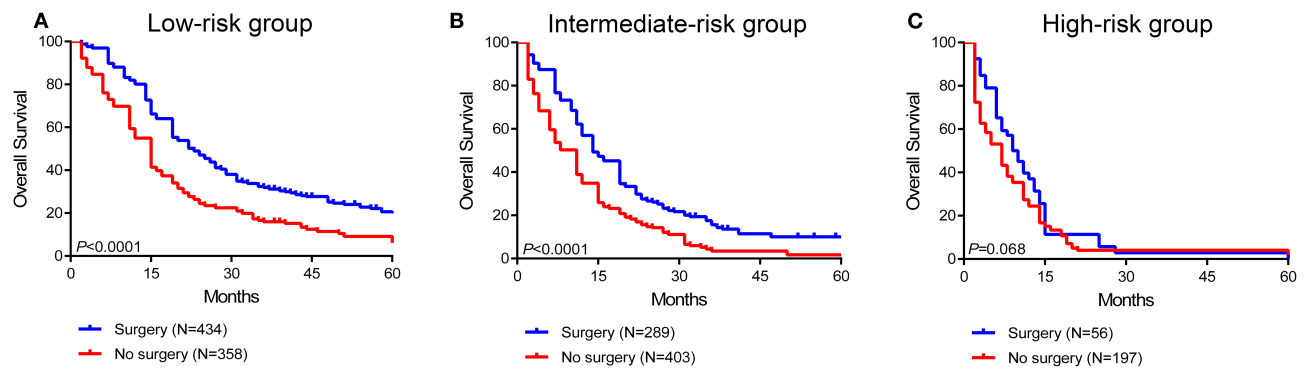

FIGURE 6 | Survival benefit of surgery in the low-risk **(A)**, intermediate-risk **(B)**, and high-risk **(C)** groups.

with synchronous metastasis, especially in patients with the molecular subtype of HR-positive/HER2-negative and HER2-positive (27). Another retrospective study in Chinese patients showed that surgical removal of the primary tumor could improve the prognosis of patients with bone metastasis alone (28). Importantly, surgery can offer solid pathological evidence for molecular classification, can alleviate clinical symptoms and can reduce tumor burden. However, not all patients can obtain a survival benefit from locoregional therapy. The ABCSG-28 trial did not indicate a survival benefit for locoregional surgery in *de novo* metastatic breast cancer (29). Another open-labeled randomized controlled trial in India also identified that breast operations could not prolong survival in patients with primary metastasis (30). Thus, personal demographic and clinicopathological parameters need to be considered carefully to make a therapeutic decision for each patient. It

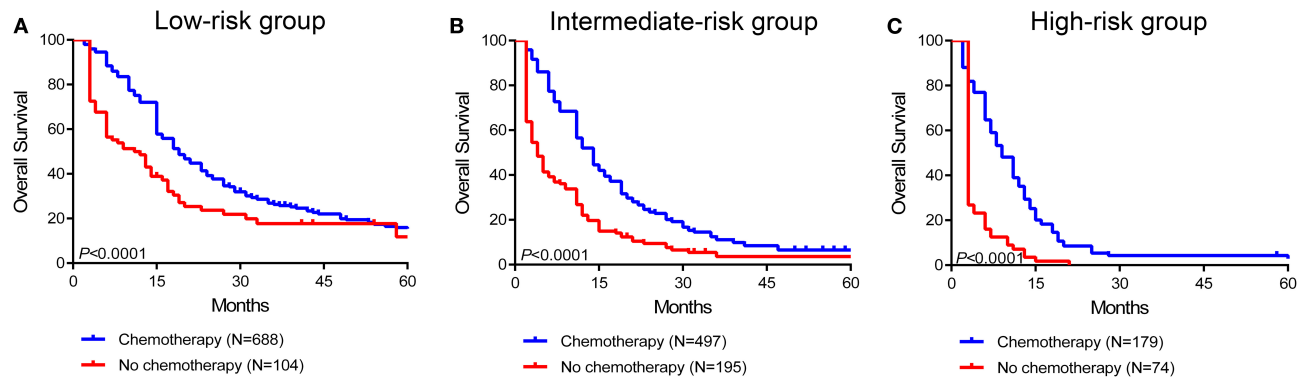

FIGURE 7 | Survival benefit of chemotherapy in the low-risk **(A)**, intermediate-risk **(B)**, and high-risk **(C)** groups.

is vital to construct a risk stratification model integrating all these parameters to precisely identify those patients who can prognostically benefit from locoregional resection. Notably, in our established model, surgery could only improve the survival outcome in low- and intermediate-risk groups, but not in high-risk groups, which provided more accurate information for therapeutic decisions.

To our knowledge, this research is among the innovative studies that have conducted a predictive nomogram for general metastatic TNBC patients. However, there may be several limitations in the present research. The first may be the retrospective nature of SEER-based research. Second, information about some potential prognostic parameters, such as the Eastern Cooperative Oncology Group (ECOG) performance status score, the detailed chemotherapy protocol and the multigene signature assessment, were not provided in the database (31–33). In addition, the database only included information on *de novo* distant metastasis. Some patients may have developed metachronous metastasis during follow-up which is unknown from the database. Last, only the patients diagnosed from 2010 to 2016 were ultimately enrolled for analysis, since distant metastatic locations and molecular classification were recorded from 2010 in the SEER database. Additionally, the majority of enrolled patients were Caucasian and black, so the nomogram needs to be validated in external cohorts, especially in Asian patients. Thus, we suggest further prospective studies be performed and that more prognostic variables be considered to improve our predictive model.

In summary, a novel predictive nomogram and risk stratification model were conducted for predicting individual survival in TNBC patients with *de novo* distant metastasis. This prognostic model may help clinical physicians make better decisions and may help in the design of future prospective studies.

DATA AVAILABILITY STATEMENT

The datasets analyzed for this study can be found in the SEER database (https://seer.cancer.gov/).

ETHICS STATEMENT

This research was based on the publicly available data from the SEER database and the data-use agreement was assigned. Patients' informed consent was not required because no direct interaction with patients was performed and no personal identification was applied in this study. In addition, this research was conducted in compliance with the Declaration of Helsinki.

AUTHOR CONTRIBUTIONS

ZW, HW, and X-SC designed this study. ZW, XS, and YF performed the search and collected data. S-SL and S-ND rechecked data. ZW and XS performed analysis and wrote the manuscript. X-SC and K-WS helped to revise the manuscript. All authors approved the final version of the manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2020.00014/full#supplementary-material

Supplementary Figure 1 | Forest plot showing the results of multivariate analysis for breast cancer-specific survival.

Supplementary Table 1 | Univariate and multivariate analyses for breast cancer-specific survival.

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Individualized Prediction of Survival Benefit From Locoregional Surgical Treatment for Patients With Metastatic Breast Cancer

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Objective: Recently, performing locoregional surgical treatment still remains debatable in patients with metastatic breast cancer (MBC). Current study aimed to develop prognostic nomograms for predicting the long-term survival in MBC patients with or without surgical intervention, thereby assisting clinicians in making individualized choice.

Methods: The training set included 5173 patients who were diagnosed with MBC in 2010–2013 from the Surveillance, Epidemiology, and End Results Program, while the validation set comprised 2924 patients diagnosed in 2014–2015. Multivariant Cox hazard model was applied to determine the independent risk factors for overall survival (OS) and breast cancer specific survival (BCSS). Then, individualized pre- and postoperative nomograms for predicting 1- or 3-year survival probabilities were constructed accordingly. Internal and external validations were conducted to determine the accuracy of these nomograms by calculating concordance index (C-index) and plotting calibration curves.

Results: The survival analysis indicated that surgical management conferred improved OS and BCSS in patients with metastatic breast cancer. Age, T stage, grade, distant metastatic site, ER, PR and HER2 status, radiation, and chemotherapy were independent risk factors for OS and BCSS both in surgery and non-surgery group. All these factors were subsequently incorporated into the nomogram which showed acceptable predictive capabilities with C-index range of 0.65–0.80 both in training set and external validation set. In addition, a preoperative nomogram incorporating variables capable of being determined before surgery was also built with C-index above 0.70 both in training and validation set.

Conclusion: Surgical management in patients with metastatic breast cancer suggests a potential survival advantage. In addition, these well-validated pre- and postoperative nomograms may provide a useful tool to assist clinicians in treatment decision-making and in evaluating patients' long term prognosis.

Keywords: metastatic breast cancer, nomogram, SEER program, prognosis, clinic utility

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INTRODUCTION

Breast cancer is the most frequently diagnosed cancer in women, and accounts for the second leading cause of cancer-related mortality in the USA (1). Although the treatment of breast cancer has made great progress in recent years, largely because of the emergence of endocrine therapy and anti-HER2 therapy, surgical treatment is still the preferred option for non-metastatic breast cancer and is considered the foundation of subsequent comprehensive treatment. Nevertheless, a substantial proportion of breast cancer patients, approximately 6%, have suffered distant metastasis when they are first diagnosed (2). It was reported that the median survival time of metastatic breast cancer (MBC) patients is approximately 18–24 months with 5– and 10–year survival rates as low as 27 and 13%, respectively (3).

Since stage IV breast cancer is still considered incurable, the primary goal of treatment is to extend life expectancy and improve quality of life. According to the NCCN guideline, the primary treatment approach for metastatic breast cancer is systemic therapy, and surgery is not recommended except for those patients requiring palliation of symptoms or with impending complications, such as skin ulceration and bleeding (4). However, although MBC might exhibit good response to systemic therapy, like chemotherapy and endocrine therapy, the majority of patients suffered disease progression after 1–2 years (5). Over the past several years, some retrospective studies have suggested a potential survival benefit from aggressive surgical excision of primary breast tumor in patients with metastatic breast cancer (6–9). However, several studies have also indicated that surgical intervention does not improve survival of patients with metastatic breast cancer (10, 11). A prospective clinical trials conducted in India (NCT00193778) demonstrated that locoregional treatment of the primary tumor does not affect overall survival in MBC patients (12). On the contrary, another prospective study named MF07-01 (NCT00557986) in Turkey reported that the initial surgery group showed statistically significant improvement in 5-year overall survival, especially in subgroup with positive hormone receptors (HR), negative HER2, or younger than age 55 (13). They hold the opinion that various factors including age, comorbidities, tumor type and metastatic disease burden should be considered before opting locoregional treatment in *de novo* stage IV breast cancer. Moreover, after combination of those two randomized clinical trials, a recent systemic review concluded that existing evidence was insufficient to make definitive conclusions on the survival benefit of breast surgery for patients diagnosed with MBC (14). Recently, clinicians still remain ambivalent about whether to perform primary tumor surgery for patients with MBC. Therefore, a more individualized approach considering potential risks and benefits of surgical intervention may be justified.

As such, this study exploited the data from SEER program to separately identify independent prognostic factors associated with survival of MBC patients who received surgical treatment or not. Several individualized nomograms were subsequently constructed for predicting the long term survival of MBC patients with or without surgery. We also designed a preoperative version of nomogram in which each factor can be determined before surgery decision. After that, those nomograms were separately validated in an external dataset. We hope that those nomograms may assist clinicians in evaluating each patient's long term survival by taking multiple risk factors into consideration, thereby allowing for more personalized stratification of the potential benefits of surgical intervention for patients suffered from metastatic breast cancer.

MATERIALS AND METHODS

Database and Patient Selection

Data were extracted from the recently released SEER database [Incidence- SEER 18 Regs Custom Data (with additional treatment fields), Nov 2018 Sub] containing information of cancer patients diagnosed from 1975 to 2016. SEER*Stat software version 8.3.6 (National Cancer Institute, USA) was used to access the database with permission from the SEER program office. A total of 17446 patients met the criteria of metastatic breast cancer (International Classification of Diseases for Oncology-3 histologic type/behavior code: 8500/3-8543/3) who were diagnosed from 2010 to 2015 were screened out from the database. Subsequently, patients who met the following criteria were excluded: (1) unknown race; (2) unknown histological grade; (3) stage T0, TX or NX breast cancer; (4) unknown specific surgery type; (5) unknown estrogen receptor (ER), progesterone receptor (PR), or HER2 status; (6) unknown information of distant metastasis; (7) unknown radiation information; (8) patients with incomplete follow-up; (9) patients with multiple primary cancer. Finally, 8097 metastatic breast cancer patients were included in this study. Of these patients, 5173 patients who were diagnosed from 2010 to 2013 were chosen as the training set, while 2924 patients diagnosed from 2014 to 2015 were used as the validation cohort. Subsequently, each cohort was further divided into two subgroups based on whether they had undergone locoregional surgical treatment or not. The flowchart of patient selection was shown in **Figure 1**.

Covariates

Variables including demographic characteristics (age at diagnosis, gender, Race), disease characteristics (T stage, N stage, histological grade, distant metastatic site, ER, PR and HER2 status), and treatment characteristics (radiation, chemotherapy, and surgery type) were involved in the analysis. Continuous variable, age at diagnosis, was transformed into categorical variables ($<$35, 35–49, 50–69, and $\geq$70). Based on specific surgery information, surgery type was categorized into two groups, lumpectomy/mastectomy (lumpectomy, subcutaneous mastectomy, or total mastectomy) and radical mastectomy (radical mastectomy, modified radical mastectomy, or extended radical mastectomy). Survival months, vital status record, and cause-specific death classification were used to calculate OS and BCSS.

Statistical Analysis

Descriptive statistics were first used to assess the baseline characteristics of metastatic breast cancer patients. Chi-square test was utilized to compare the clinicopathologic characteristics

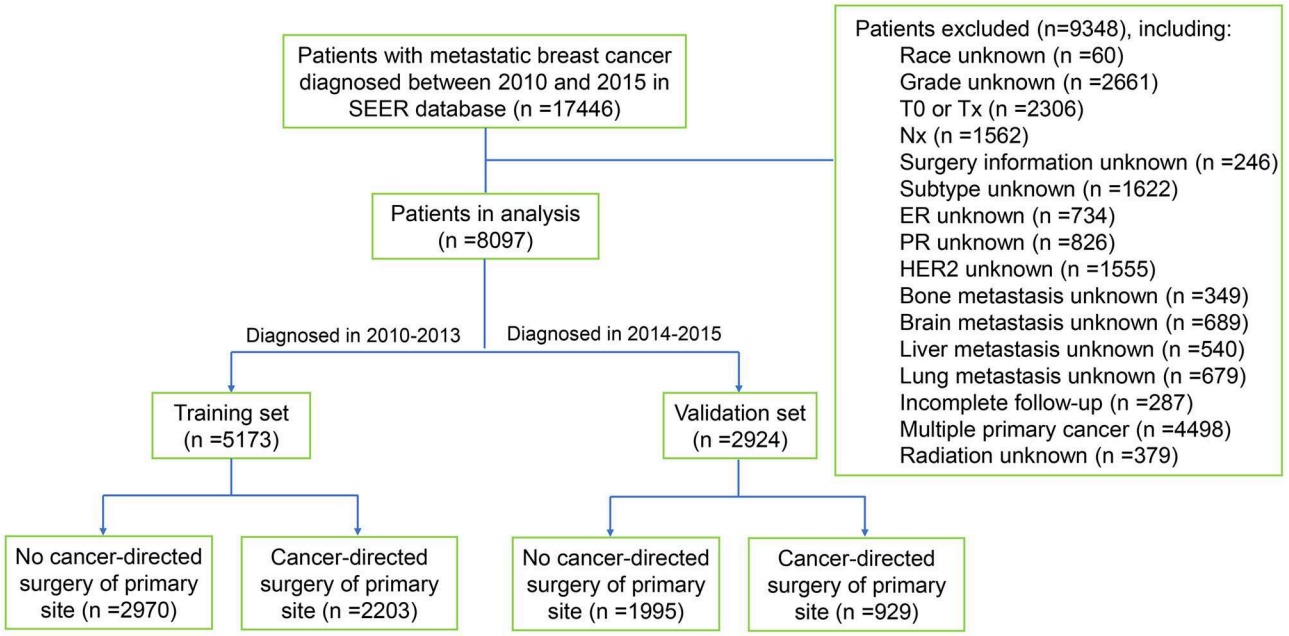

FIGURE 1 | Flowchart of data selection. SEER, Surveillance, Epidemiology, and End Results Program.

between the training and validation set. Kaplan-Meier plot and log-rank test were performed to compare differences of OS and BCSS between surgery and non-surgery group. For subgroup analyses, a multivariate Cox hazard model containing all covariates, including age, T and N stage, histological grade, distant metastatic site, ER, PR and HER2 status, record of radiation and chemotherapy, was utilized to evaluate the survival benefit of locoregional surgical treatment in each subgroup. For subsequent survival analysis in subgroups with or without surgery, univariate Cox proportional hazard model was first generated to estimate the impact of each variable on OS and BCSS. Then, all variables with p-value < 0.05 in univariate Cox model were included in multivariate Cox proportional hazard model.

Individualized nomograms for both surgery and non-surgery subgroups were developed to predict 1- or 3-year OS and BCSS according to the multivariate Cox result. Since predicting survival preoperatively makes great sense with regard to the surgical decision-making, a new version of preoperative nomogram was also constructed by including covariates that can be evaluated preoperatively either by needle biopsy or advanced imaging method, including age, T and N stage, ER, PR and HER2 status, histological grade, and distant metastatic site. The accuracies of these nomograms were evaluated by means of discrimination and calibration. Discrimination was measured using the concordance index (C-index), while calibration was assessed by graphic calibration curves which estimate the consistency between the nomogram predicted probability and actual observed outcome. We also evaluated these nomograms in the external validation set by calculating the C-index and plotting the calibration curves. All the statistical analyses were performed using SPSS 24.0 (Chicago, IL, USA). All the nomograms and calibration curves were plotted by using R software version 3.6.0. A two-tailed $p < 0.05$ was considered statistically significant.

RESULTS

Characteristics of Patients in the Datasets

Through rigorous screening and selection, a total of 8097 patients with metastatic breast cancer diagnosed from 2010 to 2015 were included in this study. All these patients were divided into training and validation set for the purpose of performing an external validation. The training set included 5173 patients diagnosed from 2010 to 2013, while the validation set comprised 2924 patients diagnosed form 2014 to 2015. The baseline characteristics of these two cohorts were shown in **Supplementary Table 1**. The proportion of breast cancer patients who had undergone surgery treatment in validation set was relatively lower (31.8 vs. 42.6 %) than training set. Moreover, patients in validation set had received less radiation therapy than training set (61.9 vs. 66.8 %). In general, the characteristics of the patients in validation set were slightly different compared with the training set, implying a higher value of external validation.

Among the 5173 breast cancer patients in training set, 2203 patients had received locoregional surgical treatment while 2970 patients had not undergone cancer directed surgery. As shown in **Table 1**, patients in the surgery group had higher proportion of 35–49-year-old age (24.6 vs. 17.8 %) compared with non-surgery group ($p < 0.001$). Patients in surgery group tended to have tumor with smaller size, higher histological grade, hormone-receptor (HR) positive, and more extent of regional lymph node involvement (all $p < 0.05$). Moreover, the non-surgery

TABLE 1 | Patient demographics and disease characteristics.

Variables	No surgery ($n = 2970$), n (%)	Surgery ($n = 2203$) n (%)	*p*-value
Age[median (IQR[a])]	60 (51–70)	57 (48–67)	$p < 0.001$
<35	99 (3.3)	102 (4.6)	$p < 0.001$
35–49	528 (17.8)	542 (24.6)	
50–69	1562 (52.6)	1124 (51.0)	
≥ 70	781 (26.3)	435 (19.7)	
Gender			
Female	2941 (99.0)	2172 (98.6)	$p = 0.153$
Male	29 (1.0)	31 (1.4)	
Race			
Black	552 (17.6)	363 (16.5)	$p = 0.542$
White	2216 (74.6)	1672 (75.9)	
Other	232 (7.8)	168 (7.6)	
T Stage			
T1	351 (11.8)	261 (11.8)	$p < 0.001$.
T2	928 (31.2)	857 (38.9)	
T3	504 (17.0)	421 (19.1)	
T4	1187 (40.0)	664 (30.1)	
N Stage			
N0	721 (24.3)	369 (16.7)	$p < 0.001$
N1	1569 (52.8)	829 (37.6)	
N2	287 (9.7)	449 (20.4)	
N3	393 (13.2)	556 (25.2)	
Grade			
High, I	225 (7.6)	131 (5.9)	$p < 0.001$
Intermediate, II	1335 (44.9)	744 (33.8)	
Low, III	1385 (46.6)	1311 (59.5)	
Anaplastic, IV	25 (0.8)	17 (0.8)	
Distant Metastasis			
Bone only	1024 (34.5)	920 (41.8)	$p < 0.001$
Liver only	191 (6.4)	206 (9.4)	
Lung only	264 (8.9)	251 (11.4)	
Brain only	32 (1.1)	22 (1.0)	
Other site	261 (8.8)	376 (17.1)	
Multiple sites	1198 (40.3)	428 (19.4)	
ER Status			
Negative	723 (24.3)	636 (28.9)	$p < 0.001$
Positive	2247 (75.7)	1567 (71.1)	
PR Status			
Negative	1164 (39.2)	940 (42.7)	$p = 0.012$
Positive	1806 (60.8)	1263 (57.3)	
HER2 Status			
Negative	2167 (73.0)	1597 (72.5)	$p = 0.707$
Positive	803 (27.0)	606 (27.5)	
Axillary Lymph Node			
Negative	41 (1.4)	299 (13.6)	$p < 0.001$
Positive	832 (28.0)	1529 (69.4)	
Not evaluated	2097 (70.6)	375 (17.0)	
Radiation			
No	2077 (69.9)	1123 (51.0)	$p < 0.001$
Yes	893 (30.1)	1080 (49.0)	
Chemotherapy			
No	1367 (46.0)	666 (30.2)	$p < 0.001$
Yes	1603 (54.0)	1537 (69.8)	

[a] *interquartile range.*

group was more likely to suffer multiple distant metastasis (40.3 vs. 19.4%), and was less likely to receive radiation (30.1 vs. 49.0%) and chemotherapy (54.0 vs. 69.8%) than surgery group (all $p < 0.001$).

Analysis of Survival Benefits From Surgery

It has been recommended by the NCCN guideline that the primary treatment approach for women with metastatic breast cancer is systemic therapy rather than surgical treatment. In order to evaluate the survival benefits of local breast surgery in patients with metastatic breast cancer, the Kaplan-Meier plot was performed to compare the OS and BCSS between patients who had, or had not undergone local breast surgical treatment. The median follow-up duration in the training set was 30 months (mean, 31.1 month; range, 0 to 83 months). Of all the 5173 patients with metastatic breast cancer, a total of 1947 patients were dead at the time of last follow-up and 1643 of which were dead directly from breast cancer. As shown in **Figure 2**, patients who had undergone surgical treatment had prominently better OS and BCSS than patients who had not ($p < 0.001$).

In order to determine if metastatic breast cancer patients in specific subgroup could benefit from surgical treatment, subgroup analysis stratified based on age, disease characteristics, and treatment were conducted. As shown in **Table 2**, the results of multivariant Cox analysis demonstrated that local surgical treatment exerted a significant survival benefit both in OS and BCSS in almost all subgroups ($p < 0.05$) except in the patients with undifferentiated breast cancer ($p > 0.05$). These results, taken together, indicated that locoregional surgical treatment was significantly associated with improved OS and BCSS in patients with metastatic breast cancer.

Risk Covariates Related With Survival in Cohorts With and Without Surgery

Initially, univariate Cox proportional models regarding to groups with and without surgery were built, respectively, to evaluate the multiple factors related with OS and BCSS (**Table 3**). Eleven parameters were incorporated into this Cox model, including one demographic variable, seven disease-related variables, and three treatment-related variables. As shown in **Table 3**, the risk of death increased dramatically with age both in cohort with and without surgery. The T staging exerted a significant prognostic factors. For patients not receiving surgery, the risk of death in patients with higher T stage (≥T3) was higher than those with T1 tumors expect T2 tumors. Meanwhile, among patients receiving surgery, T staging (≥T2) was consistently associated with worse OS (T2 vs. T1, HR = 1.33, 95% CI [1.08-1.64]; T3 vs. T1, HR = 1.54, 95% CI [1.23-1.93]; T4 vs. T1, HR = 2.13, 95% CI [1.73-2.62]) and BCSS (T2 vs. T1, HR = 1.37, 95% CI [1.10-1.70]; T3 vs. T1, HR = 1.53, 95% CI [1.21-1.94]; T4 vs. T1, HR = 2.11, 95% CI [1.70-2.63]) compared with T1 (all $p < 0.05$). The risk of death also increased in patients with poorer tumor differentiation. Patients with lung, brain or multiple sites involvement had a significantly higher risk of death than those with only bone metastases regardless of surgery or not (all $p < 0.05$). However, there was no correlation between higher N staging and poorer survival outcomes in both groups. Moreover, positive status of ER, PR

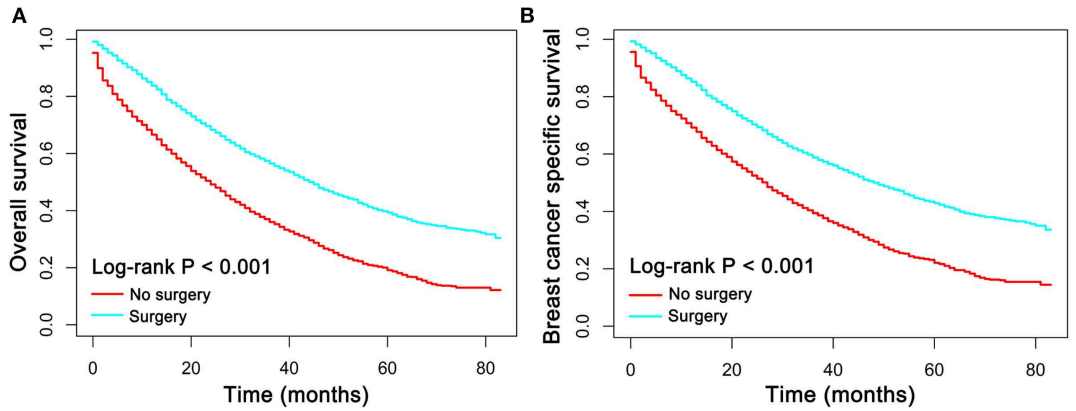

FIGURE 2 | (A) Overall survival (OS) and **(B)** breast cancer specific survival (BCSS) curves plotted by Kaplan-Meier method for patients received surgical treatment or not.

and HER2, and treatments with radiation and chemotherapy were proved to be protective factors for better OS and BCSS in both surgery and non-surgery group. Intriguingly, patients received radical mastectomy had slightly better prognosis than those undergone lumpectomy or mastectomy both in OS (HR = 1.16, 95% CI [1.04-1.29], p = 0.009) and BCSS (HR = 1.15, 95% CI [1.02-1.29], p = 0.019).

In order to eliminate possible bias, all the aforementioned variables with $p < 0.05$ in univariate Cox analysis were enlisted into multivariate analysis. The detailed results of multivariate Cox analysis were shown in **Table 4**. Notably, nine variables (age, T stage, grade, distant metastatic site, ER, PR and HER2 status, radiation, and chemotherapy) remained significantly associated with survival outcome in both groups (p <0.05). However, in surgery group, radical mastectomy no longer exerted as protective factor for improved OS as well as BCSS compared with lumpectomy/mastectomy.

Individualized Construction of Nomogram and External Validation

According to the results of multivariate Cox analysis, separate nomograms were plotted to predict the 1- and 3-year OS and BCSS among patients with or without surgery (**Figure 3**). Since N staging and surgery type exerted no statistical significance in multivariate analysis ($p > 0.05$), nine variables (age, T stage, grade, distant metastatic site, ER, PR and HER2 status, radiation, and chemotherapy) were finally incorporated into the nomograms. All the nine variables were demonstrated to be independent prognostic factors for OS and BCSS. According to the point scale in these nomograms, each patient with different clinicopathologic characteristics could get a total point that can be used to predict the survival (1- and 3-year OS and BCSS). In addition, through comparing the survival outcomes predicted by those separate nomograms, we can also determine each patient's survival prognosis when performing surgical treatment or not. In general, a higher score was considered to have worse prognosis.

Subsequently, these individualized nomograms were validated internally and externally by calculating the C-index. For OS and BCSS in surgery group, the C-index were 0.721 (95% CI: 0.707-0.735) and 0.722 (95% CI: 0.708-0.736) in the internal validation, and 0.760 (95% CI: 0.730-0.790) and 0.770 (95% CI: 0.740-0.800) in the external validation, respectively, indicating a good predictive accuracies. Moreover, the corresponding C-index in non-surgery group were 0.664 (95% CI: 0.652-0.676), 0.666 (95% CI: 0.654-0.678), 0.692 (95% CI: 0.674-0.710) and 0.696 (95% CI: 0.677-0.715). In addition, the calibration curves plotted for these nomograms indicated a good correlation between the nomogram-predicted survival probability and the observed survival probability both in the training and validation set (**Supplementary Figure 1**).

Preoperative Nomogram and External Validation

Since it makes great sense to preoperatively assess whether patients could benefit from the surgical treatment, a preoperative nomogram was designed to predict survival benefit before making surgical decisions. Seven preoperatively measurable variables were included in the preoperative nomogram (**Figure 4**). As shown in **Figures 4A,B**, T stage and distant metastasis can be detected precisely by modern imaging techniques while information of grade, ER, PR and HER2 can be ascertained by aspiration biopsy. The C-index of the preoperative nomogram for OS using bootstrap and external validation were 0.713 (95% CI: 0.699-0.727) and 0.745 (95% CI: 0.714-0.776), respectively. A similar C-index for BCSS was also gained with 0.715 (95% CI: 0.701-0.729) in internal validation and 0.758 (95% CI: 0.727-0.789) in external validation, respectively. The calibration curves based on bootstrap resampling and validation set were shown in **Supplementary Figure 2**.

DISCUSSION

It is still somewhat controversial that whether patients with MBC can get survival benefits from performing locoregional surgical treatment. Amounts of retrospective studies have outlined clear benefits for MBC patients who had undergone surgical treatment

TABLE 2 | Subgroup analysis of OS and BCSS outcomes.

Variables	OS		BCSS	
	HR (95% CI)	*p*-value[a]	HR (95% CI)	*p*-value
Age				
< 35	0.38 (0.24–0.61)	<0.001	0.38 (0.23–0.62)	<0.001
35–49	0.61 (0.51–0.73)	<0.001	0.62 (0.52–0.75)	<0.001
50–69	0.54 (0.48–0.61)	<0.001	0.55 (0.49–0.62)	<0.001
≥ 70	0.62 (0.53–0.72)	<0.001	0.66 (0.57–0.76)	<0.001
T Stage				
T1	0.46 (0.36–0.60)	<0.001	0.45 (0.35–0.59)	<0.001
T2	0.53 (0.47–0.61)	<0.001	0.55 (0.48–0.63)	<0.001
T3	0.57 (0.48–0.68)	<0.001	0.57 (0.47–0.69)	<0.001
T4	0.66 (0.59–0.75)	<0.001	0.64 (0.56–0.73)	<0.001
***N* Stage**				
N0	0.52 (0.44–0.61)	<0.001	0.53 (0.44–0.63)	<0.001
N1	0.55 (0.49–0.62)	<0.001	0.55 (0.48–0.62)	<0.001
N2	0.54 (0.44–0.65)	<0.001	0.53 (0.43–0.65)	<0.001
N3	0.72 (0.60–0.85)	<0.001	0.70 (0.58–0.83)	<0.001
Grade				
High, I	0.55 (0.39–0.77)	<0.001	0.45 (0.31–0.65)	<0.001
Intermediate, II	0.56 (0.49–0.64)	<0.001	0.56 (0.48–0.64)	<0.001
Low, III	0.60 (0.54–0.66)	<0.001	0.60 (0.54–0.67)	<0.001
Undifferentiated, IV	0.55 (0.16–1.86)	0.334	0.86 (0.23–3.19)	0.820
Distant Metastasis				
Bone only	0.51 (0.45–0.58)	<0.001	0.52 (0.45–0.59)	<0.001
Liver only	0.75 (0.57–0.99)	0.041	0.74 (0.56–0.99)	0.042
Lung only	0.58 (0.46–0.73)	<0.001	0.53 (0.41–0.67)	<0.001
Brain only	0.31 (0.14–0.69)	0.004	0.29 (0.13–0.65)	0.003
Other site	0.59 (0.46–0.75)	<0.001	0.55 (0.42–0.71)	<0.001
Multiple sites	0.61 (0.53–0.70)	<0.001	0.62 (0.54–0.71)	<0.001
ER Status				
Negative	0.54 (0.47–0.62)	<0.001	0.56 (0.49–0.64)	<0.001
Positive	0.60 (0.55–0.66)	<0.001	0.58 (0.53–0.64)	<0.001
PR Status				
Negative	0.63 (0.56–0.70)	<0.001	0.64 (0.57–0.71)	<0.001
Positive	0.55 (0.49–0.61)	<0.001	0.53 (0.47–0.59)	<0.001
HER2 Status				
Negative	0.59 (0.54–0.64)	<0.001	0.58 (0.53–0.64)	<0.001
Positive	0.52 (0.44–0.61)	<0.001	0.54 (0.45–0.64)	<0.001
Radiation				
No	0.68 (0.62–0.75)	<0.001	0.68 (0.62–0.75)	<0.001
Yes	0.43 (0.38–0.49)	<0.001	0.43 (0.38–0.49)	<0.001
Chemotherapy				
No	0.61 (0.54–0.69)	<0.001	0.60 (0.53–0.68)	<0.001
Yes	0.56 (0.50–0.62)	<0.001	0.56 (0.51–0.63)	<0.001

[a] *Multivariant Cox regression model.*

All HRs refer to Surgery versus non-surgery in the subgroup analysis.

CI, confidence interval; BCSS, breast cancer specific survival.

(9, 15–18). For example, a retrospective study by Blanchard et al. indicated that the median survival of surgically treated MBC patients was significantly longer than patients without surgical resection in a multivariate analysis ($p = 0.006$) (19). Moreover, a recent meta-analysis included a large sample size of 67272 patients from 30 observational studies showed that primary tumor resection significantly improved not only OS (HR = 0.65, 95% CI: 0.61−0.70, $p < 0.001$) but also distant progression-free survival (HR = 0.42, 95% CI: 0.29−0.60, $p < 0.001$) (20). It was reported that surgical removal of primary tumor can reduce the tumor burden, remove the source of new metastases, and potentially reverse tumor-induced immunosuppression despite the presence of metastatic disease (21). However, a limited number of prospective randomized controlled clinical trials have yielded conflicting results. A randomized trial conducted in Turkey found that, compared with the initial systemic therapy group, patients in the initial surgery group had a significant reduction in the risk of death at 5 years, but not at 3 years (13). The stratified analysis also demonstrated that patients with HR positive, HER2 negative, younger age, or solitary bone-only metastases might be the potential subgroup who can benefit from surgical treatment. On the contrary, another randomized trial conducted in India found that tumor resection after a response to chemotherapy did not significantly improve overall survival (12). However, some selection biases existed in this study may confound the conclusion. Firstly, among all the patients with HER2 positive (35%) in this trial, only 15 percent received anti-HER2 therapy due to financial issues and none of it was included in local surgery group. Secondly, most patients enrolled in this study have developed clinical symptoms due to late diagnosis, making the median survival much lower than that in developed countries. Therefore, the study was unable to accurately assess the impact of surgery on the overall prognosis of patients receiving standard chemotherapy and targeted therapy. Importantly, the results of well-designed clinical trial, ECOG E2108 (NCT01242800) conducted in United States and Canada, were eagerly awaited to clarify the actual role of surgery in MBC patients.

Nowadays, metastatic breast cancer has been considered as a heterogeneous diseases. Survival rate of metastatic breast cancer have improved dramatically over the past few decades (18, 22). It was reported that the 5-year disease specific survival (DSS) of de novo MBC has improved from 28% (1990–1998) to 55% (2005–2010) (23). This could be attributed to early diagnosis with advanced imaging modalities and multiple modern systemic therapy with remarkable response rate, including endocrine therapy, anti-HER2 therapy, CDK4/6 inhibitor and mTOR inhibitor (24–26). Due to the prolonged survival of patients with metastatic breast cancer, we considered that selected subgroup of MBC could benefit from locoregional surgical treatment.

A large cohort of MBC patients diagnosed from 2010 to 2015 in SEER program were then analyzed in this study. Patients between 2010 and 2013 were selected as training set while patients diagnosed after 2013 as validation set. There were many different characteristics between the training set and validation set, which might enhance the credibility of our findings. It was notable that patients in validation set had received less radiation therapy as well as surgical intervention than patients in training set, which might be due to the formation of ideas that stage IV disease is not curative. In this situation, treatments with minimal harm are preferred to prolong survival and enhance quality of life (27). When analyzing the cohort of MBC patients diagnosed from 2010 to 2013, we found the administration of surgical treatment was significantly associated with better OS and BCSS, which was in consistent with the SEER based published studies analyzing the MBC patients between 1988 and 2011 (28). In the subgroup

TABLE 3 | Univariant Cox models for metastasis breast cancer patients in surgery and non-surgery set.

Variables	OS				BCSS			
	No surgery		Surgery		No surgery		Surgery	
	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Age		<0.001		<0.001		<0.001		<0.001
<35	Reference		Reference		Reference		Reference	
35–49	1.06 (0.81–1.38)	0.668	1.38 (0.99–1.93)	0.061	1.08 (0.82–1.42)	0.587	1.48 (1.04–2.11)	0.028
50–69	1.32 (1.03–1.70)	0.029	1.71 (1.24–2.37)	0.001	1.33 (1.02–1.73)	0.034	1.78 (1.27–2.50)	0.001
≥70	1.81 (1.40–2.34)	<0.001	2.74 (1.96–3.82)	<0.001	1.72 (1.31–2.25)	<0.001	2.55 (1.79–3.62)	<0.001
T stage		<0.001		<0.001		<0.001		<0.001
T1	Reference	<0.001	Reference		Reference	<0.001	Reference	
T2	1.02 (0.88–1.17)	0.842	1.33 (1.08–1.64)	0.008	1.03 (0.88–1.20)	0.732	1.37 (1.10–1.70)	0.005
T3	1.18 (1.01–1.39)	0.037	1.54 (1.23–1.93)	<0.001	1.21 (1.03–1.43)	0.024	1.53 (1.21–1.94)	<0.001
T4	1.32 (1.15–1.51)	<0.001	2.13 (1.73–2.62)	<0.001	1.35 (1.17–1.56)	<0.001	2.11 (1.70–2.63)	<0.001
N stage		0.095		0.003		0.226		0.027
N0	Reference		Reference		Reference		Reference	
N1	0.91 (0.83–1.01)	0.081	0.86 (0.73–1.01)	0.074	0.95 (0.85–1.05)	0.317	0.88(0.74–1.05)	0.148
N2	1.07 (0.91–1.24)	0.415	1.02 (0.85–1.22)	0.866	1.09 (0.93–1.28)	0.286	1.01 (0.84–1.22)	0.888
N3	0.97 (0.85–1.12)	0.715	1.12 (0.95–1.33)	0.188	1.02 (0.88–1.18)	0.794	1.10 (0.92–1.32)	0.291
Grade		<0.001		<0.001		<0.001		<0.001
High, I	Reference		Reference		Reference		Reference	
Intermediate, II	1.26 (1.06–1.50)	0.008	1.26 (0.95–1.68)	0.108	1.28 (1.07–1.54)	0.008	1.45 (1.06–2.00)	0.021
Low, III	1.73 (1.46–2.05)	<0.001	2.08 (1.58–2.73)	<0.001	1.82 (1.52–2.18)	<0.001	2.46 (1.81–3.35)	<0.001
Anaplastic, IV	2.18 (1.40–3.42)	0.001	1.73 (0.88–3.40)	<0.111	2.14 (1.32–3.46)	0.002	2.21 (1.11–4.40)	0.024
Distant metastasis		<0.001		<0.001		<0.001		<0.001
Bone only	Reference		Reference		Reference		Reference	
Liver only	1.08 (0.90–1.30)	0.417	1.53 (1.25–1.86)	<0.001	1.11 (0.91–1.34)	0.309	1.51 (1.23–1.86)	<0.001
Lung only	1.26 (1.08–1.48)	0.004	1.49 (1.25–1.79)	<0.001	1.30 (1.10–1.53)	0.002	1.43 (1.18–1.73)	<0.001
Brain only	3.01 (2.07–4.37)	<0.001	3.05 (1.91–4.89)	<0.001	3.36 (2.31–4.88)	<0.001	2.94 (1.79–4.85)	<0.001
Other site	1.11 (0.94–1.30)	0.217	1.05 (0.89–1.25)	0.548	1.09 (0.92–1.29)	0.327	1.01 (0.84–1.20)	0.941
Multiple sites	1.62 (1.47–1.79)	<0.001	2.02 (1.75–2.32)	<0.001	1.68 (1.52–1.86)	<0.001	2.08 (1.80–2.41)	<0.001
ER status								
Negative	Reference		Reference		Reference		Reference	
Positive	0.54 (0.49–0.59)	<0.001	0.54 (0.48–0.61)	<0.001	0.53 (0.48–0.58)	<0.001	0.51 (0.45–0.58)	<0.001
PR status								
Negative	Reference		Reference		Reference		Reference	
Positive	0.60 (0.55–0.66)	<0.001	0.51 (0.46–0.57)	<0.001	0.58 (0.53–0.63)	<0.001	0.48 (0.42–0.53)	<0.001
HER2 status								
Negative	Reference		Reference		Reference		Reference	
Positive	0.79 (0.72–0.87)	<0.001	0.56 (0.49–0.65)	<0.001	0.80 (0.73–0.89)	<0.001	0.58 (0.51–0.67)	<0.001
Radiation								
No	Reference		Reference		Reference		Reference	
Yes	1.12 (1.02–1.22)	0.016	0.71 (0.64–0.79)	<0.001	1.14 (1.04–1.25)	0.006	0.73 (0.65–0.82)	<0.001
Chemotherapy								
No	Reference		Reference		Reference		Reference	
Yes	0.80 (0.74–0.87)	<0.001	0.76 (0.67–0.85)	<0.001	0.78 (0.72–0.85)	<0.001	0.80 (0.71–0.91)	<0.001
Surgery type								
Lumpectomy/mastectomy	–		Reference		–		Reference	
Radical mastectomy	–		1.16 (1.04–1.29)	0.009	–		1.15 (1.02–1.29)	0.019

TABLE 4 | Multivariable Cox models for metastasis breast cancer patients in surgery and non–surgery set.

Variables	OS				BCSS			
	No surgery		Surgery		No surgery		Surgery	
	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Age		<0.001		<0.001		<0.001		<0.001
< 35	Reference		Reference		Reference		Reference	
35–49	1.02 (0.78–1.33)	0.888	1.24 (0.89–1.75)	0.221	1.03 (0.78–1.36)	0.817	1.35 (0.94–1.92)	0.100
50–69	1.24 (0.96–1.60)	0.097	1.36 (0.98–1.89)	0.059	1.24 (0.95–1.61)	0.112	1.43 (1.01–2.02)	0.042
≥ 70	1.58 (1.21–2.05)	0.001	2.05 (1.45–2.88)	<0.001	1.50 (1.14–1.97)	0.004	1.93 (1.35–2.77)	<0.001
T stage		<0.001		<0.001		<0.001		<0.001
T1	Reference		Reference		Reference	<0.001	Reference	
T2	1.01 (0.87–1.16)	0.946	1.22 (0.99–1.51)	0.121	1.01 (0.87–1.18)	0.903	1.24 (0.99–1.54)	0.059
T3	1.14 (0.97–1.33)	0.115	1.36 (1.08–1.72)	0.011	1.15 (0.97–1.36)	0.105	1.32 (1.04–1.69)	0.024
T4	1.22 (1.06–1.41)	0.005	1.80 (1.45–2.25)	<0.001	1.24 (1.07–1.44)	0.004	1.75 (1.39–2.20)	<0.001
N stage				0.037		–		0.160
N0	–		Reference		–	–	Reference	
N1	–		0.87 (0.74–1.04)	0.118	–	–	0.90 (0.75–1.07)	0.241
N2	–		0.99 (0.81–1.19)	0.872	–	–	0.98 (0.81–1.20)	0.871
N3	–		1.08 (0.90–1.29)	0.438	–	–	1.07 (0.88–1.29)	0.506
Grade		<0.001		<0.001		<0.001		<0.001
High, I	Reference		Reference		Reference		Reference	
Intermediate, II	1.28 (1.07–1.52)	0.006	1.25 (0.94–1.66)	0.121	1.29 (1.07–1.55)	0.008	1.44 (1.05–1.98)	0.026
Low, III	1.68 (1.40–2.01)	<0.001	1.81 (1.36–2.40)	<0.001	1.74 (1.44–2.10)	<0.001	2.10 (1.52–2.87)	<0.001
Anaplastic, IV	2.14 (1.36–3.37)	0.001	1.73 (0.88–3.43)	0.115	2.05 (1.26–3.35)	0.004	2.24 (1.11–4.49)	0.024
Distant metastasis		<0.001		<0.001		<0.001		<0.001
Bone only	Reference		Reference		Reference		Reference	
Liver only	1.11 (0.92–1.35)	0.287	1.66 (1.35–2.04)	<0.001	1.13 (0.92–1.38)	0.250	1.57 (1.26–1.94)	<0.001
Lung only	1.02 (0.87–1.20)	0.808	1.07 (0.88–1.29)	0.514	1.05 (0.88–1.24)	0.595	0.99 (0.81–1.21)	0.942
Brain only	2.39 (1.63–3.49)	<0.001	2.44 (1.51–3.92)	<0.001	2.58 (1.76–3.77)	<0.001	2.23 (1.34–3.69)	0.002
Other site	0.93 (0.79–1.10)	0.410	0.90 (0.76–1.08)	0.256	0.91 (0.77–1.09)	0.317	0.83 (0.69–1.00)	0.055
Multiple sites	1.57 (1.42–1.74)	<0.001	1.78 (1.53–2.06)	<0.001	1.62 (1.46–1.80)	<0.001	1.82 (1.56–2.12)	<0.001
ER status								
Negative	Reference		Reference		Reference		Reference	
Positive	0.57 (0.50–0.64)	<0.001	0.78 (0.66–0.91)	0.002	0.58 (0.51–0.67)	<0.001	0.76 (0.64–0.89)	0.001
PR status								
Negative	Reference		Reference		Reference		Reference	
Positive	0.71 (0.63–0.80)	<0.001	0.54 (0.46–0.63)	<0.001	0.68 (0.60–0.76)	<0.001	0.51 (0.43–0.59)	<0.001
HER2 status								
Negative	Reference		Reference		Reference		Reference	
Positive	0.61 (0.55–0.68)	<0.001	0.43 (0.37–0.49)	<0.001	0.60 (0.53–0.67)	<0.001	0.43 (0.37–0.50)	<0.001
Radiation								
No	Reference		Reference		Reference		Reference	
Yes	1.10 (1.01–1.21)	0.037	0.79 (0.71–0.89)	<0.001	1.12 (1.02–1.24)	0.020	0.80 (0.71–0.90)	<0.001
Chemotherapy								
No	Reference		Reference		Reference		Reference	
Yes	0.68 (0.62–0.75)	<0.001	0.74 (0.64–0.85)	<0.001	0.69 (0.62–0.76)	<0.001	0.74 (0.64–0.86)	<0.001
Surgery type								
Lumpectomy/mastectomy	–		Reference		–		Reference	
Radical mastectomy	–		1.10 (0.98–1.24)	0.117	–		1.10 (0.97–1.25)	0.136

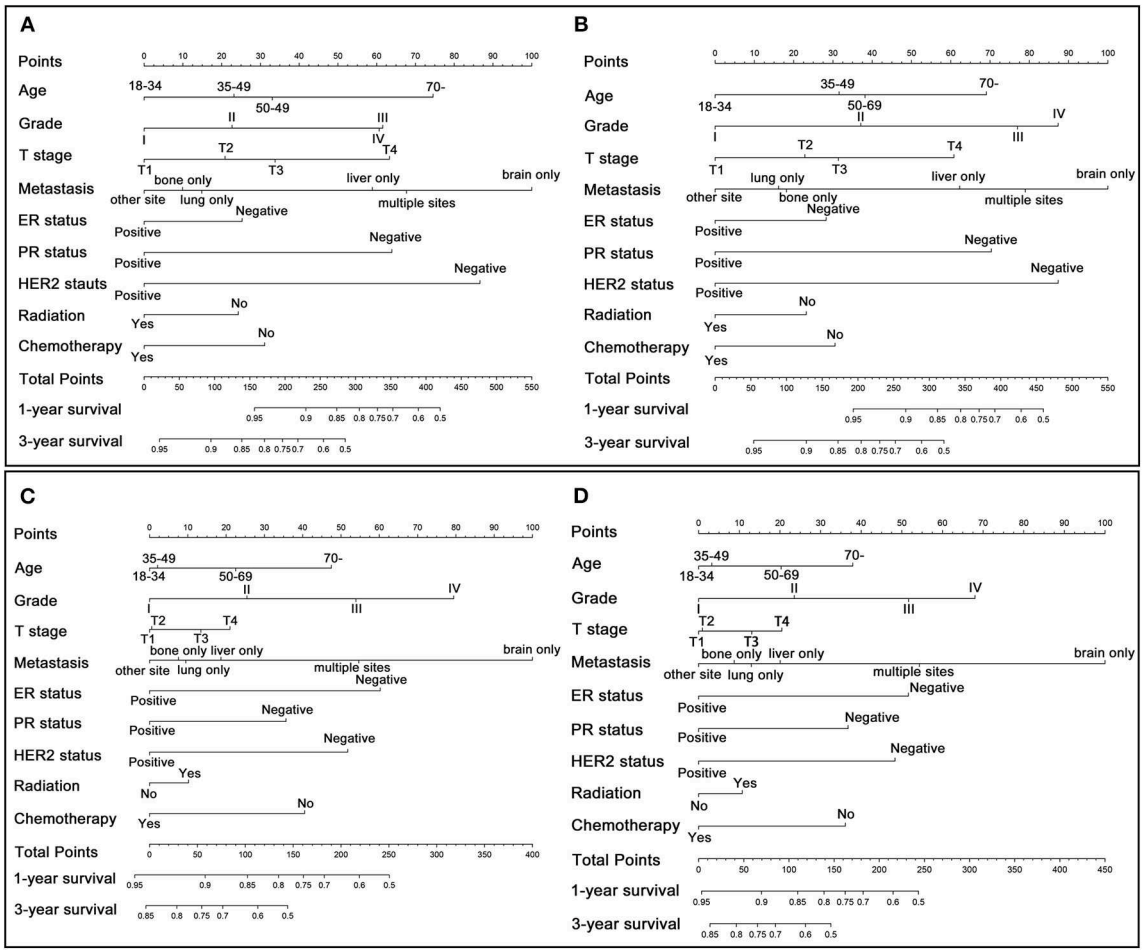

FIGURE 3 | Nomogram for predicting 1- and 3-year OS and BCSS in patients with metastatic breast cancer. **(A)** OS for patients who undergo surgical treatment. **(B)** BCSS for patients who undergo surgical treatment. **(C)** OS for patients who does not undergo surgical treatment. **(D)** BCSS for patients who does not undergo surgical treatment.

analysis, a multivariate cox analysis indicated that receiving surgery improved the OS and BCSS in almost all subgroups including patients with brain metastasis. This was different from a recent study implying that breast surgery provided no survival advantage for MBC patients with brain metastasis (29).

Since a systemic adjuvant therapy for MBC patients are still preferentially recommended by various guidelines (4, 30), we separately established univariate and multivariate Cox regression models both in surgery and non-surgery groups to identify survival-related risk factors, respectively. Our findings suggested that independent prognostic factors for worse OS and BCSS in both surgery and non-surgery cohort include older age, larger tumor size, positive HR and HER2 status, administration of radiation and chemotherapy, and the site of distant metastasis. Intriguingly, positive HER2 status, a well-known poor prognostic feature (31, 32), was proved to a protective factor in our study, largely because of widely usage of anti-HER2 therapy. Considering the uncertainty of survival benefit gotten from surgical treatment in IV stage breast cancer patients, nomograms predicting the long-term OS and BCSS with or without surgery would be useful to inform clinical decision making (33). Hence, several individualized nomograms were constructed in this study based on the result of multivariate Cox analysis. Our nomograms showed an acceptable predictive capabilities with C-index range of 0.65–0.80 both in training set and external validation set, which was comparable to some widely accepted nomograms (34–36).

We considered that a preoperative nomogram would be of great use when a untreated *de novo* metastatic breast cancer was diagnosed in patient with good performance or single/oligometastasis. Hence, a preoperative version of nomogram was designed by including seven preoperatively measurable variables. By means of aspiration biopsy, it is easy for surgeons to access information about ER, PR, HER2 and histological grade. Although T staging is usually determined postoperatively, a modern advanced imaging modalities, including breast magnetic resonance imaging (MRI), mammogram, ultrasound and Positron Emission Tomography-Computed Tomography (PET-CT), are supposed to provide precise assessment for tumor invasion and distant metastasis. Similarly, the bootstrap C-index above 0.70 both

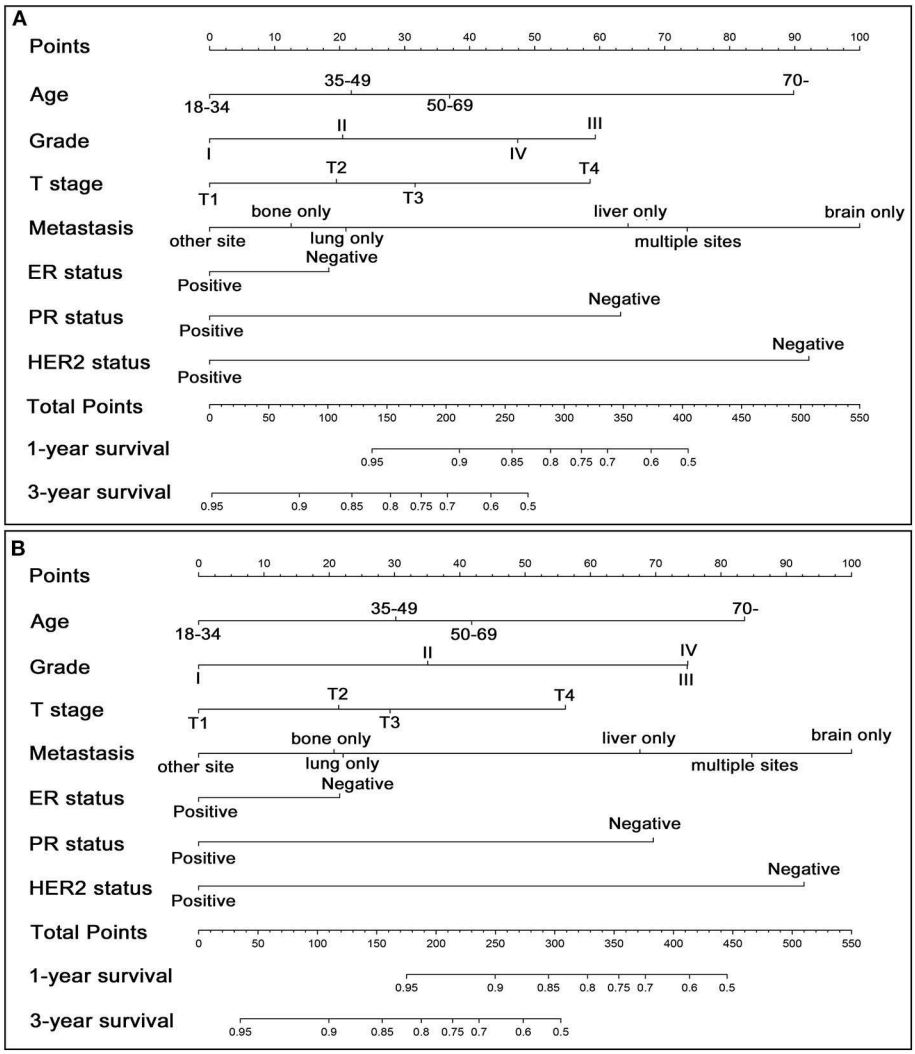

FIGURE 4 | Preoperative nomogram for predicting 1- and 3-year OS **(A)** and BCSS **(B)** in patients with metastatic breast cancer who are candidate for surgical treatment.

in training and validation set suggested a sufficient rate of accuracy. In addition, we hold the opinion that patient's state of health, expression level of Ki-67, ER and ER, and the effect of neoadjuvant chemotherapy would affect the clinician's surgical decision-making. Considering that those information were not available in SEER database, a large database containing detailed information of those variables mentioned above should be established and analyzed to further enhance the preoperative nomogram's predictive capability.

Inevitably, there are some limitations in our study. Firstly, the detailed information, such as regarding residues of tumor resection (R0, R1, or R2), endocrine therapy, sequence of chemotherapy, are not accessible in SEER database. All these factors were thought to have impact on survival of MBC patients who had undergone surgical treatment. Secondly, our study is retrospective and selection bias is inherent in the data that the MBC patients who received surgery or not were selected subjectively by the initial surgeon in the first place. We hold the opinion that a retrospective study cannot fully prove the advantage of surgery to metastatic breast cancer. The only way to investigate the exact role of locoregional surgical treatment in IV stage breast cancer would be a well-designed prospective randomized trial. Hence, we look forward to the ECOG E2108 and other ongoing clinical trials that may provide some valuable conclusions in future.

CONCLUSIONS

This study suggests potential survival benefits of surgery among patients with metastatic breast cancer by analyzing population-based data. In addition, we constructed several individualized pre- and postoperative nomograms that are capable of predicting long-term survival of metastatic breast cancer patients with or without surgery, which may assist clinicians to make the appropriate treatment choices as well as to assess their patients' prognosis.

DATA AVAILABILITY STATEMENT

Publicly available datasets were analyzed in this study. This data can be found here: https://seer.cancer.gov/.

AUTHOR CONTRIBUTIONS

YZ and QY contributed to the idea and design. YZ, GZ, KY, KL, and QY contributed to the data acquisition and analysis. YZ and QY contributed to the manuscript writing and revision. All authors have read and approved the final version of this manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2020.00148/full#supplementary-material

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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

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Introduction: Best surgical approach of axillary staging remains controversial in locally recurrent breast cancer. We evaluated the reliability of repeat sentinel lymph node biopsy (reSLNB) in patients with ipsilateral breast tumor recurrence (IBTR) after breast conserving surgery (BCS) with sentinel lymph node biopsy (SLNB) in terms of identification rate (IR) and false negative rate (FNR). To address the FNR, we identified patients who underwent sequential axillary lymph node dissection (ALND) after reSLNB.

Methods: A systematic search of PubMed, EMBASE, and Cochrane Library were conducted to identify patient-level data from articles. We searched for data of patients who underwent BCS with SLNB for primary breast cancer and who underwent sequential ALND after reSLNB due to local recurrence. Patients data was also identified by the same criteria at two institutions.

Results: In total, 197 peer-reviewed publications were obtained, of which 20 included patients who met the eligibility criteria. Data from 464 patients were collected. From the two institutions, 31 patients were identified. A total of 495 patients were pooled. The IR of reSLNB was 71.9% (356/495). To address the FNR of reSLNB, 171 patients who underwent ALND after reSLNB were identified. The FNR and accuracy of reSLNB were 9.4% (5/53) and 97.1% (165/170), respectively.

Conclusion: Our pooled data analysis showed that the FNR of reSLNB is lower than 10%, indicating that this operation is a reliable axillary surgery in patients with IBTR after they underwent BCS.

Keywords: repeat sentinel lymph node biopsy, false negative rate (FNR), recurrent breast cancer, identification rate (IR), SLNB

INTRODUCTION

Metastasis in axillary lymph nodes is the most important prognostic factor in patients with breast cancer (1). In the past, axillary lymph node dissection (ALND) has been the standard approach for axillary surgery in breast cancer. However, ALND is associated with short-term and long-term morbidities (2–5). Patients treated with sentinel lymph node biopsy (SLNB) have significantly lower post-operative complication such as lymphedema, infection, seroma, and numbness compared to those with ALND (6). Among these complication, lymphedema is one of the most common complication after ALND, and adversely affects the quality of life. Despite of different definition and measurement, the incidence of ALND has been reported up to 56% (7). Nevertheless, the benefits of ALND are limited because most patients with early stage breast cancer are node-negative. SLNB is a less invasive procedure; it can replace ALND in patients with clinically node-negative breast cancer. SLNB has been reported to have a >90% identification rate (IR) and <10% false-negative rate (FNR) (8, 9). Previous studies have reported that SLNB can accurately predict the status of the remaining axillary lymph nodes (10–12).

Because of these advantages, SLNB plays an integral role in the axillary staging for the surgical management of patients with early breast cancer. However, the role of SLNB remains controversial in the surgical management of patients with local recurrence. Ipsilateral breast tumor recurrence (IBTR) after breast conserving surgery (BCS) as the initial surgery has gradually increased; this happens because BCS is currently performed in two of every three cases of surgery for primary breast cancer (13). The 10 year-local recurrence rate after BCS or mastectomy has been reported to be 2–10% (14–16).

For removal of recurred breast lesions in remained breast after BCS, total mastectomy or second lumpectomy can be performed (17). For concurrent axillary surgery, repeat SLNB (reSLNB) might be considered (18, 19). However, most patients with IBTR have a history of undergoing SLNB and radiotherapy that could interrupt their lymphatic channels. Evidence concerning the role of reSLNB for IBTR is still lacking despite the results of previous studies (20–23). The vast majority of earlier studies included few patients and had a retrospective design. In addition, studies that included patients who underwent mastectomy or ALND were heterogeneous (21–23).

In the present study, we focused on the reliability of reSLNB in patients who underwent BCS and SLNB without ALND as the initial surgery. To address the FNR of reSLNB, we further identified patients with IBTR who underwent ALND after reSLNB. To achieve this goal, we conducted a pooled analysis using data from a systematic review and two institutions.

Abbreviations: reSLNB, repeat sentinel lymph node biopsy; IBTR, ipsilateral breast tumor recurrence; BCS, breast conserving surgery; SLNB, sentinel lymph node biopsy; IR, identification rate; FNR, false negative rate; ALND, axillary lymph node dissection; PRISMA, Preferred Reporting Items for Systemic Reviews and Meta-analysis; SLN, sentinel lymph node.

METHODS

Search Strategy

A literature search was performed in PubMed, Embase, and Cochrane Library databases of systemic review. All articles including case reports and original articles were searched. These articles were found using the following search terms in the databases: "ipsilateral breast tumor recurrence," "locally recurrent breast cancer," "recurrent breast cancer," "sentinel lymph node biopsy," "lymphatic mapping," "repeat," and "re-operative" (see Search Terms). The articles were independently selected by two researchers, and the literature search was conducted until April 2018.

Definition, Inclusion Criteria, and Data Extraction for reSLNB

IBTR was defined as recurred breast tumors or new ipsilateral primary breast tumors because it was impossible to distinguish the two diagnoses. A positive reSLNB outcome was defined as the presence of micro-metastasis (>0.2 mm and/or >200 cells, but not larger than 2 mm) and macro-metastasis, according to the American Joint Committee on Cancer, 7th edition (24). Isolated tumor cells (clusters of cells <0.2 mm and/or <200 cells) were defined as node-negative. The most selected articles did not specify exact radiation field and dose. Thus, we excluded analysis of radiotherapy because we could not distinguish whether a patient received radiation on the breast and/or axilla.

Patients included in this analysis had to meet the following criteria: (i) history of BCS for former breast cancer or ductal carcinoma *in situ* with histologically clear margins and of SLNB without ALND, (ii) IBTR or new ipsilateral primary breast tumor, and (iii) reSLNB and sequential ALND to assess the FNR of reSLNB. The following cases were excluded from the analysis: (i) presence of distant metastasis, and (ii) presence of inflammatory breast cancer. Even if the first and second operations were performed at different hospitals, patients were included if medical records from both hospitals were confirmed (see Information data extraction). With the corrected data, we attempted to answer the question (see Review questions).

This study was guided by the Preferred Reporting Items for Systemic Reviews and Meta-analyses (PRISMA) statement (25). The selection process with PRISMA standards in our study is depicted in **Figure 1**. All articles were searched independently by Chang Ik Yoon and Sung Gwe Ahn. In the literature search, patient-level data were collected. Articles not published in English, articles in which full-text articles were unavailable, review articles, duplicated articles, commentaries, editorials, poster, conference papers, and letters to the editor were excluded. Discrepancies were resolved through discussion (Chang Ik Yoon and Sung Gwe Ahn). Data obtained from the literature search and two institutions, Gangnam Severance Hospital and Yeungnam University Hospital, were analyzed together. Inclusion and exclusion criteria for patient data from the two institutions were the same as those mentioned above. The injection methods, doses, and sites for lymphatic mapping varied among studies (**Table 1** and **Supplementary Table 1**). The injection and SLNB protocol at Gangnam Severance Hospital

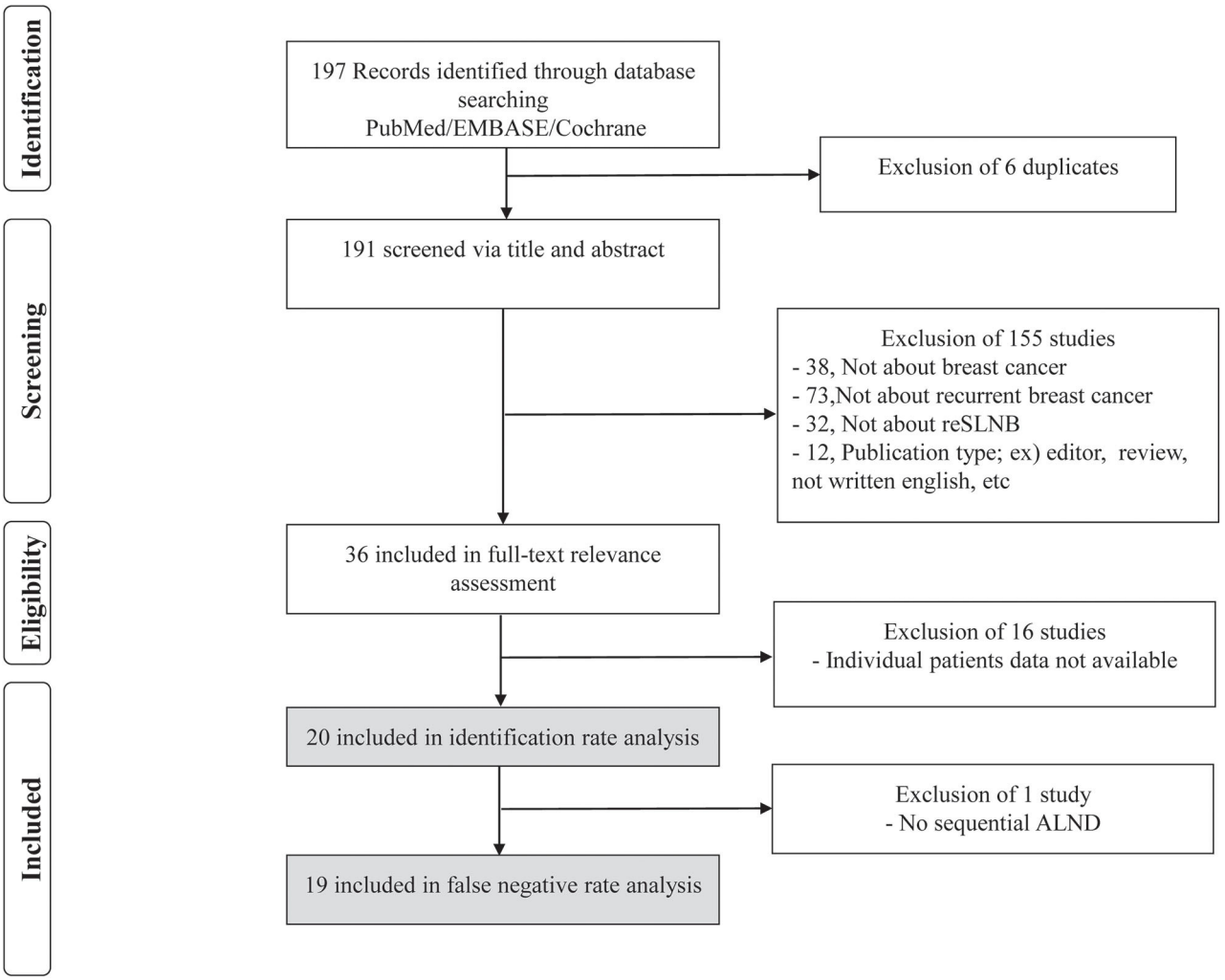

FIGURE 1 | Flowchart for the search strategy on repeat sentinel lymph node biopsy in patients with local recurrence. Our search strategy found 197 abstracts. Of these 197 abstracts, 6 were excluded due to duplication, and 155 were excluded based on predefined exclusion criteria. The remaining 36 articles were fully reviewed, of which 16 were excluded because they failed to meeting inclusion criteria.

and Yeungnam University was as follows. A radioisotope was injected into the subdermal layer of the periareolar site 15 min before surgery. Sentinel lymph nodes (SLNs) were identified and removed using a Gamma-ray detecting probe. Sequential ALND was performed in all patients after reSLNB. Breast surgery was performed with second lumpectomy or mastectomy. Harvested SLNs were fixed using 10% formalin solution. Each SLN was sectioned into 2–3-mm-thick slices, and all slices were frozen and examined microscopically.

The study was conducted in accordance with the good clinical practice guidelines and the Declaration of Helsinki, and the protocol was approved by the Institutional Review Board of Gangnam Severance Hospital (Local IRB number: 3-2018-0344).

Statistical Analysis

IR of reSLNB was defined as the number of successful cases divided by the total number of patients who underwent reSLNB. The FNR, accuracy, true-positive rate, and negative predictive value of reSLNB were calculated, respectively. The FNR of reSLNB is considered too high if the FNR is <10%. Differences in IR according to the mapping methods (dual mapping/radioisotope only/blue dye only) were compared using the chi-square test. SPSS version 23 (SPSS, Inc., Chicago, IL, USA) was used for statistical analyses. Statistical significance was defined as p-value of <0.05.

RESULTS

Search Results

In PubMed, EMBASE, and Cochrane database, we found 194 articles using the above mentioned searching terms (**Figure 1**). All articles retrieved from Embase and Cochrane Library databases were included to those extracted from PubMed.

TABLE 1 | Information of publication year, number of patients, identification rate and pathologic status for 20 studies on repeat sentinel lymph node biopsy (reSLNB).

References	Years	No.	Identification rate	TP	TN	FN	Injection site of radioisotope
*Vugts et al. (23)	2015	179	60.3% (108/179)	9	29	2	Intratumoral, periareolar, peritumoral
#Intra et al. (18)	2014	36	100% (36/36)	6	0	0	Intraparenchymal, subareolar, subdermal
#Dinan et al. (26)	2005	2	100% (2/2)	0	1	0	Intradermal, peritumoral, subareolar
#,†,*Boughey et al. (27)	2006	5	100% (5/5)	1	4	0	Intratumoral, peritumoral
*Jackson et al. (28)	2006	1	100% (1/1)	1	0	0	Subareolar
*Newman et al. (29)	2007	2	50% (1/2)	0	1	0	Subareolar
*Roumen et al. (30)	2006	2	100% (2/2)	1	0	0	Intratumoral, peritumoral
*Taback et al. (31)	2006	6	83.3% (5/6)	0	5	0	Intratumoral
*Port et al. (32)	2007	54	74.1% (40/54)	5	22	1	Intradermal
*Cox et al. (33)	2008	55	81.8% (45/55)	9	0	0	Intraparenchymal, subareolar
#Koizumi et al. (34)	2007	3	66.7% (2/3)	1	1	0	Intraparenchymal, intradermal
*Schrenk et al. (35)	2007	11	90.9% (10/11)	0	10	0	Intraparenchymal
*Tasevki et al. (36)	2009	1	100% (1/1)	0	1	0	Intraparenchymal, subareolar, subdermal
§Derkx et al. (37)	2010	12	33.3% (4/12)	0	1	0	NR
*Tokmak et al. (38)	2014	5	60% (3/5)	0	3	0	Intradermal, periareolar, peritumoral
#Cordoba et al. (39)	2014	10	50% (5/10)	1	4	0	Subareolar
*Matsuomoto et al. (40)	2015	22	81.8% (18/22)	1	0	0	Intradermal, peritumoral
*Karanlik et al. (41)	2016	21	81.0% (17/21)	6	0	0	Intradermal, peritumoral
#Folli et al. (42)	2016	30	76.7% (23/30)	2	20	1	Peritumoral, subdermal
#,*Barone et al. (43)	2007	7	100% (7/7)	NR	NR	NR	Intraparenchymal, subareolar
Total		464	72.2% (335/464)	43	102	4	
#Two institutions[a]		31	67.7% (21/31)	5	15	1	Subareolar, intradermal
Total of pooled-analysis		495	71.9% (356/495)	48	117	5	

FN, false negative; IBTR, ipsilateral breast tumor recurrence; No., Number; NR, not recorded; TN, true negative; TP, true positive; SLNB, sentinel lymph node biopsy.
[a]Two institutions: Gangnam Severance Hospital and Yeungnam University.
*Mapping method of SLNB: #radioisotope only, †blue dye only, *combined blue dye and radioisotope, §unknown.*

Adding the three articles from references in the previous meta-analysis of reSLNB (21, 22), a total of 197 articles were initially identified. Of these, there were six duplicated articles. A total of 191 abstracts were reviewed, and 155 abstracts were excluded for the following reasons: (i) not about breast cancer ($n = 38$), (ii) not about recurrent breast cancer ($n = 73$), (iii) not about reSLNB ($n = 32$), (iv) inappropriate publication types such as editorial, review, or articles not written in English ($n = 12$). A full-text review of 36 articles was conducted. A total of 20 articles finally met the inclusion criteria. From these, 19 articles analyzed the FNR of reSLNB. These articles were published from 2005 to 2016 (**Table 1**).

In addition, from 1995 to 2017, a total of 31 patients with IBTR after BCS met the inclusion criteria in the Gangnam Severance Hospital and Yeungnam University Hospital databases. These patients underwent reSLNB for their axillary staging.

Identification Rate of reSLNB

A total of 464 cases of reSLNB were found in the literature search (**Figure 2**). Of these, 335 were successful. The IR of reSLNB in articles was 72.2% (335/464). Among the 31 cases of reSLNB performed at the two institutions, 10 cases of sentinel failure occurred. The IR was 67.7% (21/31). The total IR of the pooled analysis was 71.9% (356/495) (**Table 1**).

The IR according to mapping tracers was described in **Supplementary Table 2**. The IR of dual mapping was 69.9% (251/359) and that of single mapping with a radioisotope was 79.5% (89/112). In three other reports where tracers were not clearly distinguished, the IR was 66.7%. There was no significant difference in IR according to mapping tracers (**Supplementary Table 2**, $p = 0.122$).

FNR/Diagnostic Performance of reSLNB

In 19 articles, the results of ALND following reSLNB were obtained from patient-level data of 149 patients (**Figure 2**). True positive-, false negative-, and true negative cases of reSLNB were 43, 4, and 102, respectively (**Table 1**). In addition, data from 21 patients with sequential ALND of the two institutions were added.

In a total of 170 patients who underwent ALND after reSLNB, the overall FNR was 9.4% (5/53) (**Table 2**). The overall accuracy, true positive rate (same as sensitivity), and negative predictive value of reSLNB were 97.1, 90.6, and 95.9%, respectively (**Table 2**). The FNRs of reSLNB using single or dual tracers were 11.8% (2/17) and 8.6% (3/35), respectively (**Table 3**). There were no statistically significant differences in FNR of reSLNB according to mapping method (**Table 3**, $p = 0.886$).

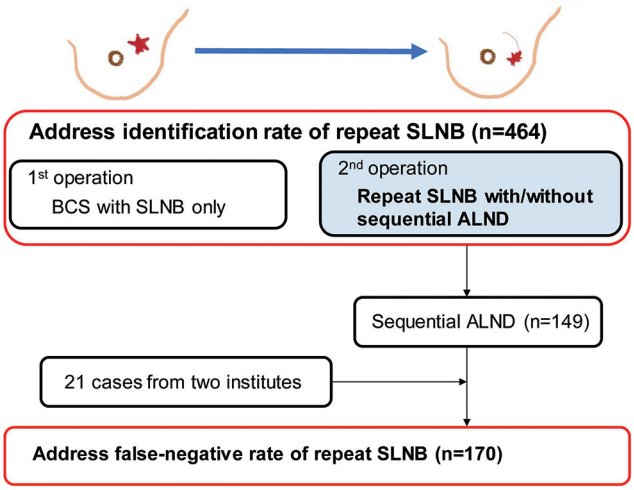

FIGURE 2 | Flowchart for data curation in order to address the identification rate and false-negative rate of repeat sentinel lymph node biopsy. A total of 1,212 cases of 20 articles were found, 464 subjects met inclusion criteria about first breast cancer surgery. Among these, repeat sentinel lymph node was performed in 335 patients, resulting in 72.2% of identification rate for reSLNB. Except 1 article, sequential ALND was performed in 149 patients in 19 articles. Then we added 21 patients who underwent sequential ALND after reSLNB from two institutions. Finally, a total of 170 patients were analyzed for false-negative rate of reSLNB. BCS, breast conserving surgery; SLNB, sentinel lymph node biopsy; ALND, axillary lymph node dissection.

TABLE 2 | Pathologic status of sentinel and axillary lymph nodes in the patients with reSLNB.

		Axillary lymph nodes	
		Positive	**Negative**
SLNs†	Positive	48 (TP)	0
	Negative	5 (FN)	117 (TN)

FN, false negative; TN, true negative; TP, true positive; SLNs, sentinel lymph nodes.
†False-negative rate: FN/(TP+FN) = 5/(48 + 5) = 9.4%; Sensitivity: TP/(TP+FN) = 48/48 + 5 = 90.6%; negative predictive value: TN/(TN+FN) = 117/117+5 = 95.9%; overall accuracy: (TP+TN)/number of patients = (48 + 117)/170 = 91.7%.

TABLE 3 | False negative rate (FNR) of reSLNB according to mapping methods.

Mapping methods of reSLNB	No. of study (n = 19)	No. of cases (n = 170#)	FNR	p-value
				0.886
Dual mapping methods	12	106	8.6% (3/35)	
Radioisotope only	5	58†	11.8%† (2/17)	
Blue dye only	0	0		
Not clearly distinguished§	2	6	0% (0/1)	

IR, identification rate; No, number; SLNB, sentinel lymph node biopsy.
†combined data of articles and two institution.
§the mapping methods of repeat-SLNB were not described or applied differently in each case, not included in statistical analysis.

DISCUSSION

In primary breast cancer with early stage, SLNB has been preferred procedure for axillary staging because it offers oncologic safety with fewer complications such as lymphedema, pain, range of motion, and sensory defect compared to ALND (5, 44, 45). However, in locally recurrent breast cancer, it lacks evidence that reSLNB could be performed for axillary staging method in terms of FNR. Since a large multi-institutional randomized study showed that the FNR of SLNB was 9.8% in clinically node-negative breast cancer (4), recent trials aimed to demonstrate a safety of SLNB if the FNR wound not be >10% in clinically node-positive breast cancer treated with preoperative chemotherapy (46–48). On the basis of these studies, we consider that reSLNB would be acceptable if the FNR of reSLNB is not >10%.

With this background, our pooled analysis used abundant data concerning reSLNB performed in patients with IBTR and demonstrated that the procedure was reliable. The FNR was 9.4%, and followed by an accuracy of 97.1% and a negative predictive value of 95.9%, although the IR was low as 71.9%

Our study has several strengths compared with previous studies evaluating reSLNB for locally recurred breasts cancer. The FNR was accurately addressed as back-up ALND was conducted after successful reSLNB in about half of patients. To address the FNR of SLNB, ALND is an inevitable procedure to rule out the chance of metastases in lymph nodes not retrieved by SLNB. However, the vast majority of patients included in earlier studies underwent axillary staging through reSLNB alone. An accurate assessment of FNR of reSLNB by sequential ALND for patients with IBTR is the novelty of our study.

In addition, we only included patients with true IBTR. Our study population underwent BCS and SLNB alone for their primary breast cancer. The homogeneity of the first surgery is distinguished from that in other studies including patients who underwent mastectomy or ALND. Moreover, we enrolled a relatively large number of patients from previously published articles and local institutional database that has strength in delicate information of patients.

Traditionally, in patients with IBTR, complete axillary clearance has been considered essential, regardless of axillary nodal involvement. However, recent advances in non-invasive diagnostic imaging have raised questions against whether sequential ALND is mandatory because more than half of the patients with IBTR had no axillary metastases (21, 22). Thus, many investigators have interests in de-escalating axillary surgery, and may accept the concept of limited axillary management (19), as long as credible sentinel lymph node detection is guaranteed. Because, in cases of IBTR, preceding axillary surgery may lead to disruption of lymphatic flow that undermines reliability of reSLNB. Also, another study reported that aberrant lymphatic drainage was visualized in two-fifths of the patients with locally recurred cancer (43.2%) (21).

However, SLNB is a minimally invasive method and has a lower chance of fully destroying common lymphatic routes from the breast to axillary SLNs than ALND. It is at least indirectly supported by the results of a previous study in which the rate of aberrant lymphatic drainage was significantly lower in patients with a history of SLNB than in those with a history of ALND (17.4 vs. 69.2%) (21).

Moreover, some studies provided evidence that a few common afferent lymphatic channels exist and drain breast tumors to axillary SLNs through several major lymphatic trunks (49, 50), implying a possibility of an alternative path from the breast to axillary lymph nodes after previous axillary surgery. Our data showed that reSLNB was successfully performed in 71.9% of the patients with IBTR, suggesting that lymphatic tracts between the breast and SLNs are intact in more than two-third of patients undergoing previous SLNB. As a consequence, reSLNB could be more reliably performed in patients with a history of SLNB alone.

A fundamental limitation of this study was the heterogeneity among the included studies. There are several differences such as surgical techniques, mapping methods of SLNB, and radiation therapy. Regarding prior radiotherapy affecting lymphatic drainage, information was missed in most patients from the articles, although a majority of patients might be treated with radiotherapy after breast conservative surgery. In addition, most articles had very few patients and a retrospective design. Also, we did not perform a statistical analysis to confirm heterogeneity among studies due to the study design of pooled data analysis which collected data of identifiable patients in each study. Despite these limitations, our study was a large-scale pooled analysis that showed that reSLNB is reliable for axillary staging in patients with IBTR and who were formerly treated with BCS and SLNB.

In conclusion, our study found that the reSLNB FNR is lower than 10% indicating that this procedure is reliable for axillary staging in patients with IBTR, even though they already underwent SLNB. It could be a feasible axillary surgery in these patients like those with primary cancer. Further validation through prospectively designed studies is warranted for these findings.

DATA AVAILABILITY STATEMENT

All datasets generated for this study are included in the article/**Supplementary Material**.

ETHICS STATEMENT

The study was conducted in accordance with the good clinical practice guidelines and the Declaration of Helsinki, and the protocol was approved by the Institutional Review Board of Gangnam Severance Hospital (Local IRB number: 3-2018-0344). The need for informed consent was waived under the approval of the IRB due to the retrospective design.

AUTHOR CONTRIBUTIONS

CY, SA, and JJ contributed conception and design of the study. CY, SA, JC, and SB organized the database. DK, CC, and SP assisted to first draft of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

SEARCH TERMS IN THE DATABASES

In PubMed

((((((ipsilateral breast tumor recurrence) OR locally recurrent breast cancer) OR recurrent breast cancer)) AND (((“Sentinel Lymph Node Biopsy”) OR sentinel lymph node biopsy) OR lymphatic mapping))) OR (((((“Sentinel Lymph Node Biopsy”) OR sentinel lymph node biopsy) OR lymphatic mapping)) AND ((repeat) OR re-operative)).

In Embase

(ipsilateral AND breast AND tumor AND recurrence OR (locally AND recurrent AND breast AND cancer) OR (recurrent AND breast AND cancer)) AND (sentinel AND lymph AND node AND biopsy OR (lymphatic AND mapping)) AND (repeat OR “re operative”).

In Cochrane Library Database

((ipsilateral breast tumor recurrence) OR (locally recurrent breast cancer)) OR ((recurrent breast cancer) OR (sentinel lymph node biopsy) OR (lymphatic mapping)) AND ((repeat) OR (re-operative)).

Information Data Extraction: The Following Information Was Collected

1. Number of patients with ipsilateral breast tumor recurrence (locally recurrent breast cancer)
2. Primary breast treatment: mastectomy with breast conserving surgery/lumpectomy
3. Primary axillary treatment: sentinel lymph node biopsy (SLNB), axillary lymph node dissection (ALND), or none
4. Adjuvant radiotherapy after primary event
5. Secondary axillary treatment: repeat sentinel lymph node biopsy (reSLNB), sequential ALND, or none
6. Mapping methods of reSLNB
7. Identification rate and false negative rate of reSLNB
8. Pathologic status of reSLNB
9. Sequential ALND and pathologic outcome.

Review Questions: With the Extracted Data, an Attempt Was Made to Answer the Following Questions

1. What is the identification rate for a reSLNB?
2. What is the mapping methods for the reSLNB procedure?
3. What is pathologic status of the repeat sentinel lymph node (reSLN)?
4. What is the false-negative rate and the identification of reSLNB?

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2020.518568/full#supplementary-material

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Redefining Criteria to Ensure Adequate Sentinel Lymph Node Biopsy With Dual Tracer for Breast Cancer

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Background: For sentinel lymph node biopsy (SLNB) in patients with breast cancer, the dual tracer of blue dye and radioisotope with the 10% rule that all nodes with radioactive count of 10% or more of the hottest node *ex vivo* should be removed is widely accepted. However, the cut-off point of radioactivity is being questioned for possibly excessive removal of negative nodes.

Methods: To compare different percentile rules and optimize the criteria for identifying SLNs, we established a database which prospectively collected the radioactivity, status of blue dye and the pathological results of each SLN in breast cancer patients who successfully underwent SLNB with a combination of methylene blue and radioisotope.

Results: A total of 2,529 SLNs from 1,039 patients were identified from August 2010 to August 2019. 16.4% (414/2,529) positive nodes were removed at a cost of 83.6% (2115/2,529) negative nodes removed excessively. Up to 17.9% (375/2,115) negative nodes were removed as radioactively hot nodes without blue staining. By gradually increasing the threshold by each 10%, the number of negative nodes identified reduced by 18.2% (385/2,115) with only three node-positive patients (1.0%) missed to be identified using the "40% + blue" rule. In patients with ≥ 2 SLNs removed, 12.3% (238/1,942) negative nodes avoided unnecessary removal with only 0.8% (2/239) positive patients missed with the "hottest two + blue" rule.

Conclusions: Our data indicated that the "40% + blue" rule or the "hottest two + blue" rule for SLNB with the dual tracer of blue dye and radioisotope may be considered as a potential alternative rule to minimize extra nodes resected. Nonetheless, it should be validated by prospective trials with long-term follow-up.

Keywords: breast cancer, sentinel lymph node biopsy, radioisotope, methylene blue, 10% rule

INTRODUCTION

The sentinel lymph node (SLN) was discovered in patients with melanoma by Cabanas in 1977 and is defined as the first draining node(s) with a direct lymphatic connection to the primary tumor site (1). Since sentinel lymph node biopsy (SLNB) was first applied to breast cancer by Krag in 1993 to predict the status of axilla and guide further treatment (2), it has become the standard care of the axilla for early stage breast cancer patients with reduced arm morbidities while still offering equivalent survival compared to axillary lymph node dissection (ALND) (3). There are various tracing methods to guide surgeons to identify a sentinel node intraoperatively including blue dye, radioisotope colloid and various novel techniques such as indocyanine green optical imaging and superparamagnetic iron oxide (3). Given the lack of radioisotope and extra requirements for equipment especially in less developed areas, SLNB using single tracer, predominantly blue dye is used in a large number of institutes (4). However, the dual-tracer method combining the radioactive colloid and blue dye with a higher SLN detection rate (>90%) and a lower false negative rate (FNR) (<5%–10%) than either single tracer is constantly recommended in many guidelines such as the 2005 American Society of Clinical Oncology (ASCO) Guideline Recommendations for Sentinel Lymph Node Biopsy in Early-stage Breast Cancer and the 2011 Chinese Anti-Cancer Association (CACA) Guidelines, and is increasingly being applied in many countries and areas such as the United States, Europe, Australia and China (5–7). Most frequently, breast surgeons who use dual tracer of radioisotope and blue dye follow the "10% + blue" rule which was originally proposed by Martin and McMasters that all nodes with a radioactivity count of at least 10% of the hottest node *ex vivo* or blue dye staining should be removed (8).

An ideal criterion of SLN selection should minimize the number of nodes removed, without significantly sacrificing the sensitivity of the procedure. While this approach can reduce the risk of missing positive nodes with a low radioactivity count, it may result in an excessive number of nodes being removed than those identified on lymphoscintigraphy. To seek an ideal cut-off point of a hot SLN, several studies have assessed the validity of the "10% + blue" rule by comparing with other alternative node harvesting rules, including the "50% + blue" rule, the "hottest + blue" rule, and the "4 nodes" rule (9–11). In our institution, we were concerned that excessive number of negative nodes were excised by the "10% + blue" rule. The more SLNs removed, the higher the cost of the procedure for added operative time, pathological charges, medical resources, and most importantly, the long-term complications after surgeries. However, there is no study comparing the "10% + blue" rule with other alternative criteria under SLNB using radioisotope and methylene blue in China.

Herein, we performed this retrospective analysis which included a large number of breast cancer patients with a prospectively constructed SLNB database at a single institution in China. We re-evaluated the "10% + blue" rule for breast cancer patients and sought to determine whether the threshold of hot nodes could be raised and what the impact it would be on both the accuracy and the number of lymph nodes excised when a higher than 10% threshold was used to define a SLN, potentially leading to patients with positive nodes being missed.

MATERIALS AND METHODS

This study was approved by our institutional review board.

Study Population

Retrospectively, we reviewed the records of breast cancer patients who underwent SLNB successfully with a combination of radioactive colloid and methylene blue at our hospital from August 2010 to August 2019. Patients who were pathologically diagnosed with invasive breast cancer were eligible. Patients who received mastectomy for ductal carcinoma *in situ* (DCIS) were excluded. Patients who received neoadjuvant chemotherapy were also excluded. All patients were clinically node negative (negative in ultrasound, mammography, and physical examination) and had no regional or distant metastases.

Surgical Techniques for SLNB

After the informed consent was obtained from each patient, Radioisotope -99mTc (Beijing Shihong Drug Development Center; Beijing, China) was injected intradermally at tumor surface and/or at periareolar site 3 to 18 h prior to the surgery, and methylene blue (Jiangsu Jichuan Pharmaceutical Co., Ltd; Jiangsu, China) was injected intradermally/subcutaneously at tumor surface and/or at periareolar site 10 to 15 min before surgery. During surgery, a hand-held gamma probe of 99mTc (Devicor Medical Products Inc.; OH, USA) was applied to identify SLNs. Any nodes with 10% or more of the *ex vivo* count of the hottest node and/or any nodes with at least one blue afferent lymphatic vessels derived from the breast were removed and designated as SLNs. Suspicious lymph nodes which were firm, enlarged and palpable but not radioactive or blue stained were also removed as non-SLNs. All nodes were evaluated with intraoperative frozen sections. ALND were performed based on the result of pathological evaluation. Generally, patients with SLNs of macrometastatasis (>2 mm) received ALND. It was recommended in the guidelines of China Anti-Cancer Association in 2017 that axillary dissection can be avoided in cT1-2N0 breast cancer patients who have 1 or 2 macrometastatic SLNs and are undergoing breast-conserving therapy and whole-breast radiation (7). Starting in 2018, for patients who meet the criteria of the ACOSOG Z0011, decisions to perform ALND or not should be made with full informed consent in our institution. Patients free of metastasis and those with SLNs of isolated tumor cells avoided further ALND. For patients with SLNs of micrometastatasis (>0.2 mm, ≤ 2 mm), decisions of ALND were made jointly by patients and the surgery group. Most of nodes removed were examined by permanent sections with hematoxylin-eosin (H&E) staining and immunohistochemical (IHC) staining for breast cancer-specific antigens if no macrometastasis was identified on routine assessment.

During surgery, the radioactivity, status of blue dye staining of nodes and lymphatic vessels, and the pathological results of

each SLN were prospectively recorded so that we could calculate the number of SLNs identified by different criteria of radioactivity in combination with the status of blue staining.

Statistical Analysis

In this study, we defined the rate of miss detection as the number of patients with positive nodes missed to be identified using alternative rules compared with the "10% + blue" rule divided by the total number of node-positive patients detected by the "10% + blue" rule. The chi-square test was used for categorical variables by SPSS 24 (SPSS Inc., Chicago, IL, USA). Figures were prepared by GraphPad Prism 8.0.1. Differences were considered significant at $p \leq 0.05$.

RESULTS

A total of 1,039 invasive breast cancer patients successfully performed SLNB by dual tracers with the "10% + blue" rule. The clinical and pathologic characteristics of the study population were represented in **Table 1**.

Results of SLNB With "10% + Blue" Rule

A total of 2,529 SLNs were identified in 1,039 patients and 16.4% (414/2,529) SLNs were positive (micrometastases or macrometastases) (**Table 2**). A mean of 2.4 SLNs were identified. 78.0% (810/1,039) patients had at least two SLNs identified and 6.64% patients had five or more SLNs removed (**Figure 1A**). 121 non-SLNs were removed for enlarged and palpable but not blue or hot, of which 38 non-SLNs were positive. In a total of 309 patients with at least one positive axillary node (micrometastases or macrometastases), 296 patients had at least one positive SLN with or without positive non-SLNs and each of the remaining 13 patients had only one positive non-SLN. We do not know how many positive lymph nodes were missed due to the lack of complementary ALND, so the probability of non-SLN metastases in patients with SLN metastases (8.4%, 25/296) in this study was lower than that in the AMAROS trial and the Z0011 trial which had approximately one-third patients with a positive non-SLN in the ALND group (12, 13). Among the 414 positive SLNs, 70.3% (291/414) had a radioactivity count of 40% or more than the hottest node and 13.3% (55/414) were blue stained with a less than 10% radiation count of the hottest node (**Figure 1B**). Among 2,115 negative SLNs, 1,413 nodes were blue stained while up to 1,792 were radioactively hot, leading to 17.9% (379/2,115) negative nodes being excessively excised as radioactively hot nodes. Numbers of positive and negative SLNs detected by radioactive colloid and blue dye were shown in **Table S1–3**, respectively.

Different Alternative Rules Compared With "10% + Blue" Rule

Different percentile rules for radioactivity were compared with the "10% + blue" rule (**Table 3**). As is shown in **Figure 2**, the balance between fewer positive nodes missed and more negative nodes reserved was between the "40% + blue" rule and the "50% + blue" rule. From the "10% rule + blue" rule to the "50% + blue" rule, the average number of SLNs identified per patients dropped from 2.43 to 2.00. Compared with the "10% + blue" rule, when the "40% + blue" rule was applied, the rate of positive SLNs increased from 14.80% to 16.58% (p>0.05) and negative SLNs decreased by 18.2% (385/2,115), resulting in a rate of miss detection of only 1.00% (3/296). If only the hottest or blue nodes were removed, seven patients with positive nodes would be

TABLE 1 | Clinical and pathologic characteristics of study population (n=1,039).

Variable	No.	%
Age, mean ± SD, y	48 ± 10.4	
≤40 y	243	23.4%
>40 y	796	76.6%
BMI, mean ± SD, kg/cm^2	22.6 ± 2.9	
<24	759	73.1%
≥24	280	26.9%
Tumor location		
Upper inner quadrant	187	18.0%
Lower inner quadrant	70	6.7%
Upper outer quadrant	393	37.8%
Lower outer quadrant	130	12.5%
3 o'clock	14	1.3%
6 o'clock	17	1.6%
9 o'clock	68	6.6%
12 o'clock	60	5.8%
Central	66	6.4%
Unknown	34	3.3%
T stage (the AJCC, 8th Edition)		
T1	625	60.2%
T2	391	37.6%
T3	23	2.2%
Histological type		
IDC	932	89.7%
Others[1]	107	10.3%
Hormone receptor status		
ER and/or PR positive	787	75.7%
ER and PR negative	215	20.7%
Unknown	37	3.6%
HER2 Status[2]		
Negative	533	51.4%
Positive	155	14.9%
Uncertain	311	29.9%
Unknown	40	3.8%
Ki-67 Status		
<15%	384	37.0%
15%-30%	297	28.6%
>30%	339	32.6%
Unknown	19	1.8%
Type of breast surgery		
Mastectomy	866	83.3%
Lumpectomy	173	16.7%
Type of axillary surgery		
SLNB only	810	78.0%
SLNB followed by ALND	229	22.0%

SD, standard deviation; AJCC, American Joint Committee on Cancer; IDC, invasive ductal cancer; DCIS, ductal carcinoma in situ; SLNB, sentinel lymph node biopsy; ALND, axillary lymph node dissection.

[1]including invasive lobular carcinoma, papillary carcinoma, mucous carcinoma, malignant phyllode tumor, secretory carcinoma, metaplastic carcinoma, squamous cell carcinoma, adenoid cystic carcinoma and mixed carcinoma.

[2]HER2 testing was performed by IHC and FISH if necessary. HER2 is positive when IHC is 3+ or IHC is 2+ with FISH is positive. HER2 is negative when IHC is 0-1+ or IHC is 2+ with FISH negative. HER2 is uncertain if IHC is 2+ without FISH. Her2 is unknown if IHC and FISH are unknown.

TABLE 2 | Outcomes of the dual tracer using a combination of blue dye and radioactive colloid with the 10% criteria.

Characteristics	No.	%
SLN identified by dual tracers	2,529	
mean number of SLNs identified, mean ± SD	2.4 ± 1.16	
positive SLN	414	16.4%
detected by blue dye	333	
detected by the radioactive colloid tracer with 10% rule	359	
negative SLN	2,115	83.6%
detected by blue dye	1,413	
detected by the radioactive colloid tracer with 10% rule	1,792	
non-SLN	121	
Positive non-SLN	38	
Negative non-SLN	83	
Patients with negative axillary nodes	730	70.3%
Patients with positive axillary nodes	309	29.7%
≥1 positive SLN with or without positive non-SLNs	296	
Only one positive non- SLN	13	
Patients with only one SLN identified	229	22.0%
Patients with two or more SLNs identified	810	78.0%

undetected, resulting in a rate of miss detection was 2.7%. Characteristics of the seven patients were shown in **Table S4**. There was no statistically significant difference found with respect to the rate of positive SLNs and the rate of miss detection when applying the criteria anywhere from 10% to the hottest for identifying SLNs compared with the "10% + blue" rule.

Finally, we assessed the "hottest two + blue" rule in 810 patients with at least two SLNs identified by the "10% + blue" rule in this study. The outcomes were presented in **Table 4**. Compared to the "10% + blue" rule, 23 positive nodes were undetected causing 0.84% (2/239) patients with positive nodes missed whereas 12.26% (238/1,942) negative nodes were reserved. Of note, among the 23 positive nodes missed to be identified, 3 nodes were from two node-positive patients who would have been missed to be detected using the "hottest two + blue" rule, and other 20 nodes were from 20 node-positive patients who could have been identified using the "hottest two + blue" rule.

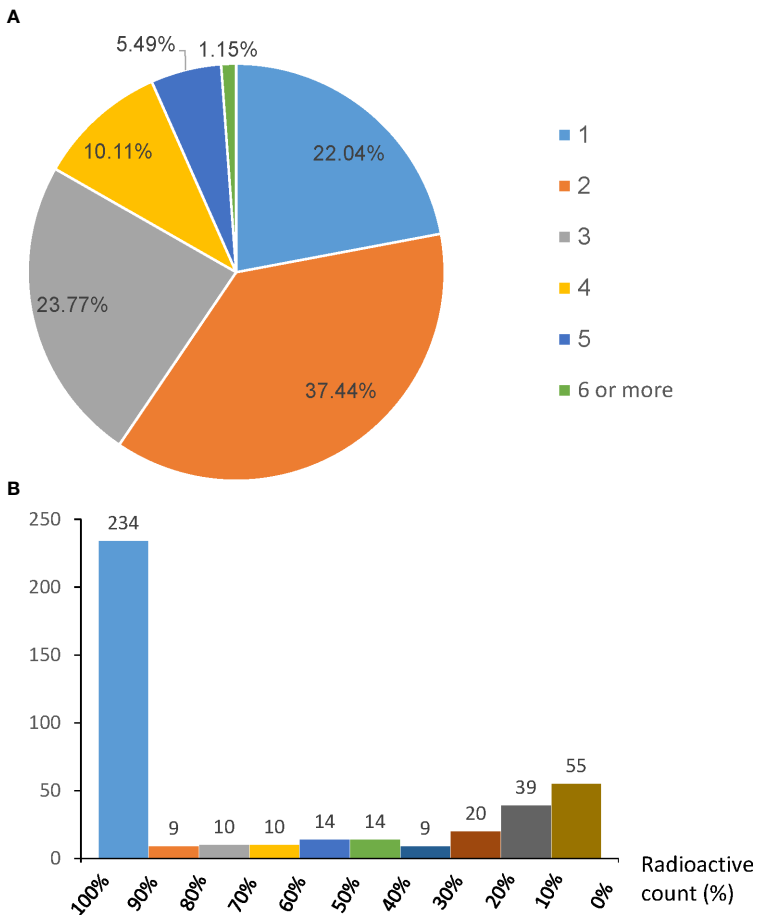

FIGURE 1 | **(A)** Percentage of patients with different No. of sentinel lymph node (SLN) per patients identified by the "10% + blue" rule. **(B)** The radioactive count distribution of 414 positive SLNs by percentile of the hottest node. * Positive nodes with radioactive count percent <10% but blue staining.

TABLE 3 | Effect of different percentage criteria on sentinel lymph node (SLN) identification positive SLN (n=1,039).

Rules	Blue SLNs	Hot SLNs	Hot and blue SLNs	SLNs detected by dual tracers	Detection rate of overall SLNs (per-SLN)	% of nodes reduced	Positive SLNs	Detection rate of positive SLNs (per-SLN)	Patients with positive SLNs	Miss rate of positive SLNs (per-patient)[1]	Detection rate of overall SLNs (per-patient)
≥10%+blue	1,746	2,151	1,368	2,529	ref	ref	414	ref	296	ref	100%
≥20%+blue	1,746	1,779	1,222	2,303	91.1%	8.9%	398	96.1%	293	1.0%	100%
≥30%+blue	1,746	1,568	1,127	2,187	86.5%	13.5%	392	94.7%	293	1.0%	100%
≥40%+blue	1,746	1,435	1,062	2,119	83.8%	16.2%	389	94.0%	293	1.0%	100%
≥50%+blue	1,746	1,342	1,015	2,073	82.0%	18.0%	381	92.0%	291	1.7%	100%
≥60%+blue	1,746	1,257	962	2,041	80.7%	19.3%	379	91.5%	291	1.7%	100%
≥70%+blue	1,746	1,190	923	2,013	79.6%	20.4%	379	91.5%	291	1.7%	100%
≥80%+blue	1,746	1,138	886	1,998	79.0%	21.0%	377	91.1%	290	2.0%	100%
≥90%+blue	1,746	1,087	854	1,979	78.3%	21.7%	376	90.8%	289	2.4%	100%
hottest+blue	1,746	1,034	822	1,958	77.4%	22.6%	373	90.1%	289	2.7%	100%
blue only	1,746	–	–	–	69.0%	31.0%	333	80.4%	261	11.8%	90.4%
≥10% only	–	2,151	–	–	85.1%	14.9%	359	86.7%	273	7.7%	99.4%

[1]*Miss rate of positive SLNs on a per-patient basis= 1- Detection rate of positive SLNs on a per-patient basis = (296-patients with positive nodes detected by each threshold)/296.*

FIGURE 2 | Positive nodes missed and extra negative removed by combing different percentage rules with blue dye.

DISCUSSION

During the last decades, the concept of the treatment strategy for breast cancer has shifted from maximum tolerated therapy to minimum effective therapy. With the improvement of imaging examination and the popularization of screening, breast cancers diagnosed at early stage have strongly increased (14–17). In non-surgical area, improvements in multimodal therapy, including advances in modern radiotherapy technology, optimization of chemotherapy, and anti-HER2 therapy regimens, novel endocrine agents, and target drugs, as well as clinical utility of immunotherapy, could further diminish breast cancer mortality and contribute to increase chances for cure in 70%–80% patients with early breast cancer (18, 19). In large clinical trials such as the AMAROS and the ACOSOG Z0011, the residual tumor burden from limited metsastatic nodes may be further reduced, resulting in an extremely low recurrence rate (<2%) (12, 13, 20). With extended survival, the quality of life is becoming more important. The dual tracer combining radioisotope and blue dye remains the mainstream in the current clinical routine, especially in institutions where materials and equipment for new tracing method are not available. Exploring optimized criteria based on the dual-tracer method is more conducive to improve the quality of life for a wide range of patients. Therefore, in this study, we merely focused on the dual tracer method of radioactive colloid and methylene blue, rather than other new techniques for SLNB such as indocyaninegreen.

Although SLNB is associated with improved quality of life and reduced arm morbidities without compromising the survival in patients with early stage breast cancer compared to ALND (21, 22), a considerable number of patients undergoing SLNB still suffer from arm and shoulder impairments. Prevalence of lymphedema one year after SLNB ranges between 3% and 17% and for pain, prevalence between 3.3% and 56.6% have been reported in SLN-negative breast cancer patients (23–25). Some studies reported that a greater number of nodes removed, especially more than ten nodes dissected, was associated with

TABLE 4 | Effect of different criteria on sentinel lymph node (SLN) identification in patients with two or more SLNs removed (n=810).

Rules	SLNs with blue staining	Hot SLNs	SLNs detected by dual tracers	Positive SLNs	Negative SLNs	Patients with positive SLNs	Patients with negative SLNs	% of negative nodes reserved	No. of SLNs per patients	Miss rate
Blue dye	1,553	–	–	286	1,267	214	596	–	1.92	10.5%
10% rule	–	1,926	–	303	1,623	216	594	–	2.38	9.6%
10%rule +blue	1,553	1,926	2300	358	1,942	239	571	Ref	2.84	ref
Hottest	–	810	–	169	639	169	641	–	1.00	29.3%
Hottest two	–	1,620	–	271	1,349	218	592	–	2.00	8.8%
Hottest two + blue	1,553	1,620	2039	335	1,704	237	573	12.3%	2.52	0.8%

an increased risk of lymphedema in ALND patients (26–28) although existing studies failed to find this association in SLNB patients (24, 29, 30). However, the observation that the arm morbidity occurs in a certain proportion of patients who received SLNB leads us to worry that a larger number of SLNs dissected may contribute to a higher risk of arm morbidity. In this study, 16.4% nodes were harvested for metastases at an expense of 83.6% negative nodes removed excessively. Furthermore, up to 17.9% negative nodes were removed as radioactively hot nodes without blue staining. Besides, 6.64% patients had five or more SLNs removed, which may weaken the advantage of SLNB as a less invasive procedure. The more SLNs removed, the higher the cost of the procedure for added time during surgery and increased pathological charges. When no metastases are detected by routine H&E, more in-depth histologic evaluation such as IHC will be applied to detect (micro-)metastases, making the procedure more expensive than routine histology (31, 32).

Is there a more reasonable guide for identifying SLNs with less unnecessary nodes removed for breast cancer? To our knowledge, several previous retrospective studies compared the dual tracer using 10% rule with various blue dye and a few studies attempted to seek alternative methods. Nagao et al. assessed the "10% + blue" rule and the "4 node" rule by involving 302 patients with Tis-T3 breast cancer who underwent SLNB with a combination of radioisotope and indigo carmine blue dye and concluded that terminating SLNB at the first three SLNs identified all node positive patients with a low false negative rate (FNR) and rate of complication (9). In a study of 475 patients with T1-2 breast cancer who underwent SLNB with a combination of radioisotope (10% rule) and blue dye (lymphazurin or methylene), Dutta et al. indicated that no more than 4 SLNs should be removed because all patients with positive nodes were identified within the first 4 SLNs removed (10). Liu et al. studied 332 patients with T1-T3 breast cancer who underwent SLNB and showed that using the "40%" rule as the criteria for removal of SLN resulted in a 10.3% FNR and "10%" rule resulted in a 6.4% FNR; however, surgeons selectively used lymphazurin blue so the radioisotope was generally used alone in the study (11). Another large retrospective study involving 6519 patients with T1-T3 breast cancer who underwent SLNB with a combination of radioisotope and isosulfan blue dye performed by Chung et al. reported that the "10% +blue" rule was a reliable guideline but they didn't determine other potential percentile cut-off of hot nodes (33). We first built the model by gradually increasing the percentile threshold of radioactivity count in a large prospectively collected database of breast cancer patients who performed SLNB by dual tracers of methylene blue and radioisotope in China. Our data demonstrated that compared with the "10% + blue" rule, the number of nodes identified would reduce by 16.2% at a cost of only three positive patients being missed (1.0%) when the "40% +blue" rule was used. Similarly, in patients with at least two SLNs removed, 12.3% negative nodes were able to avoid being removed unnecessarily with only 0.8% positive patients missed by the "hottest two + blue" criteria. The potential 16.2% and 12.3% reduction in nodes that need pathological examination may offer a considerable cost-effectiveness benefit of the procedure. Our result revealed that replacing the "10% +blue" rule with the "40% +blue" rule or the "hottest two + blue" rule can be considered as a potential alternative model to minimize extra negative nodes removed without significantly increasing the number of node positive patients missed.

The main concern for patients with SLNB is the impact of missed nodes on locoregional recurrence and survival. In the NSABP B-06 trial which was designed to determine whether SLNB achieve an equivalent survival and regional control as ALND, breast cancer patients with negative SLNs were randomly assigned 1:1 to ALND or SLNB alone. It reported that each group had less than 1% regional node recurrences as first events by eight years (ALND group vs SLNB group: 8/1,975 vs 12/2,011, p=0.22) with 9.8% FNR in the ALND group (34). The Milan trial also showed that 2 patients in the SLNB group developed axillary recurrence with 8 patients estimated to have occult axillary involvement (35). Besides, in the AMAROS trial and the Z0011 trial, the axillary recurrence was extremely low (<1%) in the SLNB group with an estimated one-third residual lesions (12, 13). In our study, only 0.29% (3/1,039) node-positive patients were missed when we changed the "10% +blue" rule to the "40% +blue" rule and 0.25% (2/810) when we replaced the "10% +blue" rule with the "hottest two + blue" rule. In the era of subsequent effective and complete adjuvant therapy, the residual lesions may be further reduced. We therefore would expect to see an extremely low recurrence rate.

Some limitations of this study should be mentioned. First, in this retrospective study, ALND was not performed in patients with negative SLNs because of ethical issues. A small number of SLN-positive patients chose to avoid further ALND starting in 2018, which was a bit behind the clinical trials and guidelines. Therefore, the actual sensitivity, specificity, accuracy and FNR of SLNB were unlikely to be calculated. What we were most concerned about was the FNR of alternatives to the "10% + blue" rule. Thus we defined the term "the rate of miss detection" similar to Liu and Murphy (36, 37)

and no statistically significance was found anywhere from the "10% +blue" rule to the "hottest + blue" rule. Besides, in our institution, to ensure a low FNR within 5%, at least 40 cases were required for the learning curve for SLNB before surgeons could contribute to this database so that our conclusion could not be affected by the shortcoming of unknowing true FNR. Second, patients with micrometastatic SLNs were offered observation or ALND with full informed consent, which was somewhat behind the latest guidelines and the IBCSG 23-01 trial which indicated that ALND should be avoided in SLN-micrometastatic patients receiving breast-conserving surgery (38). Besides, we didn't group patients prospectively and the study was a single monocentric experience without confirmation in an external dataset, so we did not know the local control of patients undergoing SLNB with different criteria. Though the effect of missing positive patients on survival was not expected to be great according previous literature as discussed above, the results of this study should be validated by multiple-center prospective studies with long-term follow up for prognosis.

CONCLUSIONS

Our data demonstrated that the "40% + blue" rule or the "hottest two + blue" rule can be considered as a potential alternative model to minimize extra negative nodes removed without significantly increasing the number of node-positive patients missed. The results should be further validated in prospective clinical trials with long-term follow up.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Westchina hospital, Sichuan University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

Study conception and design: QL. Data collection: ZD, FL, YX, QYL, JC, and HZ. Data analysis: LX and JY. Data interpretation: QL, ZD, LX, and JY. Manuscript preparation: LX and JY. All authors contributed to manuscript revision, read, and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2020.588067/full#supplementary-material

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Post-Operative Complications and Nipple Necrosis Rates Between Conventional and Robotic Nipple-Sparing Mastectomy

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Purpose: This study is to directly compare surgical outcomes between conventional nipple-sparing mastectomy (CNSM) and robot-assisted nipple-sparing mastectomy (RNSM).

Materials and Method: For this case–control study, 369 cases of 333 patients who underwent CNSM or RNSM with immediate reconstruction between November 2016 and January 2019 at Severance Hospital in Seoul, Republic of Korea were reviewed. Patients with stage IV breast cancer (n = 1), receiving neoadjuvant chemotherapy (n = 43), or subjected to previous operations (n = 14) or radiotherapy on the breasts were excluded. The main outcomes were comparing rates of post-operative complications, of high-grade post-operative complications as defined by the Clavien-Dindo classification, and nipple necrosis between the CNSM and the RNSM groups.

Results: A total of 311 cases, including 270 CNSMs and 41 RNSMs, were analyzed. The rates of post-operative nipple necrosis ($p = 0.026$, 2.4 *vs.* 15.2%) and of high-grade post-operative complications ($p = 0.031$, 34.8 *vs.* 17.1%) in the RNSM group were significantly lower than those in the CNSM group.

Conclusion: RNSM was associated with lower rates of high-grade post-operative complications and nipple necrosis than CNSM for patients with small breast volumes and less ptotic breasts.

Keywords: breast neoplasms, robotic mastectomy, nipple-sparing mastectomy, minimal invasive surgery, nipple necrosis

INTRODUCTION

Nipple-sparing mastectomy (NSM) has been widely applied to women with early breast cancer or *BRCA 1/2* mutations (1–4). Because NSM preserves the nipple areolar complex (NAC) and overlying skin, NSM results in better cosmetic outcomes coupled with oncologic safety for those patients, compared to conventional total mastectomy or skin-sparing mastectomy (4–9).

Nipple necrosis is one of the most common complications after NSM (1, 2, 10, 11). Previous studies reported 0–48% of nipple ischemia or nipple necrosis in patients undergoing NSM with immediate reconstruction (1, 12). In order to reduce nipple ischemia or necrosis, various techniques have been proposed in previous studies (12, 13). Rusby et al. showed that placement of incisions far from the NAC and reconstruction using a tissue expander (T/E) reduced the risk of NAC necrosis (12). Petit et al. reported that leaving a layer 5 mm of glandular tissue beneath the NAC for preserving its blood supply is beneficial to reduce NAC necrosis (13). However, there is no universal solution for reducing nipple necrosis after NSM.

Many surgeons have tried to develop various incisions in NSM to deliver better cosmetic outcomes (14–16). Robot-assisted nipple-sparing mastectomy (RNSM) is a procedure that uses robotic systems through axillary or lateral incisions, which results in no scars in the overlying skin. A previous study reported that RNSM presented with low rates of nipple necrosis (17–19). However, there has been, to our knowledge, a lack of comparisons between RNSM and conventional NSM (CNSM) in terms of nipple necrosis rates.

This study aimed to evaluate nipple necrosis rates between RNSM and CNSM. Additionally, grades and rates of complications after the two procedures were analyzed and compared.

MATERIALS AND METHODS

Patients

A total of 333 patients in the present study had undergone CNSM or RNSM between November 2016 and January 2019 at Severance Hospital, Seoul, Korea. Their medical records and post-operative photographs taken by plastic surgeons were retrospectively reviewed. The photographs were taken on 1, 2, 3, 5, 7, and 9 days after the operation of autologous reconstruction routinely. After a prosthetic reconstruction, post-operative photographs were taken on 1, 2, 4, 6, and 8 days after the operation. In an outpatient department, plastic surgeons take the photographs as needed. Exclusion criteria were the presence of stage IV disease (n = 1), treatment with neoadjuvant chemotherapy (n = 43), and previous operation or radiation history (n = 14). This resulted in a total of 311 cases, 270 cases with CNSM and 41 cases with RNSM, from 275 patients being enrolled in the study (**Figure 1**). Among them, 36 patients underwent either bilateral CNSM or RNSM. There was no male patient in this study because patients who underwent immediate reconstruction after mastectomy were collected.

Clinicopathologic features, including age, BMI, breast volume, ptosis, disease entities, TNM stage, estrogen and progesterone receptor, human epidermal growth factor receptor (HER) 2 status, Ki 67 levels, adjuvant therapies, reconstruction methods, duration of hospital stays, and operation times were analyzed. Post-operative complications through 1–28 months, including nipple ischemia or necrosis, skin ischemia or necrosis, infection, bleeding, lymphedema, limitation of shoulder movement, contracture, seroma, wound dehiscence, and arterial thrombus, were also analyzed. Nipple ischemia in this study was defined as a clinical ischemic color change in the NAC. Nipple necrosis was defined as full-thickness necrosis of the NAC requiring surgical intervention (1). Grades of post-operative complications were analyzed according to the Clavien-Dindo classification (20).

Procedures

CNSM was performed using various methods by three breast surgeons (**Figure 2**). Immediate reconstruction, including tissue expander (T/E), direct-to-implant (DTI), Latissimus dorsi (LD) flap, and transverse rectus abdominis musculocutaneous (TRAM) flap, was performed according to surgeons' and patients' preferences by three plastic surgeons. A deep inferior epigastric perforator flap was included in the TRAM flap. RNSM was performed *via* single axillary or lateral incision by a breast surgeon. Gas or gasless technique in robotic mastectomy was

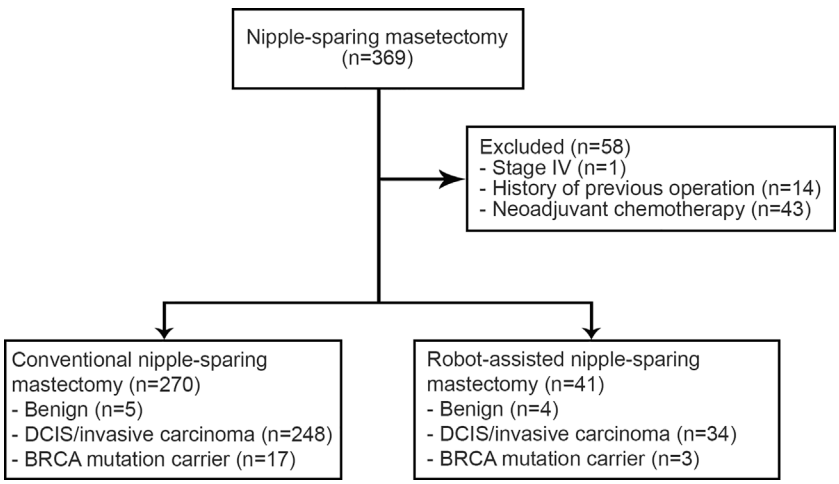

FIGURE 1 | Schematic diagram of the study population.

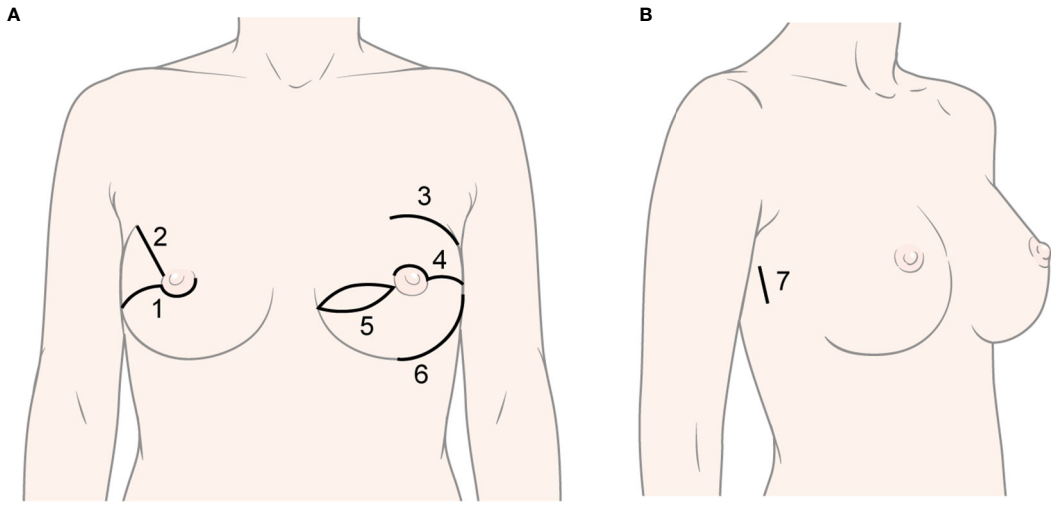

FIGURE 2 | Various types of incisions in conventional nipple-sparing mastectomy and robot-assisted nipple-sparing mastectomy. **(A)** Types of incision in conventional nipple-sparing mastectomy: 1) Lower-periareolar incision with/without extension, 2) Radial incision, 3) Curvilinear incision, 4) Upper-periareolar incision with/without extension, 5) Elliptical incision, 6) Inframammary fold incision; **(B)** Type of incision in robot-assisted nipple-sparing mastectomy: 7) Lateral incision.

applied to patients with early breast cancer or *BRCA* mutations (17–19, 21). The detailed techniques were described in previous studies (17–19, 21). T/E insertion or DTI was applied for immediate reconstruction in those patients (19, 21).

Pathologic Evaluations

Estrogen receptor (ER), progesterone receptor (PR), HER2 status, and Ki 67 levels were analyzed by immunohistochemistry (IHC), as described in previous studies (22). In brief, positivity for ER and PR was defined as ≥1% nuclear staining in IHC. HER2 2+ in IHC and amplification in fluorescence *in situ* hybridization/silver *in situ* hybridization or 3+ in IHC were considered overexpression according to ASCO/CAP guidelines (23). The cut-off values for Ki 67 staining for low and high proliferative index were < and ≥14% staining in IHC, respectively (24). TNM stage was classified according to anatomic stage as in the AJCC 8th edition. Nipple margins were reviewed from both intra-operative frozen and post-operative permanent pathologic evaluations.

Adjuvant Therapies

Chemotherapy, endocrine therapy, and radiation therapy were delivered according to standard guidelines or physicians' preferences (25). Patients with HER2-positive disease and tumor sizes ≥1 cm routinely received adjuvant trastuzumab therapy.

Statistics

A learning curve of RNSM for total operation time was analyzed using three-day moving average curves (3D-MAC), and the cumulative sum (CUSUM) technique. 3D-MAC is used to analyze the existence of a learning curve (26). This simple moving average is defined as the mean value of previous 3 days data points (27). The CUSUM technique is a statistical method to assess the learning curve quantitatively and to calculate the sequential difference between the individual and the mean value of all data (28). The CUSUM is estimated by $CUSUM = \sum_{i=1}^{n}(xi - \mu)$, where xi is an individual operation time, and μ is the mean value of overall operation time (29).

Categorical variables were analyzed using either Chi-square test or Fisher's exact test, if indicated. Continuous variables were analyzed using either Student's t test or Mann–Whitney test, if indicated. All tests were two-sided. Multivariate analysis was performed using binary regression with backward elimination (conditional) to evaluate risk factors related with high-grade complications (Clavien-Dindo classification ≥grade III). A p-value less than 0.05 was considered to be statistically significant. All statistical analyses were performed using the SPSS software, version 25 (SPSS Inc., Chicago, IL). We did not use a statistical matching technique due to the limited sample size. Missing values were imputed as null values.

Ethics

This study was approved by the institutional review board at Severance Hospital (4–2019–0510).

RESULTS

The clinicopathologic features of the enrolled patients are shown in **Table 1**. The mean age of patients was 45.93 ± 8.34 (data not shown). There were no differences in clinicopathologic features between the CNSM and RNSM groups, except in breast volumes, laterality, and ptosis. Ptotic breasts were more frequent and breast volumes were larger in the CNSM group. Others subgroup in *BRCA* mutation included three cases with *PALB2* mutations (**Table 1**).

Post-operative outcomes, including length of hospital stay and operation times are shown in **Table 2**. The length of hospital stay in

TABLE 1 | Clinicopathologic characteristics of the study population.

		CNSM (n = 270)	RNSM (n = 41)	*p*-value[b]
Age (years)		46 ± 8.0	44 ± 10.0	0.075[c]
BMI (kg/m^2)		22.5 ± 3.1	21.7 ± 2.3	0.065[c]
Breast volume (g)		428 ± 222.0	326 ± 143.0	0.002[c]
Laterality	Unilateral	216 (80.0)	23 (56.1)	0.001
	Bilateral	54 (20)	18 (43.9)	
Ptosis	Normal	136 (50.4)	32 (78.0)	0.004
	Mild	56 (20.7)	8 (19.5)	
	Moderate	36 (13.3)	0 (0.0)	
	Severe	38 (14.1)	1 (2.4)	
	Pseudoptosis	2 (0.7)	0 (0.0)	
BRCA1 mutation	No	89 (81.7)	16 (94.1)	0.913
	Yes	11 (10.1)	1 (5.9)	
	VOUS	6 (5.5)	0 (0.0)	
	Others	3 (2.8)	0 (0.0)	
BRCA2 mutation	No	89 (81.7)	10 (58.8)	0.050
	Yes	12 (11.0)	6 (35.5)	
	VOUS	5 (4.6)	1 (5.9)	
	Others	3 (2.8)	0 (0.0)	
Diagnosis	Benign	5 (1.9)	4 (9.8)	0.069
	DCIS	63 (23.3)	9 (22.0)	
	Invasive carcinoma	185 (68.5)	25 (61.0)	
	BRCA mutation carrier	17 (6.3)	3 (7.3)	
ER[a]	Negative	49 (19.8)	3 (8.8)	0.123
	Positive	199 (80.2)	31 (91.2)	
PR[a]	Negative	64 (25.8)	8 (23.5)	0.775
	Positive	184 (74.2)	26 (76.5)	
HER2[a]	Negative	174 (76.3)	21 (63.6)	0.117
	Positive	54 (23.7)	12 (36.4)	
Ki 67[a]	Low (<14%)	108 (44.3)	13 (38.2)	0.632
	High (≥14%)	136 (55.7)	21 (61.8)	
Histologic grade[a]	Grade I	59 (23.8)	5 (14.7)	0.445
	Grade II	144 (58.1)	21 (61.8)	
	Grade III	45 (18.1)	8 (23.5)	
T[a]	Tis	67 (27.0)	11 (32.4)	0.615
	T1	144 (58.1)	20 (58.8)	
	T2	37 (14.9)	3 (8.8)	
N[a]	N0	210 (86.1)	30 (88.2)	0.653
	N1	29 (11.9)	3 (8.8)	
	N2	4 (1.6)	1 (2.9)	
	N3	1 (0.4)	0 (0.0)	
TNM stage[a]	0	68 (27.4)	8 (23.5)	0.766
	I	126 (50.8)	20 (58.8)	
	II	48 (19.4)	5 (14.7)	
	III	6 (2.4)	1 (2.9)	
Adjuvant chemotherapy[a]	No	167 (67.3)	23 (67.6)	0.971
	Yes	81 (32.7)	11 (32.4)	
Radiotherapy[a]	No	220 (88.7)	30 (88.2)	0.935
	Yes	28 (11.3)	4 (11.8)	
Hormone therapy[a]	No	58 (23.4)	5 (14.7)	0.254
	Yes	190 (76.6)	29 (85.3)	
Target therapy[a]	No	231 (93.1)	29 (85.3)	0.161
	Yes	17 (6.9)	5 (14.7)	
Recurrence[a]	No	246 (99.2)	41 (100.0)	> 0.999
	Yes	2 (0.8)	0 (0.0)	

Values are represented as mean ± SD or number (percentage).

BMI, body mass index; CNSM, conventional nipple-sparing mastectomy; DCIS, ductal carcinoma in situ, ER, estrogen receptor; HER, human epidermal growth factor receptor; PR, progesterone receptor; RNSM, robot-assisted nipple-sparing mastectomy; VOUS, variants of unknown significance.

[a]*29 cases of benign disease or BRCA mutation carriers were not included (n = 282).*

[b]*Chi-square test or Fisher's exact test.*

[c]*Student's t test or Mann–Whitney test.*

TABLE 2 | Surgical methods and post-operative outcomes.

		CNSM (n = 270)	RNSM (n = 41)	*p*-value[b]
Hospital stay (days)		12 ± 3	14 ± 4	0.001[c]
Total operation time (min)		303.9 ± 195.9	308.9 ± 75.5	<0.001[c]
Mastectomy time (min)		104.5 ± 40.5	181.5 ± 44.7	<0.001[c]
Console time (min)		–	64 ± 40	–
Reconstruction time (min)		196.8 ± 182.5	140.5 ± 52.5	0.019[c]
Operation site	Left	139 (51.5)	19 (46.3)	0.616
	Right	131 (48.5)	22 (53.7)	
Reconstruction types	T/E	190 (70.4)	21 (51.2)	<0.001
	DTI	5 (1.9)	20 (48.8)	
	TRAM	73 (27.0)	0 (0.0)	
	LD	2 (0.7)	0 (0.0)	
Incision types	IMF	51 (18.9)	0 (0.0)	<0.001
	Radial	32 (11.9)	0 (0.0)	
	Upper-periareolar with extension	120 (44.4)	0 (0.0)	
	Lower-periareolar with extension	52 (19.3)	0 (0.0)	
	Curvilinear	3 (1.1)	0 (0.0)	
	Elliptical	12 (4.4)	0 (0.0)	
	Lateral or axillary	0 (0.0)	41 (100.0)	
SLNB[a]	No	20 (7.7)	2 (5.9)	>0.99
	Yes	239 (92.3)	32 (94.1)	
ALND[a]	No	224 (86.5)	31 (91.2)	0.592
	Yes	35 (13.5)	3 (8.8)	
Margin status[a]	No	240 (96.8)	32 (94.1)	0.404
	Yes	3 (1.2)	1 (2.9)	

Values are represented as mean ± SD or number (percentage).

ALND, axillary lymph node dissection; CNSM, conventional nipple-sparing mastectomy; DTI, direct-to-implant; IMF, inframammary fold; LD, latissimus dorsi flap; RNSM, robot-assisted nipple-sparing mastectomy; SLNB, sentinel lymph node biopsy; T/E, tissue expander; TRAM, transverse rectus abdominis musculocutaneous flap.

[a]*29 cases of benign disease or BRCA mutation carriers were not included (n = 282).*

[b]*Chi-square test or Fisher's exact test.*

[c]*Student's t test or Mann–Whitney test.*

the RNSM group was greater than in the CNSM group ($p < 0.001$, 14 ± 4 *vs.* 12 ± 3 days), and the same held for total operation time ($p < 0.001$, 308.9 ± 75.5 *vs.* 303.9 ± 195.9 min). Mastectomy time was longer in the RNSM group than the CNSM group ($p < 0.001$, 181.5 ± 44.7 *vs.* 104.5 ± 40.5 min), Reconstruction time was longer in the CNSM group than the RNSM group ($p = 0.019$, 196.8 ± 182.5 *vs.* 140.5 ± 52.5 min).

T/E was the most common method for immediate reconstruction in both groups (**Table 2**). TRAM is the second most common method for immediate reconstruction in the CNSM group. Approximately half of the patients underwent DTI after RNSM.

Incision types are described in **Table 2**. Periareolar with extension was the most common incision in the CNSM group, followed by IMF, radial, elliptical, and curvilinear incision. Lateral or axillary incision was only used in the RNSM group. Incision types between the two groups were significantly different ($p < 0.001$). There was no significant difference of margin status between two groups. The CNSM group included one nipple and two superficial margins of tumor involvement. The RNSM group had one superficial margin involvement of tumor (**Table 2**). One patient who underwent RNSM showed false negative in subareolar mass in frozen section. Because the final pathology revealed invasive ductal carcinoma in the mass, NAC was sacrificed.

Figure 3 shows grades of post-operative complications and nipple necrosis rates between the two groups. Post-operative complication rates were not different between the CNSM and RNSM groups ($p = 0.176$, 58.5 *vs.* 46.3%). There was no significant difference in implant loss and infection rates between the groups (for implant loss, $p = 0.347$, 0.7% for the CNSM group *vs.* 2.4% for the RNSM group, for infection, $p = 0.101$, 2.2% for the CNSM group *vs.* 7.3% for the RNSM group, data not shown). Post-operative complications requiring surgical intervention, such as wound revision, drain re-insertion, fat graft injection for volume defects, and implant removal were more common in the CNSM group ($p = 0.031$, grade ≥III, 34.8% *vs.* 17.1%). Nipple necrosis rate was significantly lower in the RNSM group than in the CNSM group ($p = 0.026$, 2.4 *vs.* 15.2%).

Multivariate analysis was conducted to evaluate risk factors related to high-grade complications. The rate of high-grade complications (grade ≥III) was statistically associated with the methods of the mastectomy and the operation time ($p = 0.046$ and $p < 0.001$) (**Table 3**).

DISCUSSION

Our study demonstrated the advantage of RNSM compared to the CNSM in terms of nipple necrosis rate. Previous studies suggested that certain incision types are significantly associated with nipple necrosis because the viability of the NAC is mainly maintained by blood supply from dermal layers (4, 30). Another

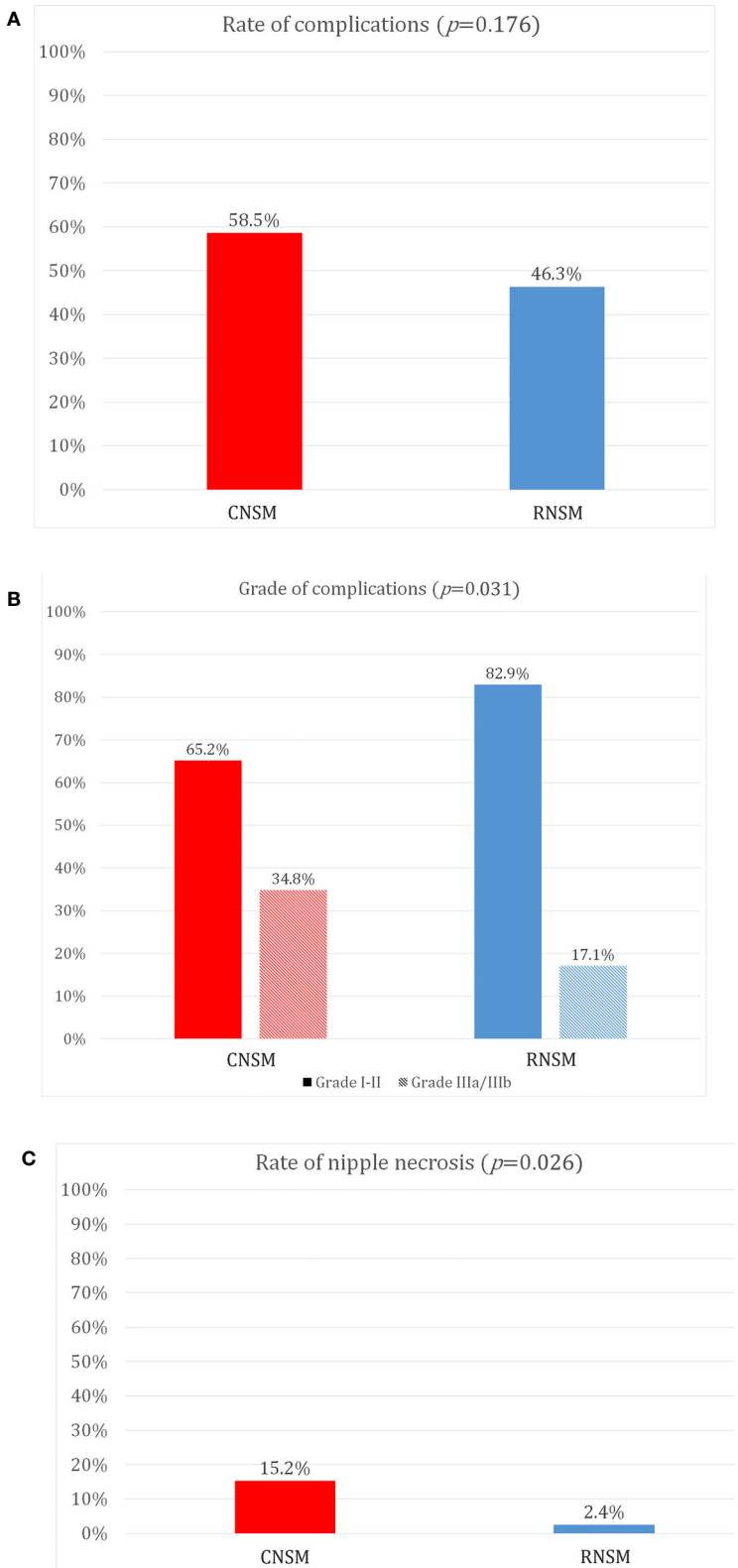

FIGURE 3 | Comparison of post-operative complications between conventional nipple-sparing mastectomy and robot-assisted nipple sparing mastectomy. **(A)** Rate of complications, **(B)** Grade of complications, **(C)** Rate of nipple necrosis.

TABLE 3 | Multivariate analysis for risk factors related with high-grade complications.

	Clavien-Dindo Classification ≥Grade III	
	OR (95% CI)	***p*-value**
Age (≤50 *vs.* >50)	0.751 (0.381–1.480)	0.408
Breast volume (≤310 g *vs.* >310 g)	1.638 (0.862–3.111)	0.132
Ptosis (Normal *vs.* Ptotic)	0.904 (0.489–1.673)	0.748
Operation time (min)	1.005 (1.004–1.007)	<0.001
Operation method (CNSM *vs.* RNSM)	0.406 (0.167–0.986)	0.046

CNSM, conventional nipple-sparing mastectomy; RNSM, robot-assisted nipple-sparing mastectomy.

study presented that a transaxillary incision could be the incision of choice for NSM with valid, oncological safe, and excellent cosmetic results in breast cancer patients or *BRCA* mutation carriers (31). For this reason, small axillary or lateral incisions in RNSM may have beneficial effects on the integrity of overlying skin and the NAC.

The rate of complications was not statistically different between the RNSM and the CNSM groups. Grades of post-operative complications were significantly different between the two groups. Compared to CNSM, RNSM showed lower rates of high-grade complications in the univariate and multivariate analysis. This different rate of high-grade complication may be due to different types of immediate reconstruction procedures. A previous study in our institution reported that reconstruction with TRAM free flap, LD flap with implant, and DTI presented with more post-operative NAC necrosis than reconstruction with a T/E (1). Similarly, another study reported that higher grades of post-operative complications occurred more commonly in patients with autologous reconstructions compared to those with implant-based reconstructions (32). In the present study, approximately one third (27.7%) of patients in the CNSM group underwent autologous reconstructions, and this may influence the higher grade of post-operative complications in this group. Therefore, it is important to consider types of reconstruction procedure as a stratification factor when conducting randomized clinical trials in the future.

In the present study, RNSM was mainly performed on patients with small- to medium-sized breasts without ptosis. This is concordant with previous studies (19). Toesca et al. mainly enrolled women with small- to medium-sized breasts with low grade ptosis in their randomized clinical trial (19, 33). This may be due to the fact that implant-based reconstruction is suitable for small- to medium-sized breasts with low grade ptosis. Implant-based reconstructions constituted the major reconstruction method after RNSM because LD or TRAM flap requires additional incisions compared to implant-based reconstruction. Autologous reconstruction after RNSM remained as a technical challenge of robotic surgery.

Operation times for mastectomy were longer in the RNSM group than in the CNSM group in this study. Robotic surgery, including thyroidectomy, colectomy, and gastrectomy, presented with longer operation times than conventional surgery (34–36).

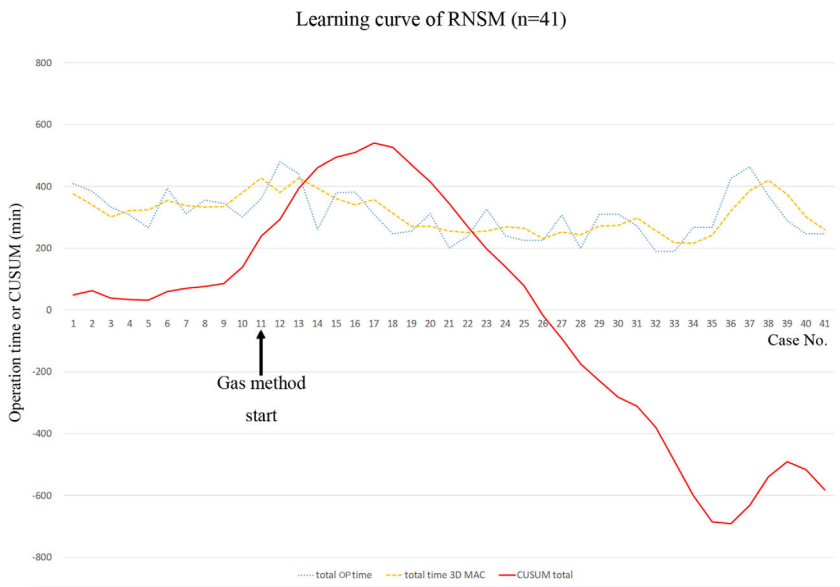

FIGURE 4 | Learning curve of robot-assisted nipple-sparing mastectomy. *CUSUM*, cumulative sum technique; *OP*, operation; *RNSM*, robot-assisted nipple-sparing mastectomy; *3D MAC*, 3-day moving average curve.

This is due to the development of the working space, the robot docking, and surgeon's experience (37). This is also the case with RNSM. Mean mastectomy time in the RNSM group was 181.5 min, and it was longer than mastectomy time in the CNSM group (95.5 min). However, as RNSM is a new technique, there was a learning period in the initial cases in this study. Even though operation times during RNSM decreased over time (**Figure 4**), a significant learning curve associated with a new technique such as RNSM may account for longer operation times compared to conventional procedures. Despite increased duration of mastectomy, console time in RNSM was approximately 1 hour (**Table 2**). Further studies regarding learning curves are necessary for comparisons of the two groups in terms of duration of operation.

Hospital stays were longer in the RNSM group than in the CNSM group. However, with a difference of only two days, there was no significant impact on clinical outcomes because there are differences in hospital stays according to surgeons' preferences (data not shown).

There are several limitations to this study. The retrospective design of this study may have led to selection bias. Propensity matching would be an alternative method to reduce the limitations of a retrospective study. Also, the numeric disparity between the RNSM and CNSM groups was another limitation. Patient satisfaction and cosmetic outcomes, which may be one of the main advantages of RNSM, were not measured. A lack of detailed information on reconstructive techniques, such as subpectoral or prepectoral techniques, was another limitation of the study. Oncologic outcomes, such as loco-regional recurrence-free survival, disease-free survival, and overall survival, are important end-points in the treatment of patients with breast cancer. Prospective studies with longer follow-ups are needed to overcome these limitations. However, to the best of our knowledge, this is the largest study to evaluate differences in terms of grades of complications and rates of nipple necrosis between RNSM and CNSM. Moreover, the results of the current study support the feasibility and safety of robotic mastectomy as a treatment option for women with breast cancer or *BRCA* mutations.

CONCLUSION

This study indicated that RNSM may have some advantages in terms of lower nipple necrosis and grade of post-operative complications. Further multicenter studies evaluating the clinical implications of RNSM should be conducted in the future.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the institutional review board at Severance Hospital (4–2019–0510). Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

HSP, a principal investigator, conceived the ideas of the study. JL and HSP wrote the manuscript, and conducted the data analysis and interpretation. All authors contributed to the article and approved the submitted version.

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The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Effectiveness of Cyanoacrylate in Reducing Seroma Formation in Breast Cancer Patients Post-Axillary Dissection: A Randomized Controlled Trial

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Background/Purpose: Seroma is a common complication after axillary dissection in women with node-positive breast cancer. We aim to determine the effect of Cyanoacrylate on reducing seroma formation in patients undergoing axillary dissection. This a randomized clinical trial.

Methods: This is a single-center, randomized, single-blinded, and two-arm parallel study. Women with node-positive breast cancer eligible for axillary dissection were enrolled. Patients with a Body Mass Index (BMI) greater than 35 kg/m^2, those who underwent immediate breast reconstruction, and/or received neoadjuvant chemotherapy were excluded. Patients were randomized in a 1:1 ratio, and were stratified according to their age, BMI, tumor size, and operation type. The primary endpoint was the total seroma volume (the total drained volume and the total aspirated volume after drain removal). Data presented as mean and range when applicable.

Results: 111 patients were randomized (Cyanoacrylate 57; control 54). 105 patients were analyzed. Sixty-nine patients underwent breast conserving surgery, and 36 underwent modified radical mastectomy. There was no difference in the total seroma volume between the Cyanoacrylate vs. control arms (1,304 (60–4,950) vs. 1,446 (100–5,223) ml, p=0.458). Wound infection, flap necrosis, number of manual aspirates, and hematoma formation were not statistically different between the two groups. Time to drain removal was shorter in the Cyanoacrylate arm (11.04(3–23) vs. 13.84(3–37) days, p=0.015). The use of Cyanoacrylate was not cost effective ($586.93 (550–748) vs. $29.63 (0–198), p<0.001). Higher seroma volume was correlated with modified radical mastectomy, older age, and BMI more than 30 kg/m^2.

Conclusion: Cyanoacrylate did not reduce seroma formation and its use was not cost effective.

Clinical Trial Registration: clinicaltrials.gov, identifier NCT02141373.

Keywords: cyanoacrylate, seroma, breast cancer, breast surgery, axilla

INTRODUCTION

Axillary dissection is still considered an essential procedure in the treatment of node positive breast cancer patients. Seroma formation remains the most common complication after axillary dissection with reported incidence of 15%–90% (1–6).

Although most seromas resolve within few weeks of surgery, seroma formation and its aspiration result in significant postoperative morbidity in terms of pain, discomfort, delayed wound healing, skin flap necrosis, and infection (7–9). These complications may delay adjuvant treatment and affect patient recovery along with increased financial burden on health care system.

The pathophysiology of seroma formation is not very well understood with some data implicating dead space, lymphatic leakage, and exudate as possible etiologies (10–15).

No consensus exists despite numerous suggested strategies to reduce seroma formation including drains, buttress sutures, fibrin glue or patches, tetracycline sclerosing agents, methylprednisolone, somatostatin, and shoulder exercises (13, 15–24).

The reduction of dead space after surgery is one of those strategies that can be achieved through chemical (25) and/or mechanical means (26, 27). Fibrin enriched compounds have shown seroma reduction in smaller studies, but this effect was lost in large randomized trials (23, 24, 26, 28). Surgical glue has many uses, particularly in pediatric urogenital operations, to decrease incidence of hematomas, leak, and in the treatments of lymphocele (24, 29, 30). Cyanoacrylate is a synthetic biodegradable glue (N-butyl-2-cyanoacrylate) that has shown potential for internal and external use. It has high tensile, adhesive, and hemostatic properties (31). Once it polymerizes, it creates an efficient antiseptic barrier against the most diffuse infective or pathogenic agents during surgical interventions (32).

Although Cyanoacrylate can induce a significant decrease of activated partial thromboplastin time (aPTT), no significant variations of prothrombin activity, fibrinogen, platelet number, and leukocyte cytotoxicity were identified (33). Additionally, the level of evidence to support toxicity or carcinogenicity of surgery grade Cyanoacrylate is insufficient at best (33). There were also no reports on related adverse events from the surgical use of Cyanoacrylate (30, 34, 35), this supports the safety of Cyanoacrylate in the clinical setting. Therefore, the risk of using Cyanoacrylate as surgical glue is considered minimal until new evidence suggests otherwise.

Cyanoacrylate may have the potential to reduce seroma formation after axillary dissection. The proposed mechanisms are through Cyanoacrylate's adhesive and hemostatic properties that may impact the level and the degree of seroma formation by obliterating the dead space and creating a sealed surface to decrease lymphatic leak. The aim of this study is to investigate whether the use of Cyanoacrylate in axillary dissection reduces postoperative seroma formation.

METHODS

Study Design

We conducted a single-center, randomized, single-blinded, and two-arm parallel study. The inclusion criteria were consenting patients aged 18 years or older who had node-positive breast cancer proven by fine-needle aspiration (FNA) or sentinel lymph node biopsy (SLNB) and were eligible for axillary dissection with or without surgical intervention for the primary tumor.

Exclusion criteria included a platelet count less than 100,000/ul, Body Mass Index (BMI) more than 35 kg/m^2, immediate breast reconstruction surgery, patients on anticoagulation therapy or have coagulation disorders, pregnant or lactating patients, ongoing steroid therapy, prior chest radiotherapy, and patients who received neoadjuvant chemotherapy.

Post-surgery participants were excluded from statistical analysis if they developed postoperative hematoma requiring their return to the operating theatre for evacuation.

The primary outcome was the difference between the two groups in the total volume of seroma, which was calculated as the total drained volume plus the total aspirated volume after drain removal.

Secondary outcomes included safety, cost-effectiveness, time to drain removal along with the number of seroma aspirations.

The study was conducted at King Hussein Cancer Center (KHCC) Amman, Jordan, approved by the Institutional Review Board (IRB), and registered in ClinicalTrials.gov NCT02141373.

Sample Size Calculation

A power calculation was performed before recruitment. Considering two treatment groups, testing and control group, we assumed a testing of equality where the null hypothesis is an equal means between the control and test group. Considering testing at a level of significance of 5%, powering the study at 80% and a difference of 10% or less in the means of total drained volumes (clinically irrelevant difference), 136 subjects were considered sufficient to conduct this study. However, due to slow recruitment of patients as a result of the increasing usage of neoadjuvant chemotherapy and immediate breast reconstruction (part of our exclusion criteria), an alternative approach was adopted. We reviewed the literature for likewise trials. Clement et al. conducted a multicenter, prospective, double-blinded, randomized controlled trial comparing seroma volume

following mastectomy as a primary outcome. Patients were randomized into Cyanoacrylate and normal saline arms. The mean seroma volume in the control group was 1,203 ml compared to 766 ml in the Cyanoacrylate group (36). Assuming a likewise reduction in seroma volume in our study and control arms; 106 patients would be required to have an 80% chance of detecting, as significant at the 5% level, a 36% decrease in the primary outcome measure from 1,203 ml in the control group to 766 ml in the experimental group.

Randomization and Blinding

Eligible patients were randomized in a 1:1 ratio using the randomization plan into one of the two arms: Cyanoacrylate vs. no Cyanoacrylate. The randomization process employed Excel randomization formulas and macros. The research study coordinator kept the randomization plan and informed the Operating Room (OR) manager to dispense the appropriate product accordingly. The surgeons were blinded to the patient allocation until the end of surgery when it was either required to use the product or not.

Randomization was done by Urbaniak, G. C., & Plous, S. (2013) Research Randomizer (Version 4.0) Retrieved on June 22, 2013, from http://www.randomizer.org/

Recruitment

Between January 2014 and April 2018, 111 patients were recruited. Surgeons identified potential candidates at outpatient clinics before the planned surgery. Participants who met the inclusion criteria received a verbal explanation along with the patient information sheet. After the selection criteria were satisfied, the surgeon obtained a written informed consent. Because of the increasing role of neoadjuvant chemotherapy and the increasing number of immediate breast reconstruction (both are part of our exclusion criteria) with a parallel decrease in the number of patients eligible for axillary dissection according to the updated institutional guidelines reflecting the results from the Z011 (37), the IBCSG 23-01 (38) and the AMAROS trial (39) as standard of care, recruitment time was extended.

Surgical Technique

All surgeries were performed by experienced breast surgeons. Axillary dissection was defined as dissection of at least level 1 and 2 axillary lymph nodes. The long thoracic and thoracodorsal nerves were routinely preserved, while the intercostobrachial nerve was preserved when feasible. Homeostasis was accomplished by knot-tie ligation or electrocautery with no vessel-sealing device allowed. Inconsistent results regarding the effect of vessel-sealing devices on seroma formation have been reported with some groups suggesting a significant increase in seroma volume compared to improved results with the use of vessel sealing (40, 41).

The wound was irrigated by saline solution, and one or two 16 Fr closed suction drain were placed. Wound closure was accomplished with a continuous intradermal suture line with 3/0 Vicryl (polyglactin 910) suture. In the Cyanoacrylate arm, wound closure was started medially, and 2 ml of Cyanoacrylate was sprayed into the axillary wound from a distance of 10–15 cm with a pressure-spraying device. The material was sprayed to cover the whole area dissected around the axillary vein and thoracodorsal bundle where the bulk of lymphatics in the axilla reside. A gentle compression was then applied to the chest wall for 2–3 min to allow the Cyanoacrylate to completely adhere, (**Figures 1–3**).

Study Outcomes

Follow-Up

During the in-hospital stay, drain output was recorded by a research coordinator. At discharge, patients were instructed to begin exercising their arm 24 h after surgery.

Patients were provided with scaled bottles. They were educated to empty the drain, measure the volume of drained fluid and record it in the appropriate section of the patient diary.

Prescheduled visits into the outpatient clinic were arranged at days 5 and 14 then at 1, 2, and 3 months after the surgery at which the drain output was reviewed from the patient's diary. The drain was removed if the output dropped to less than 50 ml/24 h.

Patients were assessed for seroma if the drain was removed. They were also assessed for signs of skin flap necrosis, wound dehiscence and wound infection. Patients who had their drain removed were instructed to visit the emergency room if they developed swelling or tension under the wound. If clinically

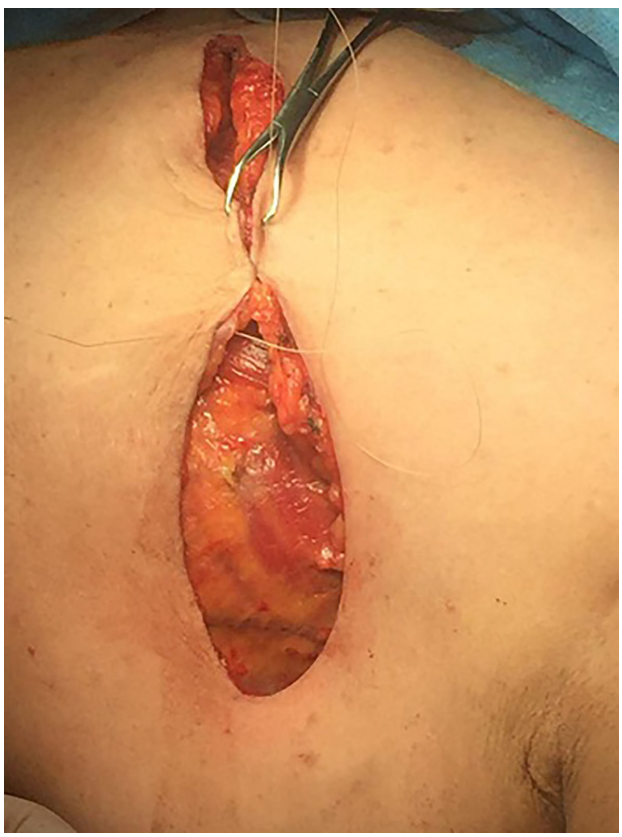

FIGURE 1 | Wound closure.

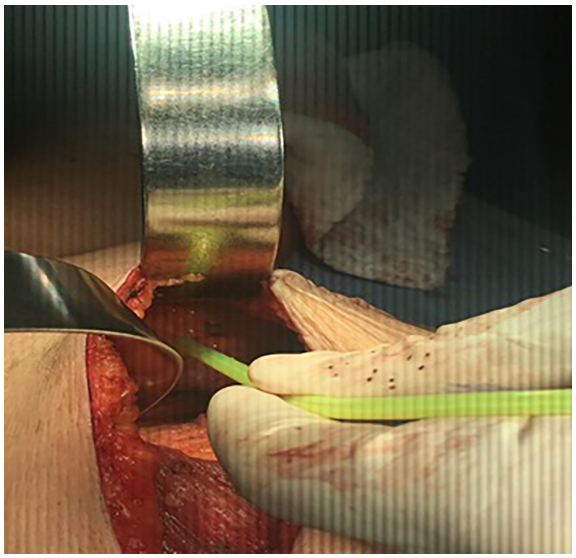

FIGURE 2 | Spraying cyanoacrylate.

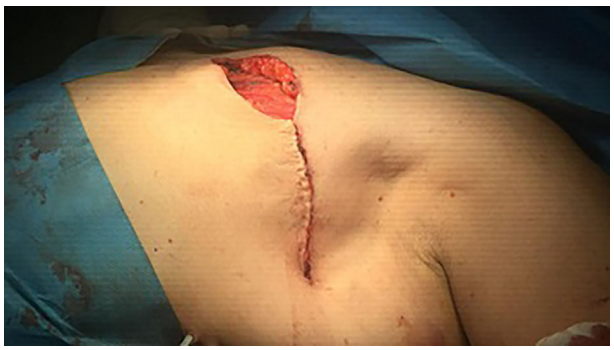

FIGURE 3 | Obliteration of dead space in the axilla.

indicated, further visits to clinic were arranged and any aspirated seroma or relevant clinical findings were registered by the treating physician.

Statistical Analysis

Descriptive statistics were used to describe patients' demographics such as age, BMI, T stage, N stage and operation type. Mean and range were used for the continuous variables (operation time (mins), blood loss (ml), total seroma volume (ml), aspirated seroma volume (ml), drained seroma volume (ml) and time to drain removal (days)). Patients' demographics among the intervention vs. control groups were compared using Chi-square test.

The continuous variables (operation time (mins), blood loss (ml), total seroma volume (ml), aspirated seroma volume (ml), drained seroma volume (ml), time to drain removal (days), and the cost (USD)) were compared between the groups using t-test.

The surgical outcomes like wound infection and flap necrosis were compared using Chi-square test as appropriate.

All significant factors out of the univariate analysis were adjusted using multivariate logistic regression analysis. Odds ratio out of the model were reported.

A significance criterion of $p \leq 0.05$ was considered significant and used in the analysis.

All statistical analyses of the data were carried out using IBM SPSS statistics version 24.

RESULTS

Between January 2014 and April 2018, 111 patients were enrolled in the study. The CONSORT chart of the study is shown in **Figure 4**. Six enrolled patients were excluded, four were lost to follow up. Two developed postoperative hematoma that required their return to the operating room. Results from 105 patients (56 in the Cyanoacrylate arm and 49 in the control arm) were subjected to statistical analysis.

The groups were comparable in terms of age, BMI, clinical T and N stages, and the frequency of breast-conserving surgery versus mastectomy (**Table 1**).

The use of Cyanoacrylate did not affect the total volume of seroma with a mean value of 1304.68 ml versus control group 1,446.51 ml, p=0.548 (**Table 2**), (**Figure 5**). The time to drain removal was significantly shorter in the Cyanoacrylate group with a mean of 11.04 days in the Cyanoacrylate arm vs. 13.84 days in the control arm, p=0.015 (**Table 2**), (**Figure 6**). There was no difference in the incidence of either wound infection or flap necrosis between the two study arms. By calculating the total cost including manual aspiration, clinic visit, and Cyanoacrylate cost; the use of Cyanoacrylate was associated with a significantly higher cost compared to the control arm with a mean of $586.93 in the Cyanoacrylate arm vs. $29.63 in the control arm, p=<0.001 (**Table 2**).

Univariate and multivariate analyses of variables influencing the total seroma volume included age, BMI, type of surgery (mastectomy vs breast-conserving surgery (BCS)), number of lymph nodes harvested in addition to Cyanoacrylate use (**Table 3**). Higher seroma volume was independently associated with a BMI greater than 30 kg/m^2, older age, and mastectomy rather than breast-conserving surgery (BCS) (**Table 4**). The number of lymph node harvested, and Cyanoacrylate use did not affect the total volume of seroma (**Table 3**).

DISCUSSION

In the current trial, the use of Cyanoacrylate in patients undergoing axillary dissection didn't affect seroma formation but was associated with earlier drains removal. No increase in the incidence of flap necrosis or wound infection were noted even in patients with high risk of seroma formation (defined as BMI > 30, age > 60 and those undergoing mastectomy), (**Table 4**).

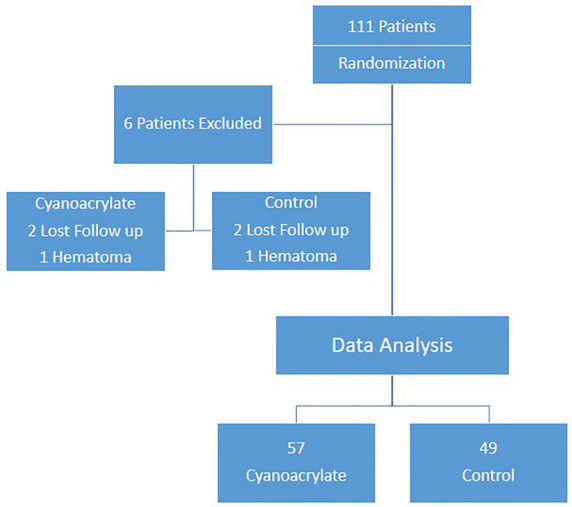

FIGURE 4 | The CONSORT chart of the study.

And the use of Cyanoacrylate in this high risk group did not affect seroma formation (**Table 5**).

Axillary surgery in the form of axillary dissection is the standard of care in the management of node positive axilla. Although major changes emerged to minimize the extent of surgical intervention in the axilla. Axillary dissection is associated with significant morbidity with seroma formation being the most common ranging from 15-90% (1–6). This may delay adjuvant treatment and affect patients' recovery along with increased financial burden on health care systems. Various methods have been tested to decrease seroma formation either by obliterating the dead space or sealing the lymphatics with no consensus on a best single method.

Our study identified BMI more than 30 kg/m^2, age greater than 60, and mastectomy compared to BCS as independent predictors of higher volume seroma. Those findings correspond with those reported by others (42–44). A linear association between increasing BMI and seroma formation in breast surgery may be explained by the tendency of adipose tissue to culminate in higher exudate rate (45). In addition, older age group was associated with higher level of seroma due to

TABLE 1 | Patients' clinical and pathological characteristics.

	Value	All patients (*n* = 105)	Cyanoacrylate (*n* = 56)	Control (*n* = 49)	*P* Value
Patient age	<50	39	25	14	0.157
	50-65	40	17	23	
	≥65	26	14	12	
BMI	<30	51	29	22	0.481
	≥30	54	27	27	
T Stage	Tis	2	1	1	0.230
	1	26	18	8	
	2	62	32	30	
	3	14	5	9	
	4	1	0	1	
N Stage	1	57	32	25	0.786
	2	29	15	14	
	3	19	9	10	
Operation	BCS	69	38	31	0.621
	Mastectomy	36	18	18	
Operation Time (mins)	Mean	–	138	135	0.726
	Range		(80-320)	(65-200)	
Blood Loss (ml)	Mean	–	95	77	0.775
	Range		(20-500)	(10-300)	

BMI, body mass index; BCS, breast conserving surgery.

TABLE 2 | Outcomes.

	Value	All patients (n = 105)	Cyanoacrylate (n = 56)	Control (n = 49)	*P* Value
Total Seroma Volume (ml)	Mean Range	1,370.87(60–5,223)	1,304.68(60–4,950)	1,446.51(100–5,223)	0.548
Aspirated Seroma Volume (ml)	MeanRange	240(0–1,890)	259.11(0–1,890)	218.16(0–1,810)	0.627
Drained Seroma Volume (ml)	MeanRange	1,130.87(50–5,223)	1,045.57(60–4100)	1,228.35(50–5,223)	0.255
No. of Manual Aspiration	MeanRange	1.52(0–9)	1.68(0–9)	1.35(0–9)	0.429
Time to Drain Removal (Days)	MeanRange	12.34(3–37)	11.04(3–23)	13.84(3–37)	0.015
Wound Infection	YesNo	699	254	445	0.312
Flap Necrosis	YesNo	4101	155	346	0.247
Cost (USD)	MeanRange	326.86(0–748)	586.93(550–748)	29.63(0–198)	< 0.001

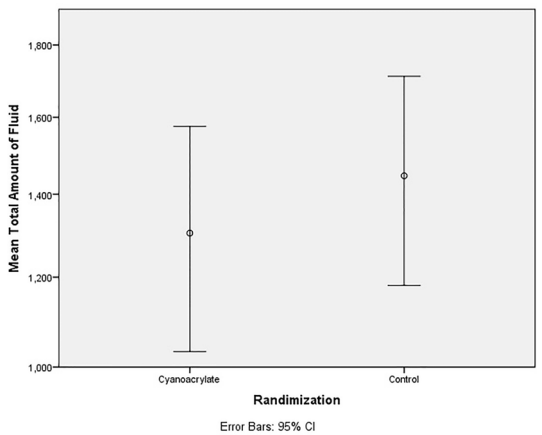

FIGURE 5 | Dot plot; Mean Total Amount of Fluid (ML).

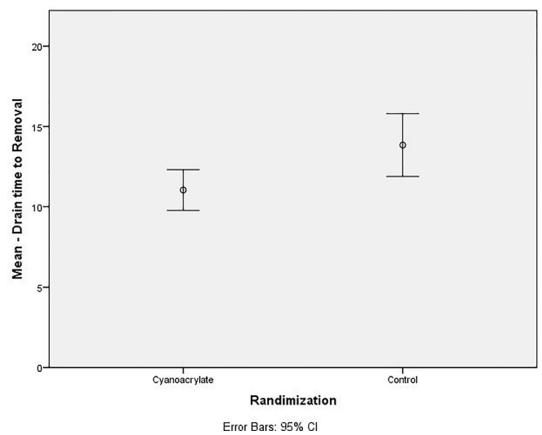

FIGURE 6 | Dot Plot; Drain to time removal (Days).

the possible influence of senile changes on lymphatics and capillaries.

Neoadjuvant chemotherapy and breast reconstruction were considered part of exclusion criteria because of the conflicting evidence regarding their role in seroma formation. In addition, breast reconstruction changes in the axillary dissection pocket geometry after reconstruction (5, 42, 43, 45).

To the best of our knowledge, only two randomized controlled trials addressed the use of Cyanoacrylate in breast cancer surgery. The results from these trials are conflicting.

The study from Greece by Kalliopi et al. (44) detected a significant reduction in seroma formation, duration of drainage, and amount of drainage with the use of Cyanoacrylate. In this trial, 128 women with breast cancer were scheduled for a modified radical mastectomy or quadrantectomy with lymph node dissection. Cyanoacrylate adhesive was applied to the operative field after the removal of the tumor and lymph nodes (n=64 patients) while controls received saline (n=64 patients).

TABLE 3 | Univariate Analysis of factors influencing total seroma volume.

	Value	*P* Value
Age	<50	< 0.001
	50–65	
	≥65	
BMI	<30	0.004
	≥30	
Operation Type	Mastectomy BCS	0.043
Lymph Nodes Harvested	11–20	0.726
	21–30	
	31–40	
	41–50	
Randomization	Cyanoacrylate Control	0.458

BMI, body mass index; BCS, breast conserving surgery.

TABLE 4 | Multivariate Analysis of factors influencing total seroma volume.

	Value	Odd Ratio	*P* Value
Age	<50	16.1	< 0.001
	50–65		
	≥65		
BMI	<30	16.1	0.004
	≥30		
Operation Type	Mastectomy BCS	4.2	0.043

BMI,body mass index; BCS,breast conserving surgery.

TABLE 5 | High Risk Group Analysis of factors influencing total seroma volume.

	Value	Cyanoacrylate Mean (Std.Div)	Control Mean (Std.Div)	*P* Value
Age	≥60 years	2,048.78(1172.37)	1,604.45(811.59)	0.166
BMI	≥30	1,649.00(1101,60)	1,614.11(1007.29)	0.904
Operation Type	Mastectomy	1,062.72(718.73)	1,148.67(812.21)	0.739

BMI, body mass index.

The distribution of the type of surgery in each arm was not stated. The authors recommended the use of Cyanoacrylate for patients with high risk of seroma formation after surgery for breast cancer (44).

A study from Australia by Clement et al. (36) compared the use of Cyanoacrylate versus normal saline during the wound closure in participants (n=76 patients) undergoing mastectomy with or without axillary dissection. The trail showed no benefit to the use of Cyanoacrylate in mastectomy and axillary surgery as far as reduction in the risk of seroma formation was concerned. Moreover, in elderly and obese participants, the use of Cyanoacrylate showed an increase in seroma formation and postoperative wound infection. The results described by Clement et al. are in consistent with our observations. No added benefit was found for Cyanoacrylate in decreasing seroma after breast cancer surgery. In our study, Cyanoacrylate did not show significant reduction in seroma formation for the overall study population as well as the high-risk groups identified. When comparing the seroma volume to control arm for this subset of patients, it was not statistically different.

For the time being, the only effective way that can decrease the morbidity associated with axillary dissection is to minimize surgical intervention in the axilla, further studies are needed to establish the role of Cyanoacrylate in breast cancer surgery.

CONCLUSION

Cyanoacrylate use in axillary dissection did not affect seroma formation and its usage in axillary dissection was not cost effective.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary materials. Further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Dr. Maysa Al-Hussaini Chairperson, Institutional Review Board at the King Hussein Cancer Center. Written informed consent to participate in this study was obtained from all participants.

AUTHOR CONTRIBUTIONS

MA-M, FA, FD, AE, BH, HA-N, RA-M, and MA contributed to the design and implementation of the research, to the analysis of the results, and to the writing of the manuscript. All authors contributed to the article and approved the submitted version.

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Association of Axillary Lymph Node Evaluation With Survival in Women Aged 70 Years or Older With Breast Cancer

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Background: Survival in elderly patients undergoing sentinel lymph node biopsy (SLNB) and axillary lymph node dissection (ALND) has not been specifically analyzed. This study aimed to explore the association between different types of axillary lymph node (ALN) evaluations and survival of elderly breast cancer patients.

Methods: A retrospective cohort study was conducted of invasive ductal breast cancer patients 70 years and older in the Surveillance, Epidemiology, and End Results database (2004–2016). Analyses were performed to compare the characteristics and survival outcomes of patients who received surgical lymph node dissection and those who did not. Breast cancer specific survival (BCSS) and overall survival were compared by using Cox proportional hazards regression analysis and propensity score matching (PSM) methods to account for selection bias from covariate imbalance.

Results: Of the 75,950 patients analyzed, patients without ALN evaluation had a significantly worse prognosis, while there was no significant difference for BCSS between using a sentinel lymph node biopsy (SLNB) and an axillary lymph node dissection (ALND) after adjustment for known covariates [adjusted hazard ratio (HR) = 0.991, 95% confidence interval (CI) = 0.925–1.062, p = 0.800]. In the stratification analyses after PSM, the ALND did not show a significant BCSS advantage compared with SLNB in any subgroups except for the pN1 stage or above. Furthermore, after PSM of the pN1 stage patients, SLNB was associated with a significantly worse BCSS in hormone receptor negative (HR–) patients (HR = 1.536, 95%CI = 1.213–1.946, p < 0.001), but not in the hormone receptor positive (HR+) group (HR = 1.150, 95%CI = 0.986–1.340, p = 0.075).

Conclusion: In our study, ALND does not yield superior survival compared with SLNB for elderly patients with pN1 stage HR+ breast cancer. Although our findings are limited by the bias associated with retrospective study design, we believe that in the absence of

results from randomized clinical trials, our findings should be considered when recommending the omission of ALND for elderly breast cancer patients.

Keywords: sentinel lymph node biopsy, axillary lymph node dissection, elderly breast cancer, propensity score matching, Surveillance Epidemiology and End Results database

INTRODUCTION

Since the early 2000s surgical techniques for axillary treatment and staging of patients with primary breast cancer have become less extensive and more focused on minimizing the risk related to surgery (1). Sentinel lymph node biopsy (SLNB) could reduce the side effects of axillary lymph node dissection (ALND) within a certain range of adaptation and provide an equivalent outcome. The National Surgical Adjuvant Breast and Bowel Project (NSABP) B32 trial (2) validated that the usage of SLNB for avoiding ALND in patients with clinically node-negative (cN0) breast cancer had no impact on prognosis. The American College of Surgeons Oncology Group (ACOSOG) Z0011 trial (3) eliminated the demand for ALND for breast cancer patients with one or two positive sentinel lymph nodes who were treated with breast conserving surgery (BCS) and whole breast irradiation.

However, there are no clinical studies specifically for elderly breast cancer patients previously, and the evidence of optimal axillary lymph node evaluation is limited. In 2012, the International Society of Geriatric Oncology (SIOG) and European Society of Breast Cancer Specialists (EUSOMA) (4) updated their recommendations regarding elderly breast cancer (EBC) patients. It was proposed that elderly patients with cN0 breast cancer could be exempted from axillary lymph node evaluation. Since no survival improvement with ALND was identified in relevant studies (5, 6), the Society of Surgical Oncology Choosing Wisely Guidelines recommended in 2016 that surgeons "do not routinely use sentinel node biopsy in clinically node-negative women ≥70 years of age with hormone receptor-positive (HR+) invasive breast cancer". This recommendation aroused extensive discussion (7–9) about whether cN0 elderly breast cancer patients can be exempted from axillary lymph node evaluation. No clinical studies have yet been conducted to investigate the difference in survival between SLNB and ALND in elderly breast cancer patients.

A sentinel lymph node biopsy is minimally invasive compared with axillary lymph node dissection, with the risk of lymphedema being only 3–7% for SLNB while it is 15–20% for ALND (10). In the era of precision medicine, our study aimed to explore the association between different types of axillary lymph node evaluations with survival and provide new insight into axillary management for elderly breast cancer patients.

METHODS

Data Source and Study Population

Women 70 years and older with invasive ductal breast cancer diagnosed between January 2004 and December 2016 were retrieved from the Surveillance, Epidemiology, and End Results (SEER) Program (Nov 2018 Submission). We utilized the SEER*Stat version 8.3.6 to extract the target population's information. Patients with missing or unknown T-, N-, M-stage, grade, estrogen receptor (ER) status, progesterone receptor (PR) status, number of lymph nodes (LNs) removed, surgery type, or survival data were excluded from this study, so were patients with metastatic disease (**Supplemental Figure 1**). The data elements included patient characteristics, cancer staging, type and timing of first course of treatment, as well as survival outcome information. The SEER database did not specify the axillary surgery type as ALND or SLNB. Therefore, we use the number of nodes examined as an alternative in this study. According to the definition of ALND, which was set as a standard by the American Joint Commission on Cancer (AJCC), ALND should involve at least six lymph nodes. Hence, we used five examined lymph nodes as the cut-off value for SLNB and ALND. Patients with five or fewer lymph nodes examined were categorized as having received SLNB, while patients with six or more nodes examined were categorized as having undergone ALND (11, 12).Those with 0 to 5 positive regional lymph nodes were included into this study. Patients with more than five positive lymph nodes, who might have a worse prognosis, would be directly assigned into the ALND group within the classification rules.

For the general population, the study groups were defined as those who underwent surgical LN evaluation, including SLNB (fewer than six lymph nodes examined) and ALND (six or more lymph nodes examined) and aim to identify the survival differences among the three groups, then to obtain relevant information on whether axillary assessment could be exempted. For the pathological stage N1 cohort, the survival of SLNB and ALND patients was further evaluated and compared in order to get information on the conditions under which ALND can be avoided when a small number of lymph nodes are positive. The primary endpoint of this study was breast cancer specific survival (BCSS).

Statistical Analysis

Patient characteristics are summarized with *N* (%) of inclusion categorical variables and *mean* (SD) of the number of examined nodes and survival time. Associations between axillary surgery modality, patient demographics, and clinical pathological characteristics were assessed using the Pearson χ^2 or Fisher's exact test and the Wilcoxon rank sum test for continuous variables. The Kaplan–Meier method was applied to generate unadjusted survival curves, while the log-rank test was used to assess the differences. Univariable and multivariable Cox proportional hazards regression analysis was conducted to estimate the association between different types of axillary lymph node evaluations and survival after adjusting for exploratory variables that were shown to have a significant effect on survival.

To avoid the impact of the different characteristics between the two study groups (SLNB group *vs.* ALND group), we adopted the 1:1 nearest neighbor propensity score matching (PSM)

method to eliminate the imbalance. Within the matched patient groups, we assessed survival outcomes of different axillary surgery effects with stratification analyses and explored the different effects in patient-, tumor-, and treatment-level subgroups. Kaplan–Meier estimators were calculated for each group and were compared by using the log-rank test.

All tests were two-sided, and a p value less than 0.05 was considered to be statistically significant. All statistical analyses were performed using IBM SPSS software version 24.0 (IBM Corp., Armonk, USA) and R version 3.6.2 (The R Project for Statistical Computing, Vienna, Austria).

RESULTS

Basic Characteristics and Survival Analyses of the Overall Population

A total of 75,950 eligible elderly breast cancer patients (the median follow-up time was 64 months) were included in this retrospective analysis, of whom 46,253 (60.9%) underwent SLNB, 18,346 (24.2%) underwent ALND, and 11,351 (14.9%) did not receive LN evaluation (the No group) with the median follow-up time of 58, 84 and 58 months respectively. Patient characteristics are listed in **Supplemental Table 1**. Elderly patients had more Luminal-type breast cancer, and among them the ER positive-type made up 84.2% and among the PR positive-type 72.9%. There were fewer human epidermal growth factor receptor-2 (HER2) positive patients (7.1%) than HER2 negative patients (52.1%). Fewer patients received LN evaluation in the older age groups. The proportion of elderly breast cancer patients undergoing SLNB who were diagnosed after 2010 (52.8%) was higher than that in 2004–2009 (34.8%). The patients in the SLNB group received more lumpectomies (75.3%) and more radiotherapy (55.1%), while the ALND group had more mastectomies (58.3%).

The results of univariable and multivariable Cox proportional hazard regression analyses are shown in **Supplemental Table 2**. It was found that age, race, marital status, grade, T stage, N stage, ER, PR, HER2 status, and different types of adjuvant treatments were independent prognostic factors for elderly breast cancer patients. Survival curves stratified by different types of axillary lymph node evaluations before matching are reported in **Figure 1**. In the univariate analysis, the SLNB group had a better BCSS performance than the ALND group (HR = 0.457, 95%CI = 0.430–0.485, $p < 0.001$). However, after adjusting for the other prognostic factors, there were no significant differences in BCSS between the two groups (SLNB group *vs.* ALND group: adjusted HR = 0.991, 95%CI = 0.925–1.062, $p = 0.800$), while the cohort without a LN evaluation had the worst prognosis.

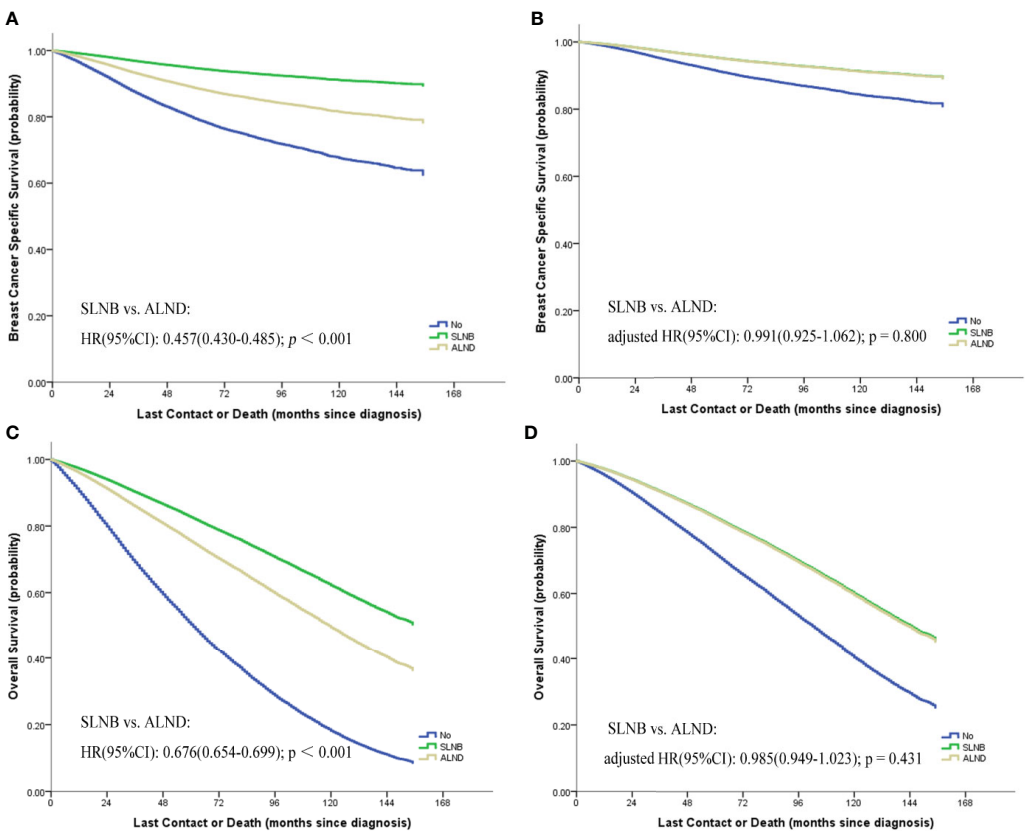

FIGURE 1 | Kaplan–Meier curves [**(A)** breast cancer specific survival; **(C)** overall survival] and the survival curves of adjusted by other prognostic factors [**(B)** breast cancer specific survival; **(D)** overall survival] stratified by different types of axillary lymph node evaluations.

Stratification Analyses of the Matched SLNB and ALND Groups

We performed a 1:1 PSM with maximum allowed differences of ±0.5% for propensity scores on the SLNB and ALND groups (**Supplemental Figure 2**). Relevant results of the matched stratification analyses are displayed in **Table 1**. In the matched groups, the SLNB group and the ALND group did not show significant BCSS differences (HR 0.994, 95%CI = 0.916–1.078,

TABLE 1 | The matched stratification analyses of breast cancer specific survival (BCSS).

	SLNB group			ALND group			BCSS	
Variables	**No. of patients**	**No. of events**	**Survival Rates**	**No. of patients**	**No. of events**	**Survival Rates**	**HR (95%CI)**	***P value***
Total	13,246	1141	91.4%	13,246	1,162	91.20%	0.994(0.916–1.078)	0.877
Year at diagnosis								
2004-2009	6,847	781	88.6%	6,588	804	87.8%	0.945(0.856–1.042)	0.258
2010-2016	6,399	360	94.4%	6,658	358	94.6%	1.115(0.963-1.291)	0.145
Age								
70–74	5,270	310	94.1%	5,358	343	93.6%	0.945(0.810–1.101)	0.467
75–79	3,939	325	91.7%	3,942	347	91.2%	0.927(0.797–1.079)	0.329
80–84	2,553	281	89.0%	2,576	282	89.1%	1.013(0.859–1.195)	0.875
85+	1,484	225	84.8%	1,370	190	86.1%	1.114(0.918–1.352)	0.273
Race								
White	1,0843	968	91.1%	11,124	953	91.4%	1.054(0.964–1.153)	0.246
Black	1,125	112	90.9%	1,220	142	88.4%	0.843(0.658–1.080)	0.176
Other	1,278	61	95.2%	902	67	92.6%	0.675(0.477–0.954)	0.026
Marital								
Married	5,526	412	92.5%	5,648	424	92.5%	1.019(0.890–1.167)	0.782
Single	7,130	681	90.4%	7,042	694	90.1%	0.978(0.880–1.087)	0.675
Unknown	590	48	91.9%	556	44	92.1%	0.950(0.630–1.431)	0.806
Laterality								
Right	6,397	518	91.9%	6,562	545	91.7%	0.981(0.870–1.106)	0.755
Left	6,849	623	90.9%	6,684	617	90.8%	1.003(0.897–1.121)	0.959
Grade								
I	2,691	71	97.4%	2,695	105	96.1%	0.683(0.506–0.923)	**0.013**
II	5,951	386	93.5%	5,954	404	93.2%	0.999(0.869–1.149)	0.990
III	4,604	684	85.1%	4,597	653	85.8%	1.027(0.922–1.143)	0.633
T Stage								
T1	8,171	406	95.0%	8,108	421	94.8%	0.956(0.834–1.096)	0.517
T2	4,367	552	87.4%	4,366	589	86.5%	0.977(0.870–1.097)	0.690
T3	396	88	77.8%	424	79	81.4%	1.206(0.890–1.635)	0.226
T4	312	95	69.6%	348	73	79.0%	1.716(1.264–2.331)	**0.001**
N Stage								
N0	8,771	550	93.7%	8,709	644	92.6%	0.819(0.731–0.918)	**0.001**
N1	4,268	521	87.8%	4,242	472	88.9%	1.243(1.097–1.408)	**0.001**
N2	183	61	66.7%	267	44	83.5%	2.886(1.950–4.271)	**<0.001**
N3	24	9	62.5%	28	2	92.9%	5.465(1.180–25.307)	**0.030**
Type of Surgery								
No	14	4	71.4%	16	4	75.0%	1.019(0.253–4.103)	0.979
BCS	6,579	417	93.7%	6,662	454	93.2%	0.950(0.832–1.085)	0.451
Mastectomy	6,653	720	89.2%	6,568	704	89.3%	1.013(0.913–1.124)	0.812
Radiation								
Yes	5,567	372	93.3%	5,432	385	92.9%	0.957(0.830–1.104)	0.546
No/Refused	7,679	769	90.0%	7,814	777	90.1%	1.019(0.922–1.126)	0.715
Chemotherapy								
Yes	2,651	277	89.6%	2,746	251	90.9%	1.206(1.017–1.431)	**0.031**
No/Unknown	10,595	864	91.8%	10,500	911	91.3%	0.943(0.859–1.034)	0.213
ER Status								
Positive	10,724	729	93.2%	10,730	766	92.9%	0.976(0.882–1.081)	0.645
Negative	2,522	412	83.7%	2,516	396	84.3%	1.005(0.876–1.154)	0.941
PR Status								
Positive	9,084	535	94.1%	9,202	604	93.4%	0.920(0.819–1.034)	0.163
Negative	4,162	606	85.4%	4,044	558	86.2%	1.041(0.928–1.167)	0.497
HER2 Status								
Positive	916	71	92.2%	964	61	93.7%	1.347(0.956–1.897)	0.088
Negative	5,331	281	94.7%	5,527	285	94.8%	1.088(0.923–1.284)	0.314
Borderline	152	8	94.7%	167	12	92.8%	0.677(0.277–1.657)	0.393
Not 2010+	6,847	781	88.6%	6,588	804	87.8%	0.945(0.856–1.042)	0.258

$p = 0.877$) (**Figure 2A**) and OS differences (HR = 0.965, 95% CI = 0.923–1.009, $p = 0.113$) (**Figure 2B**). Similar results were observed in the different patient, tumor, and treatment subgroups, except in the Grade 1, T4 stage, and different N stage subgroups. In the pN0 stage subgroup, the SLNB group had a better breast cancer prognosis. On the contrary, the prognosis of the ALND group was better with N1 stage and above.

Exploratory Analyses of pN1 Stage Matched Groups

For exploratory analyses of the pN1 stage cohort, elderly breast cancer patients treated with SLNB were matched 1:1 to patients from the ALND group (**Supplemental Figure 3**); the baseline characteristics before and after matching are listed in **Supplemental Table 3**. Regardless of matching or not, all the variables were identified to be significantly associated with BCSS except for the marital status and HER2 status (**Table 2**). Kaplan–Meier curves of the whole cohort in the two axillary surgery groups revealed no significant differences (HR = 0.972, 95%CI = 0.878–1.077, $p = 0.591$) (**Figure 3A**). However, after adjustments using other prognostic factors, the risk of death in the ALND group was significantly lower than in the SLNB group, both before and after matching cohorts (**Table 2**; **Figure 3B**).

We further evaluated whether the BCSS advantage of ALND still existed when considering different numbers of positive lymph nodes or different hormone receptor status (**Figures 3C–E**). It demonstrates that the SLNB group still showed a survival disadvantage in BCSS compared to the ALND group even though there was only one positive lymph node (HR = 1.205, 95%CI = 1.031–1.409, $p = 0.019$) (**Figure 3C**). Moreover, the survival differences between the two groups was also affected by the hormone receptor status. In the hormone receptor positive (HR+) subgroup the ALND group patients no longer had an absolute BCSS advantage (HR = 1.150, 95%CI = 0.986–1.340, p = 0.075) (**Figure 4A**). Whereas, the hormone receptor negative (HR–) subgroup had similar outcomes (SLNB group *vs.* ALND group: HR = 1,536, 95%CI = 1.213–1.946, $p < 0.001$) (**Figure 4B**).

Further Exploratory Analysis in Number of Positive Lymph Nodes and Hormone Receptor Status

We confirmed that the baseline characteristics of the HR+ and HR– subgroups were comparable in the matched SLNB group and ALND group (**Supplemental Table 4**). **Figure 5** shows the hazard ratios (HRs) of the SLNB group *versus* the ALND group on the basis of various combinations of hormone receptor status and number of positive lymph nodes. In the HR+ subgroup the SLNB groups were comparable with the ALND groups in BCSS performance regardless of the number of positive lymph node. While for the HR– subgroup, the BCSS of SLNB group was worse than that of the ALND group although only one lymph node was positive, and the SLNB group had worse survival when there were more positive lymph nodes.

DISCUSSION

More than 30% of breast cancers are diagnosed in patients older than 70 years old (13, 14). By now, the average life expectancy of women over the age of 65 is 86.6 years, with one in four women achieving an age above 90 years old (15). Our study is of particular importance in light of the aging population and serves as a reference since there is a lack of randomized data to guide clinical decision-making. The most common manifestation of breast cancer in elderly patients is a higher grade and HR-positive invasive ductal carcinoma (**Table 1**). Some studies have also indicated that the incidence of ER+ breast cancer increased and that of HER2 decreased with age (14, 16, 17).

Previously published high-quality prospective studies of axillary treatments did not focus on elderly patients exclusively (2, 3, 18, 19). These studies paid more attention to whether

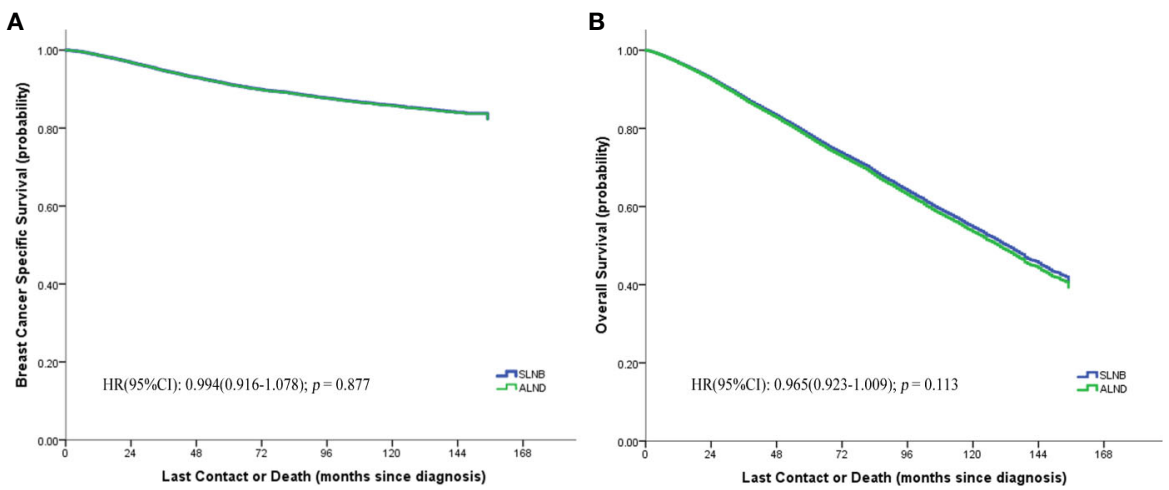

FIGURE 2 | Breast cancer specific **(A)** and overall **(B)** survival curves of the two matched study groups.

TABLE 2 | Multivariate analysis by Cox proportional hazard model in before and after matching pN1 stage cohorts.

Variables		Before Matching		After Matching	
		HR (95%CI)	*P* value	HR (95%CI)	*P* value
Age	**70–74**	Ref		Ref	
	75–79	1.225(1.074–1.396)	**0.002**	1.215(1.014–1.454)	**0.034**
	80–84	1.450(1.258–1.672)	**<0.001**	1.422(1.174–1.723)	**<0.001**
	85+	1.716(1.463–2.014)	**<0.001**	1.729(1.408–2.124)	**<0.001**
Race	**White**	Ref		Ref	
	Black	1.139(0.981–1.323)	0.088	1.112(0.898–1.377)	0.331
	Other	0.680(0.534–0.865)	**0.002**	0.635(0.456–0.885)	**0.007**
Marital	**Married**	Ref		Ref	
	Single	1.017(0.914–1.132)	0.759	1.050(0.911–1.211)	0.502
	Unknown	0.870(0.659–1.149)	0.327	0.867(0.598–1.257)	0.451
Grade	**I**	Ref		Ref	
	II	1.975(1.560–2.500)	**<0.001**	1.897(1.426–2.522)	**<0.001**
	III	3.112(2.450–3.951)	**<0.001**	3.035(2.269–4.061)	**<0.001**
T Stage	**T1**	Ref		Ref	
	T2	1.900(1.686–2.141)	**<0.001**	1.900(1.629–2.216)	**<0.001**
	T3	3.214(2.639–3.914)	**<0.001**	2.905(2.204–3.829)	**<0.001**
	T4	3.413(2.799–4.163)	**<0.001**	2.922(2.240–3.810)	**<0.001**
The Number of Positive LN	**1**	Ref		Ref	
	2	1.273(1.133–1.430)	**<0.001**	1.224(1.044–1.433)	**0.012**
	3	1.473(1.281–1.694)	**<0.001**	1.539(1.234–1.920)	**<0.001**
Type of Surgery	**No**	Ref		Ref	
	BCS	0.280(0.203–0.386)	**<0.001**	0.127(0.047–0.342)	**<0.001**
	Mastectomy	0.295(0.217–0.403)	**<0.001**	0.135(0.050–0.364)	**<0.001**
Type of Axillary Surgery	**SLNB**	**Ref**		**Ref**	
	ALND	**0.763(0.682–0.853)**	**<0.001**	**0.781(0.686–0.889)**	**<0.001**
Radiation	**Yes**	Ref		Ref	
	No	1.464(1.299–1.651)	**<0.001**	1.427(1.220–1.668)	**<0.001**
Chemotherapy	**Yes**	Ref		Ref	
	No	1.457(1.292–1.645)	**<0.001**	1.541(1.302–1.824)	**<0.001**
ER Status	**Positive**	Ref		Ref	
	Negative	1.559(1.352–1.798)	**<0.001**	1.404(1.162–1.698)	**<0.001**
PR Status	**Positive**	Ref		Ref	
	Negative	1.644(1.437–1.880)	**<0.001**	1.757(1.477–2.089)	**<0.001**
HER2 Status	**Positive**	Ref		Ref	
	Negative	1.090(0.880–1.348)	0.430	0.989(0.763–1.283)	0.935
	Borderline	0.938(0.546–1.612)	0.816	1.085(0.574–2.050)	0.802
	Not 2010+	1.247(1.018–1.528)	0.033	1.061(0.824–1.365)	0.648

Bold P values mean that the difference is statistically significant.

axillary evaluation could be omitted (5–8, 20). The International Society of Geriatric Oncology (SIOG) and European Society of Breast Cancer Specialists (EUSOMA) in 2012 (4) and the Society of Surgical Oncology of the Choosing Wisely campaign in 2016 recommended that elderly breast cancer patients could be exempted from axillary lymph node evaluation when it was clinically determined that axillary lymph nodes were negative (5, 6). A subsequent meta-analysis composed of two randomized controlled trials involving 692 patients found that omission of axillary evaluation would not result in significant difference of overall breast cancer specific mortality (21).

In our study we demonstrated that, after adjustment by other factors, axillary lymph node surgery (both SLNB and ALND) raised the breast cancer-specific survival by more than 40% compared to patients who did not receive lymph node assessment (**Table 2**). Similarly, Chagpar et al. (7) revealed that after controlling for tumor size, grade, patient age, comorbidities, and treatment factors, patients who did not have LN evaluation had a worse survival compared with those who had axillary evaluation. It was also indicated that axillary surgery was associated with higher rates of adjuvant therapy and improved overall survival for elderly cN0 breast cancer patients in a study from Tamirisa et al. (22). Lymph node evaluation was shown to provide important information for determining their adjuvant therapy options (7).

It is well known that SLNB is minimally invasive, with a 2–7% risk of upper extremity lymphedema, in comparison with the 15–20% risk associated with ALND (10, 23). Therefore, in the social context of population aging and precision medicine, it is necessary and imperative to identify whether elderly patients need ALND or not. To the best of our knowledge, this is the largest cohort that has been evaluated to compare SLNB and ALND in elderly breast cancer patients. We performed PSM analyses to address the limitations of a retrospective study from a large SEER sample of patients who underwent axillary surgery. After reliable Cox regression analyses and matched stratification analyses, SLNB did not imply higher breast cancer specific mortality among the cohort, in both subgroups with or without other kind of treatments and regardless of the ER, PR, and HER2 status.

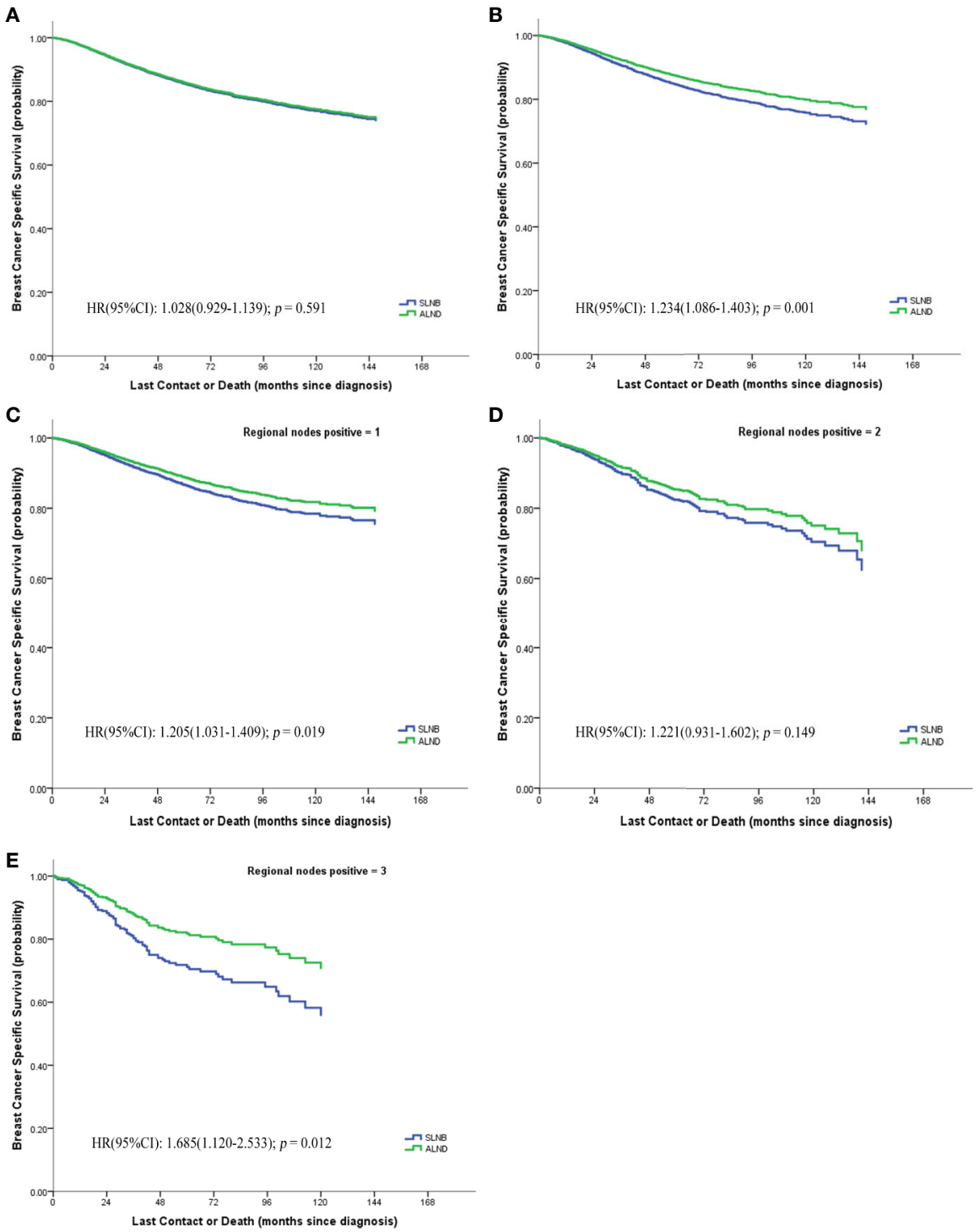

FIGURE 3 | Breast cancer specific survival of pN1 stage, **(A)** before matching; **(B)** after matching; **(C–E)** the numbers of positive lymph node respectively are 1, 2, 3.

We were concerned that the survival of SLNB group patients is concentrated in the stage N0 patients; in the stage N1 and above patients ALND still needs to be selected. A meta-analysis based on four trials showed no significant differences in OS and DFS between ALND and regional nodal irradiation (RNI) in short- or long-term outcomes (24). Hence, RNI may be an alternative treatment for adjuvant management of the axilla in selected patients, and an optimal radiation

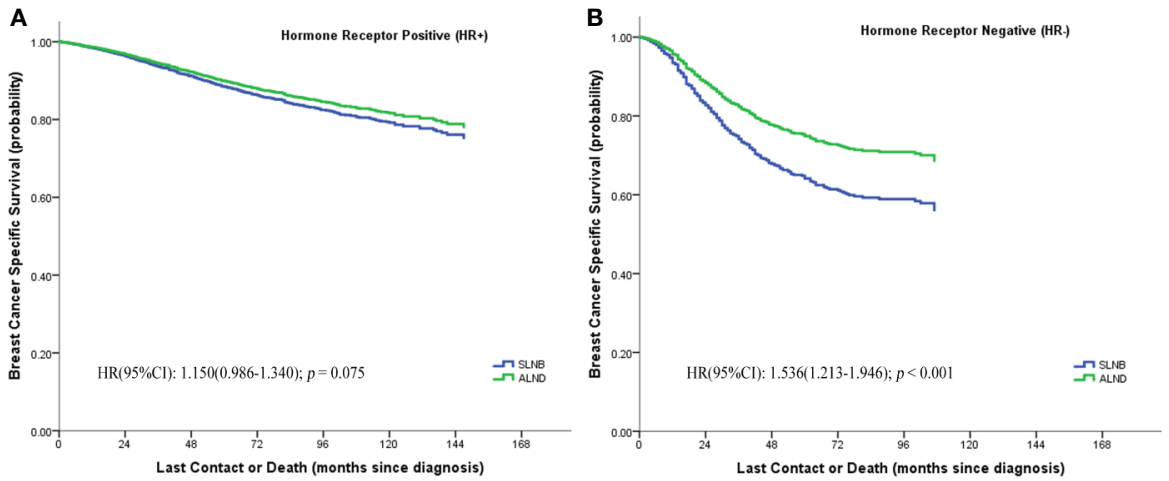

FIGURE 4 | Breast cancer specific survival of hormone receptor positive (HR+) **(A)** and hormone receptor negative (HR–) **(B)** stratified by SLNB and ALND in the matching pN1 stage patients.

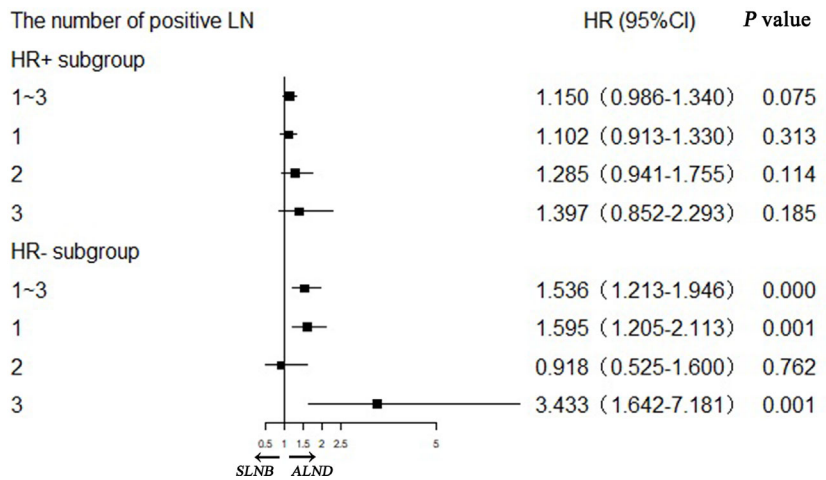

FIGURE 5 | Stratification analyses of hormone receptor positive (HR+) and hormone receptor negative (HR–) subgroups with different positive lymph node numbers in matching pN1 stage patients.

strategy approach for elderly patients warrants further study. However, it is undeniable that local control of the axilla isõ still important in the treatment of elderly breast cancer patients.

Our exploratory analyses for the stage N1 cohort detected that with HR+ breast cancer in elderly patients with 1 to 3 positive lymph nodes, you could omit further lymph node dissection: True in both the with and without radiation subgroups. The HR– patients still required ALND even when there was only one positive lymph node. Some studies have concluded that the adjuvant therapy strategies for HR+ elderly breast cancer should only be followed by endocrine therapy, and the axillary lymph node dissection can be avoided (5, 20). At present, the guidelines for breast cancer therapy recommend that the standard adjuvant endocrine therapy for postmenopausal patients is five years of aromatase inhibitor (AI). And for patients at high risk, a prolonged AI treatment can reduce the risk of relapse (25–28). In elderly patients with HR+ breast cancer, endocrine therapy plays an important role in the adjuvant therapy. Therefore, we hypothesize from our observations that the method of performing intensive endocrine therapy is more important than local treatment in the case of sentinel lymph nodes.

Inevitably, there are several limitations related to the design and data source in our study. Firstly, the number of examined recorded in the SEER database is the final total removed number, and unfortunately, we cannot determine the exact procedure of the axilla surgery. Even though the analyses based on PSM could

effectively reduce the effects of the observed confounding factors, it cannot address unobserved confounding factors, nor the unavoidably cases lost. Secondly, the data about endocrine therapy in the SEER database is inaccessible despite the importance in adjuvant treatment of HR+ breast cancer, which makes the analyses of adjuvant therapy for elderly breast cancer incomplete. Thirdly, locoregional recurrence or disease-free survival is not included in the SEER database, and this precludes assessment of these end points. Lastly, it is unfortunate that cases receiving neoadjuvant chemotherapy could not be identified in the SEER database, which may lead to changes in axillary management.

To summarize, our findings suggest that ALND can be omitted in elderly patients with pN1 stage HR+ breast cancer. This study is the first to use a large number of cases of elderly patients for evaluation of the relative effectiveness between SLNB and ALND with BCSS as the primary endpoint. Although our findings are limited by the bias associated with retrospective study design, we believe that in the absence of randomized clinical trials, our findings should be considered when recommending the omission of ALND for elderly breast cancer patients. However, we still need further accurate prospective randomized studies to optimize patient selection for the omission of ALND.

DATA AVAILABILITY STATEMENT

Publicly available datasets were analyzed in this study. This data can be found here: https://seer.cancer.gov/.

AUTHOR CONTRIBUTIONS

S-PL and JZ conceptualized and designed the study. S-PL, JZ, and Q-SW developed the methodology. S-PL, JZ, and Y-XL took part in the acquisition, analysis, and interpretation of the data. S-PL, JZ, and C-GS wrote, reviewed, and/or revised the manuscript. C-GS and JZ supervised the study. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2020.596545/full#supplementary-material

Supplementary Figure 1 | Flow diagram for identifying eligible elderly patients (≥70 years old) with breast cancer.

Supplementary Figure 2 | The histogram **(A)** and dot plots **(B)** of before and after propensity score matching on SLNB group and ALND group of the total cohort.

Supplementary Figure 3 | The histogram **(A)** and dot plots **(B)** of before and after propensity score matching on SLNB group and ALND group of the pN1 stage cohort.

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ORIGINAL RESEARCH
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Nomogram Predicts the Role of Contralateral Prophylactic Mastectomy in Male Patients With Unilateral Breast Cancer Based on SEER Database: A Competing Risk Analysis

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Background: Contralateral prophylactic mastectomy (CPM) in female breast cancer (FBC) is supported by multiple clinical studies and consensus guidelines, but knowledge of preventive contralateral mastectomy in male breast cancer (MaBC) is very limited and its benefits are still controversial.

Methods: A retrospective cohort study was enrolled with 4,405 MaBC patients who underwent unilateral mastectomy (UM) or CPM from the Surveillance, Epidemiology, and End Results (SEER) database from 1998 to 2015. A nomogram was built based on the corresponding parameters by competing risks regression to predict the 3-year, 5-year, and 8-year probabilities of BCSD (breast cancer-specific death). C-index and calibration curves were chosen for validation. Net reclassification index (NRI) and integrated discrimination improvement (IDI) were used to estimate the nomogram's clinical utility.

Results: A total of 4,197 patients received UM and 208 patients received CPM, with 63-months median follow-up. In the competing risks regression, six variables (surgery, marital status, T-stage, N-stage, histology, tumor grade) were significantly associated with BCSD. Based on these independent prognosis factors, a nomogram model was constructed. The C-index 0.75 (95%CI: 0.73-0.77) in the training cohort and 0.73 (95% CI: 0.71-0.74) in the internal validation group suggested robustness of the model. In addition, the calibration curves exhibited favorably. The NRI values (training cohort: 0.54 for 3-year, 0.55 for 5-year, and 0.49 for 8-year BCSD prediction; validation cohort: 0.51 for 3-year, 0.45 for 5-year, and 0.33 for 8-year BCSD prediction) and IDI values (training cohort: 0.02 for 3-year, 0.03 for 5-year, and 0.04 for 8-year BCSD prediction; validation cohort: 0.02 for 3-year, 0.04 for 5-year, and 0.04 for 8-year BCSD prediction) indicated that the model performed better than the AJCC criteria-based tumor staging alone.

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Conclusions: The administration of CPM was associated with the decrease in risk of BCSD in patients with MaBC. The nomogram could provide a precise and personalized prediction of the cumulative risk in patients with MaBC after CPM.

Keywords: male breast cancer, contralateral prophylactic mastectomy, SEER, competing risk analysis, nomogram

INTRODUCTION

Contralateral prophylactic mastectomy (CPM) is a controversial but hot topic in the world. The application of CPM could reduce risk of contralateral breast cancer (CBC) for female patients with unilateral breast cancer (1–5). However, almost all prospective clinical trials concerning CPM are conducted in female breast cancer (FBC) patients. Consequently, the benefit of CPM on male breast cancer (MaBC) patients remains unknown due to its rarity (6).

As a rare primary breast malignancy, MaBC accounts for less than 1% of all breast cancers (7–10). Compared with FBC, previous studies suggested that patients with MaBC had different biological characteristics such as advanced age, a higher percentage of lymph node metastases, and were estrogen receptor-positive (ER+) (9, 11, 12). In contrast to FBC, MaBC tends to present BRCA2 mutation rather than BRCA1 mutation (13). Therefore, more clinical evidence for surgical strategies and subsequent treatment methods are needed for MaBC patients since current guidelines are based on female clinic data.

To further explore and identify the curative effects of CPM in patients with resectable MaBC, we followed a large cohort of males with MaBC from 1998 to 2015 from the population-based database Surveillance, Epidemiology, and End Results (SEER) cancer registry program. In the study, we established a competing risks nomogram to predict and identify those patients who could benefit from CPM.

MATERIALS AND METHODS

Data Resource

The recent version of the SEER 18 registries' custom data (with additional treatment fields) was used as the data source for the present population-based investigation. This database consists of 18 population-based cancer registries and covers approximately 26% of the US population across several geographic regions (14). SEER*-Stat Software version 8.3.6 (https://seer.cancer.gov/seerstat/) (Information Management Service, Inc. Calverton, MD, USA) was used to generate the case listing. All procedures were performed in accordance with approved guidelines. This study was approved by the Ethics Committee of the First Affiliated Hospital of Xi'an Jiaotong University. Informed patient consent was not required to access and use SEER data.

Patient Cohort

Male patients diagnosed with unilateral breast cancer from 1998 to 2015 were enrolled in the study. Patients were included by following criteria: 1) primary breast cancer; 2) TNM (Breast-Adjusted American Joint Committee on Cancer, AJCC 6th) stages 0, I, II, or III; and 3) unilateral mastectomy (UM) or CPM. The demographic and clinicopathological variables were shown as follows: sex (male), age, race, site, behavior years of diagnosis, tumor grade, tumor T stage, tumor N stage, type of surgery, radiotherapy, chemotherapy, ER status, PR status, survival months, vital status, reasons of death, marital status, and breast-adjusted AJCC 6th TNM stage.

After the preliminary selection, patients were excluded by following criteria: (1) unknown AJCC stage; (2) the follow-up type of autopsy or death certificate; (3) distant metastasis (M1); (4) aged below 20 years; (5) missing surgical records; and (6) survival months is zero. **Figure 1** shows the entire screening process.

In total, 4,405 patients with MaBC were included in our cohort. To estimate the impact of CPM on prognosis, the study cohort was classified into two groups by different operation selections: UM group and CPM group. "No radiation and/or cancer-directed surgery" were regarded as no radiotherapy. "No/Unknown" chemotherapy records were regarded as no chemotherapy.

End Points

Patients were followed up until November 2015, and the median follow-up was 63 months (ranging from 1 month to 227 months). The primary indexes, breast cancer-specific death (BCSD) and breast cancer-specific survival (BCSS), were defined as the time interval between the date of diagnosis and death due to breast cancer. The secondary outcome measurement was overall survival (OS) which was deemed as the interval from the date of diagnosis to the date of death for any reason.

Statistical Analysis

All analyses were performed by using R statistical software version 3.6.3 (https://www.r-project.org). We used descriptive statistics to summarize demographic and clinical variables, continuous variables with normal distribution were described as means and standard deviations, categorical variables were compared using Chi-squared test or Fisher's exact test as appropriate. Firstly, Kaplan-Meier curves and log-rank test were performed to determine the statistical differences among groups of overall survival (OS) and breast cancer-specific survival (BCSS). Secondly, a Cox proportional hazards model was constructed to find prognostic factors of MaBC by the R package of rms. Thirdly, the competing risk analysis model was used to estimate the hazard of the cumulative incidence function while controlling for the competing risks of death, which predicted BCSD by the R package of cmprsk and competing risks regression (15, 16). Fourthly, in order to predict the

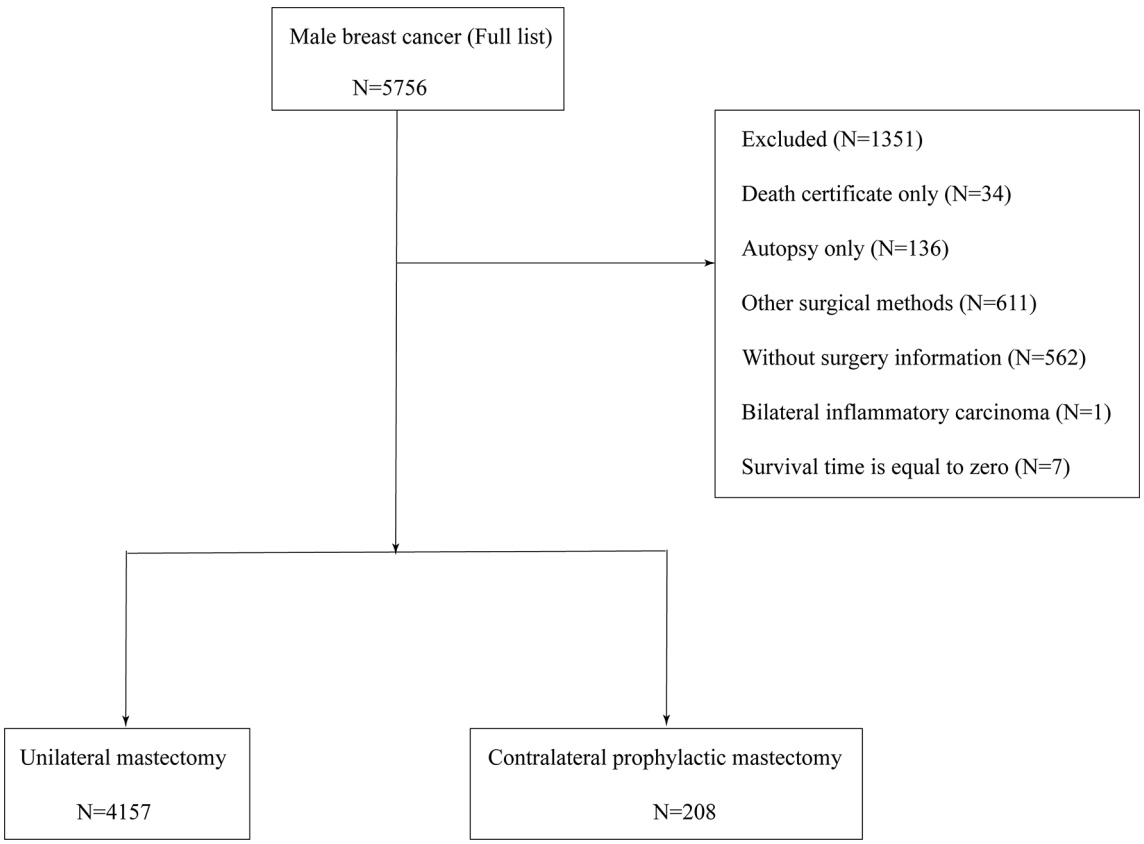

FIGURE 1 | Eligibility, inclusion, and exclusion criteria of study population.

prognosis of MaBC after three, five, and eight years, based on the coefficients from the competing risks regression models, a nomogram was built by the R packages mstate and regplot (17). Lastly, during the validation process, concordance indexes (C-index) and calibration curves were used to determine predictive accuracy and discriminability. Net reclassification index (NRI) and integrated discrimination improvement (IDI) were performed to estimate the nomogram's clinical utility compared with the AJCC-TNM stage system. All *P*-values were bilateral and $P< 0.05$ was considered to be statistically significant.

RESULT

Baseline Characteristics

Among the 4,405 patients from our study cohort, 95.3% (4,197/4,405) of patients received UM, while 4.7% (208/4,405) had CPM. Among these men, 82.5% of patients were white, 52.7% of patients had moderate differentiated tumors, 85% of patients had infiltrating duct carcinoma, 49.5% of patients were in the early T-stage (T0 and T1), 56.2% of patients were in the N0 stage, 23.7% of patients received chemotherapy and 38% of patients received radiation, 90.8% of patients were ER-positive (ER+), 81.2% of patients were PR-positive (PR+), and 69.7% of patients were married. Compared with patients who received UM, patients who received CPM were younger in age (59 ± 12 years versus 67 ± 12 years), and more likely to receive chemotherapy (49% versus 37.4%), while the ratio of T2 stage (38.5% versus 41.2%) and grade II (44.7% versus 53.1%) were lower. There were no statistical significance in race, histology, N stage, received radiation, ER status, PR status, and marital status. Detailed information is shown in **Table 1**.

Kaplan–Meier Analysis of OS and BCSS

A total of 1,757 (39.89%) patients died in this cohort study, and 30.05% (528/1,757) of them had a breast cancer-specific death, while 69.95% (1,229/1,757) did not. The OS after three, five, and eight years was 93.3%, 85.9%, and 75.7% in the CPM group, respectively; and 84.9%, 73.3% and 59.4% in the UM group, respectively (**Figure 2A**). The BCSS after three, five, and eight years was 98.5%, 95.1%, and 92.1% in the CPM group, respectively; and 93.7%, 87.3% and 79.8% in the UM group, respectively (**Figure 2B**).

The hazard ratio (HR) summarized the risk of OS and BCSS. As shown in **Figures 2A**, **B**, the CPM group was significantly correlated with better OS (HR=0.48, 95%CI: 0.34-0.69, $P<0.001$) and BCSS (HR=0.34, 95%CI: 0.17-0.68, $P<0.001$) in comparison with the UM group.

TABLE 1 | The baseline characteristics of patients with different surgery procedures in the SEER database.

Items	Total		CPM		UM		χ^2	P-value
	N	%	N	%	N	%		
	4405	100	208	4.7	4197	95.3		
Age (mean ± SD)	66.98 ± 12.26		59.26 ± 12.34		67.36 ± 12.13			<0.001
Race							5.9	0.052
White	3633	82.5	177	85.1	3456	82.3		
Black	551	12.5	28	13.5	523	12.5		
Other/unknown	221	5.0	3	1.4	218	5.2		
Grade							6.58	0.04
I	540	12.3	34	16.3	506	12		
II	2322	52.7	93	44.7	2229	53.1		
III or IV	1543	35.0	81	38.9	1462	34.8		
Histology							1.09	0.3
Infiltrating duct carcinoma	3743	85.0	171	82.2	3572	85.1		
Other	662	15.0	37	17.8	625	14.9		
AJCC 6th T							10.33	0.02
T0-1	2181	49.5	112	53.8	2069	49.3		
T2	1809	41.1	80	38.5	1729	41.2		
T3	114	2.6	10	4.8	104	2.5		
T4	301	6.8	6	2.9	295	7		
AJCC 6th N							0.82	0.85
N0	2476	56.2	115	55.3	2361	56.3		
N1	1306	29.6	61	29.3	1245	29.7		
N2	412	9.4	23	11.1	389	9.3		
N3	211	4.8	9	4.3	202	4.8		
Radiation							0.4	0.84
Yes	1044	23.7	51	24.5	993	23.7		
No	3361	76.3	157	75.5	3204	76.3		
Chemotherapy							10.9	0.001
Yes	1672	38	102	49	1570	37.4		
No	2733	62	106	51	2627	63.6		
ER status							2.61	0.27
Negative	110	2.5	7	3.4	103	2.5		
Positive	3998	90.8	192	92.3	3806	90.7		
Unknown/other	297	6.7	9	4.3	288	6.9		
PR status							1.16	0.56
Negative	461	10.5	25	12	436	10.4		
Positive	3578	81.2	169	81.2	3409	81.2		
Unknown/other	366	8.3	14	6.7	352	8.4		
Marital status							0.15	0.93
Married	3070	69.7	143	68.8	2927	69.7		
Single	1158	26.3	57	27.4	1101	26.2		
Unknown	177	4	8	3.8	169	4.1		

SEER, Surveillance, Surveillance, Epidemiology, and End Results; AJCC, American Joint Committee on Cancer; ER, estrogen receptor; PR, progesterone receptor; BCSD, breast cancer-specific death; OCSD, other cause-specific death; UM, unilateral mastectomy; CPM, contralateral prophylactic mastectomy.

Univariate and Multivariate Cox Regression Model Analysis of MaBC Patients

As shown in **Table 2**, through univariate Cox analysis, a total of nine variables, such as age, race, histology, tumor grade, T-stage, N-stage, surgery, receiving chemotherapy, and marital status, were significantly associated with OS and BCSS. To further explore the independent predictive consequences of OS and BCSS, multivariate Cox proportional hazard regression analyses were performed. After adjustment of the clinical features in the Cox model, CPM was only significantly correlated with better BCSS (HR=0.44, 95%CI: 0.22-0.89, *P*=0.02) and threshold value of OS (HR, 0.72, 95% CI: 0.51-1.02, *P*=0.07). In addition, race, tumor grade, histology, tumor T stage, tumor N stage, age, and marital status were independent predictive factors in OS and BCSS.

Nomogram Variable Screening by Competing Risk Analysis

Of the 1,757 deaths from 4,405 patients, the whole cumulative incidence of BCSD was only 11.99% (528/4,405), but the cumulative OCSD (other cause-specific death) incidence was as high as 27.9% (1,229/4,405). In the univariate analysis by a competing risk model (**Table 3**), twelve variables (age, race, tumor grade, histology, T-stage, N-stage, radiation, chemotherapy, surgery, ER status, PR status, marital status), the *P*-value of which presented less than 0.05, were screened for competing risks regression analysis. Patients in the CPM group

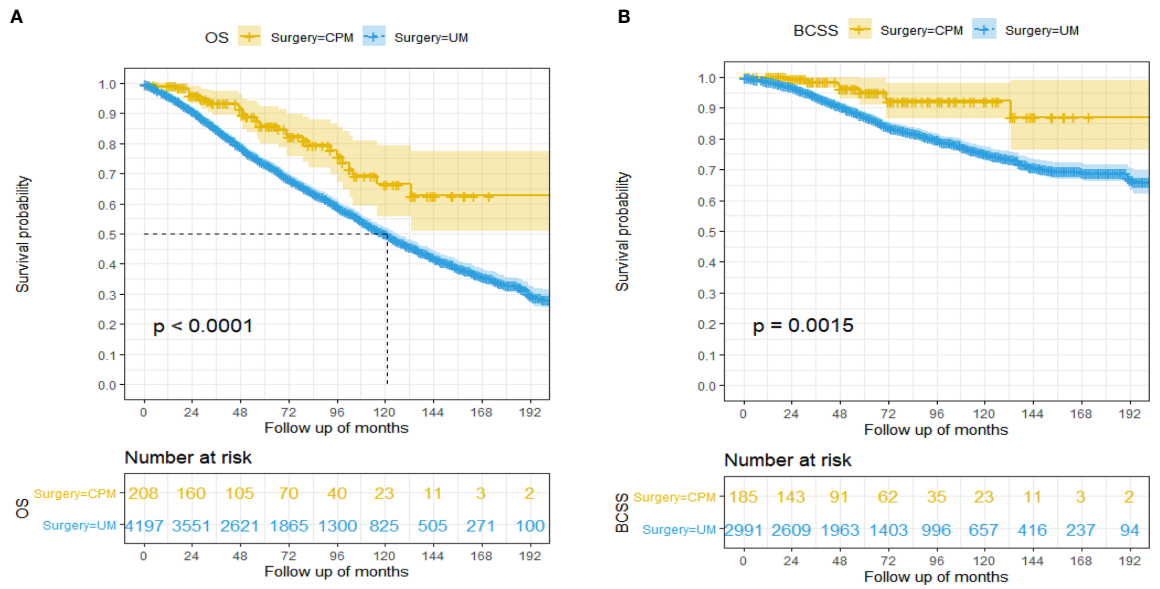

FIGURE 2 | Kaplan-Meier survival analysis for male breast cancer patients. **(A)** Overall survival curves in the CPM group and UM group. **(B)** Breast cancer-specific survival curves in the CPM group and UM group.

had both lower cumulative BCSD incidence (Gray's test, P=0.02) and OCSD incidence (Gray's test, P=0.003) than those in the UM group (**Figure 3**).

In the multivariate analysis by competing risks regression, the results suggested that histology and six variables (tumor grade, T-stage, N-stage, surgery, and marital status) were still the independent predictive factors of BCSD (**Table 4**). Results showed that CPM was significantly associated with better BCSD (HR=0.44, 95%CI: 0.22-0.88, P=0.02). In addition, patients with highly differentiated (grade I), T0-I stage, and N0 stage tumors, other histology, and those who were married tended to have significantly better BCSD than the corresponding group (P<0.05).

Construction of Competing Risks Regression Nomogram Model

Based on screening variables, the nomogram model established by competing risks regression models was used for forecasting the BCSD of every patient after three, five, and eight years, adjusted variables pointed to a score deriving from the scale, then we could get a total score by adding up all scores (**Figure 4**). The predictive cumulative probabilities of BCSD after three, five, and eight years could be evaluated by the total score according to the bottom scale. By using the nomogram, we forecasted a given patient after three, five, and eight years a BCSD of 9.2%, 19.5%, and 31.8%, respectively.

Clinical Value of the Nomogram Compared With the AJCC-TNM Stage

A portion of the cohort (30%) was chosen at random for internal validation. As shown in **Table 5**, the C-index was 0.76 (95%CI: 0.75-0.77) in the training cohort and 0.75 (95%CI: 0.74-0.77) in the validation cohort, implying improved prediction capability compared with AJCC-TNM stage (training cohort: 0.72, 95%CI, 0.71-0.73; validation cohort: 0.69, 95% CI, 0.69-0.72, respectively). Calibration curves also reflected the favorable consistency between nomogram-predicted and observed BCSD at 3-year, 5-year, and 8-year intervals (**Figures 5A**, **B**).

The NRI and IDI were also performed to compare the efficiency between the nomogram and AJCC-TNM stage (**Table 5**). In the training cohort, the NRI values for the 3-year, 5-year, and 8-year BCSD were 0.54 (95%CI: 0.31-0.69), 0.55 (95%CI: 0.27-0.67), and 0.49 (95%CI: 0.24-0.61), respectively, the IDI values for the 3-year, 5-year, and 8-year BCSD were 0.02 (95%CI: 0.01-0.03), 0.03 (95%CI: 0.01-0.04), and 0.04 (95%CI: 0.02-0.06), respectively. While using the nomogram in the validation cohort, the NRI values for the 3-year, 5-year, and 8-year BCSD were 0.51 (95%CI: 0.07-0.83), 0.45 (95%CI: 0.02-0.74), and 0.33 (95%CI: 0.16-0.34), respectively, the IDI values for the 3-year, 5-year, and 8-year BCSD were 0.02 (95%CI: 0.003-0.04), 0.04 (95%CI: 0.01-0.07), and 0.04 (95%CI: 0.004-0.04), respectively. In summary, the abovementioned results suggested that the competing risks regression nomogram model had significantly enhanced precision and reliability for BCSD prediction compared with the TNM stage system.

DISCUSSION

In this retrospective study, we conducted Cox regression models and competing risk analysis based on 4,405 male patients with non-metastatic breast cancer in the SEER database from

TABLE 2 | Univariate and multivariate Cox regression model analysis of MaBC patients.

Characteristics	OS						BCSS					
	Univariate analysis			Multivariate analysis			Univariate analysis			Multivariate analysis		
	Hazard ratio	95% CI	*P*-value	Hazard ratio	95% CI	*P*-value	Hazard ratio	95% CI	*P*-value	Hazard ratio	95% CI	*P*-value
Age	1.06	1.05-1.07	<0.001	1.06	1.05-1.07	<0.001	1.02	1.01-1.03	0.001	1.02	1.01-1.03	<0.001
Race												
White		as reference			as reference			as reference			as reference	
Black	1.19	1.03-1.36	0.02	1.39	1.21-1.6	<0.001	1.46	1.16-1.84	0.001	1.34	1.05-1.7	0.020
Other/unknown	0.64	0.49-0.84	0.001	0.82	0.63-1.08	0.15	0.64	0.4-1.03	0.07	0.70	0.44-1.12	0.14
Histology												
Other		as reference			as reference			as reference			as reference	
Infiltrating duct carcinoma	1.16	1.01-1.33	0.03	1.17	1.02-1.35	0.02	1.62	1.23-2.14	<0.001	1.41	1.06-1.87	0.02
Grade												
I		as reference			as reference			as reference			as reference	
II	1.23	1.05-1.44	0.01	1.11	0.94-1.3	0.22	2.21	1.48-3.29	<0.001	1.67	1.11-2.49	0.01
III or IV	1.59	1.35-1.87	<0.001	1.42	1.19-1.67	<0.001	4.14	2.79-6.15	<0.001	2.61	1.75-3.91	<0.001
AJCC 6th T												
0-I		as reference			as reference			as reference			as reference	
II	1.59	1.44-1.76	<0.001	1.39	1.25-1.54	<0.001	3.01	2.47-3.68	<0.001	2.08	1.69-2.56	<0.001
III	1.81	1.38-2.37	<0.001	1.65	1.25-2.17	<0.001	4.29	2.82-6.5	<0.001	2.94	1.91-4.53	<0.001
IV	2.78	2.39-3.26	<0.001	1.09	1.76-2.48	<0.001	6.26	4.71-8.31	<0.001	3.54	2.61-4,81	<0.001
AJCC 6th N												
0		as reference			as reference			as reference			as reference	
I	1.14	1.03-1.27	0.02	1.81	1.44-2.27	<0.001	2.17	1.75-2.68	<0.001	1.88	1.49-2.35	<0.001
II	1.65	1.42-1.92	<0.001	2.85	2.16-3.76	<0.001	4.39	3.43-5.62	<0.001	3.30	2.49-4.37	<0.001
III	2.06	1.7-2.5	<0.001	4.99	3.68-6.78	<0.001	7.28	6.57-9.53	<0.001	4.90	2.66-6.59	<0.001
Surgery												
UM		as reference			as reference			as reference			as reference	
CPM	0.48	0.34-0.69	<0.001	0.72	0.51-1.02	0.07	0.002	0.17-0.68	<0.001	0.44	0.22-0.89	0.02
Radiation												
No		as reference						as reference			as reference	
Yes	1.07	0.96-1.19	0.23				1.87	1.59-2.23	<0.001	0.86	0.7-1.06	0.17
Chemotherapy												
No		as reference			as reference			as reference			as reference	
Yes	0.70	0.63-0.77	<0.001	0.79	0.71-0.9	<0.001	1.53	1.29-1.82	<0.001	0.92	0.74-1.14	0.45
ER status												
Other		as reference						as reference				
Negative	1.17	0.86-1.58	0.32				1.62	0.97-2.72	0.07			
Positive	0.87	0.75-1.02	0.10				0.90	0.65-1.24	0.52			
PR status												
Unknown/other		as reference						as reference				
Negative	1.02	0.84-1.24	0.83				1.39	0.98-1.97	0.06			
Positive	0.91	0.78-1.05	0.20				0.90	0.67-1.2	0.46			
Marital status												
Married		as reference			as reference			as reference			as reference	
Single	1.59	1.43-1.76	<0.001	1.45	1.31-1.61	<0.001	2.03	1.69-2.42	<0.001	1.69	1.41-2.04	<0.001
Unknown	0.96	0.73-1.25	0.75	1.02	0.78-1.34	0.87	0.70	0.39-1.25	0.23	0.88	0.49-1.57	0.67

SEER, Surveillance, Surveillance, Epidemiology, and End Results; AJCC, American Joint Committee on Cancer; ER, estrogen receptor; PR, progesterone receptor; OS, overall survival; BCSS, breast cancer-specific death; UM, unilateral mastectomy; CPM, contralateral prophylactic mastectomy.

TABLE 3 | Univariate competing risk model analysis of death causes in MaBC patients.

ITEMS	BCSD					OCSD				
	Event (n)	3-year (%)	5-year (%)	8-year (%)	*P-value*	Event	3-year (%)	5-year (%)	8-year (%)	*P*-value
Age					0.002					<0.001
≤65	271	3.8	7.9	13.8		247	4	6.8	11	
>65	257	4.6	8.8	12.1		982	15.7	26.5	40.1	
Race					0.002					0.02
White	423	4	7.7	12.1		1045	10.6	18.1	27.4	
Black	87	6.9	13.5	18.6		147	11.8	18.3	29.1	
Other/unknown	18	1.6	6.2	12.1		37	6.9	11.5	15.7	
Grade					<0.001					0.96
I	27	1.4	2.3	4.8		160	10.7	16.3	25.5	
II	231	2.9	6.4	10.4		635	10.4	17.4	27.4	
III or IV	270	7.2	13.5	19.5		434	10.7	18.9	27.3	
Histology					0.002					0.88
Infiltrating duct carcinoma	473	4.5	9	13.6			10.5	17.7	27.2	
Other	55	3	4.8	8.7		182	11.1	18.3	26.6	
AJCC 6th T					<0.001					<0.001
T0-1	147	1.5	3.3	6.8		595	8.8	15.8	25.4	
T2	284	5.9	12.5	18.2		486	11.1	18.5	27.5	
T3	26	12.2	17.3	24.5		30	12.1	16.8	25.4	
T4	71	12.1	18.4	23.6		118	19.7	29.3	38.1	
AJCC 6th N					<0.001					<0.001
N0	160	2.5	4.4	7.2		748	10.9	18.8	29	
N1	183	4.1	9.2	15.1		333	10.8	17.4	25.3	
N2	104	8.5	17.6	25.3		110	9.7	17	27.5	
N3	81	17.9	31.3	40.9		38	6.1	10.9	15.3	
Surgery					0.02					0.003
UM	520	4.4	8.5	13.1		1206	10.8	18.1	27.5	
CPM	8	1.3	4.1	6.4		23	5.4	10.1	17.9	
Radiation					<0.001					<0.001
Yes	197	6.1	13.3	19.9		243	6.9	13.3	21.9	
No	331	3.7	6.9	10.7		986	11.7	19.2	28.7	
Chemotherapy					<0.001					<0.001
Yes	293	5	10.9	17.7		282	4.5	8.5	14.5	
No	235	3.8	6.8	9.9		947	14.3	23.5	34.8	
ER status					0.04					0.08
Negative	22	14.3	16.7	19.3		33	16.3	19.8	29.2	
Positive	465	3.9	8	12.7		1063	10.1	17.3	26.6	
Unknown/other	41	4.8	9.9	12.9		133	14.4	23.1	32	
PR status					0.001					0.1
Negative	84	6.5	11.1	17.4		128	12.2	17.6	22.5	
Positive	393	4	7.8	12.4		944	10	17.4	27.2	
Unknown/other	51	4.7	9.7	12.4		157	13.6	21.5	31.6	
Marital status					<0.001					<0.001
Married	324	3.2	6.6	11		817	9.3	16.4	25.1	
Single	192	7.2	13.5	18.7		368	13.4	21.7	32.8	
Unknown	12	1.8	5.9	7.2		44	12.9	17.5	24.4	

SEER, Surveillance, Surveillance, Epidemiology, and End Results; AJCC, American Joint Committee on Cancer; ER, estrogen receptor; PR, progesterone receptor; BCSD, breast cancer-specific death; OCSD, other cause-specific death; UM, unilateral mastectomy; CPM, contralateral prophylactic mastectomy.

1998 to 2015. The application was significantly associated with better BCSS and BCSD. Based on the corresponding parameters by competing risks regression, we built a nomogram to predict the 3-year, 5-year, and 8-year breast cancer-specific death (BCSD). To our knowledge, this was the first and largest population-based nomogram model to predict the impact of CPM on MaBC by competing risk analysis.In our study, surgery procedure was associated with improvement in BCSS and OS, which were objective and bias-free measurements for patients with MaBC. In the Kaplan-Meier curve analysis, significant improvements in BCSS and OS were observed in the CPM group rather than the UM group. To reduce the estimation bias and further investigate the efficiency of CPM on BCSS and OS for patients with MaBC, the multivariate Cox regression models analysis was performed. After adjusting for demographic, clinicopathological, and therapeutic variables, we found that administration of CPM could prolong BCSS, but had the threshold value of benefit in OS in comparison with UM. These findings were inconsistent with the previous trials where the application of CPM played a vital role in MaBC treatment (18–20). Multiple single and multi-institution studies reported the CPM's positive effect on OS and disease-free survival (DFS). Four single (21, 22) and three multi-institution (23–25) studies demonstrated that CPM could have benefit in DFS, while two

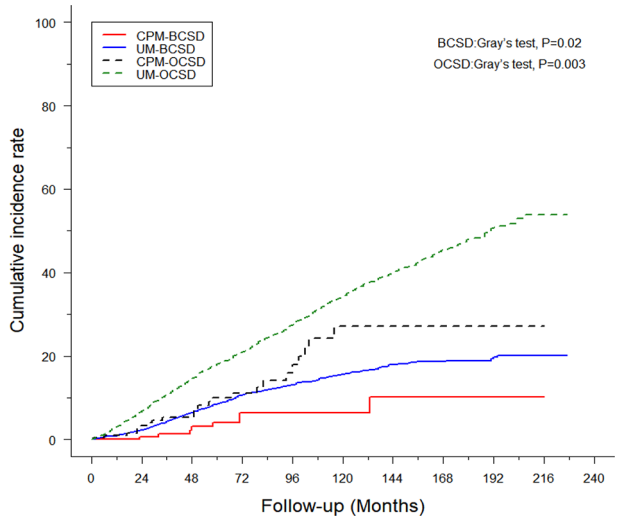

FIGURE 3 | Cumulative incidence of breast cancer-specific death (BCSD) and other cause-specific death (OCSD) in the CPM group and UM group.

single (21, 26) and three multi-institution (23–25) studies indicated an OS benefit. A recent review study showed that patients who received CPM might be more healthy and had access to more advanced treatments than patients who did not undergo CPM (27).

To eliminate the estimation bias from other causes of death and further investigate the efficacy of CPM on BCSD, competing multivariable regression models analysis which is common in oncology research was performed (28–31). After performing competing risks regression, we found that the patients in the CPM group had better BCSD in comparison with the UM group. The main reasons might be that most of the research involving CPM was conducted in patients with FBC rather than patients with MaBC. Several studies concentrated on the prevention of contralateral breast cancers (CBCs) through the administration of CPM (20, 23, 32, 33). And BRCA mutation carriers, who had a high risk of CBCs, also obtained a survival benefit from CPM (34–36). Many patients consequently tended to select CPM to reduce the risk of CBCs. Many studies have shown that CBCs tend to have more favorable tumor features, and patients who develop CBCs in a short interval from their primary cancer have worse prognosis than those who develop CBCs at a longer interval, especially in young patients with large tumors, and those who are node-positive (37–41). However, it is controversial whether worse survival is caused by the CBCs, which represents the aggressive biology of the primary tumor, distant metastatic disease, and older, inferior systemic treatments.

In addition, MaBC and FBC have different biological characteristics, such as the rate of ER-positive tumors and age at diagnosis. In our study, the rate of ER and PR-positive tumors were as high as 90.8% and 81.2%, respectively, but the percentage of ER-positive tumors and PR-positive tumors in FBC patients were only 78% and 64% in a previous study (42, 43).

TABLE 4 | Competing risks regression of BCSD.

Characteristics	BCSD		
	Hazard ratio	95% CI	*P*-value
Age	0.99	0.98-1.01	0.12
Race			
White		as reference	
Black	1.21	0.95-1.54	0.13
Other/unknown	0.81	0.49-1.3	0.38
Histology			
Other		as reference	
Infiltrating duct carcinoma	1.38	1.04-1.83	0.03
Grade			
I		as reference	
II	1.58	1.06-2.36	0.02
III or IV	2.27	1.52-3.4	<0.001
AJCC 6th T			
0-I		as reference	
II	1.95	1.6-2.4	<0.001
III	2.62	1.71-3.99	<0.001
IV	2.19	1.62-2.97	<0.001
AJCC 6th N			
0		as reference	
I	1.81	1.44-2.27	<0.001
II	2.85	2.16-3.76	<0.001
III	4.99	3.68-6.78	<0.001
Surgery			
UM		as reference	
CPM	0.44	0.22-0.88	0.02
Radiation			
No		as reference	
Yes	0.99	0.8-1.21	0.89
Chemotherapy			
No		as reference	
Yes	1.14	0.91-1.41	0.25
ER status			
Unknown/other		as reference	
Negative	1.19	0.5-2.81	0.69
Positive	0.87	0.44-1.73	0.70
PR status			
Unknown/other		as reference	
Negative	1.48	0.77-2.84	0.24
Positive	1.09	0.59-2.02	0.78
Marital status			
Married		as reference	
Single	1.35	1.12-1.63	0.002
Unknown	0.79	0.45-1.39	0.41

SEER, Surveillance, Surveillance, Epidemiology, and End Results; AJCC, American Joint Committee on Cancer; ER, estrogen receptor; PR, progesterone receptor; BCSD, breast cancer-specific death; UM, unilateral mastectomy; CPM, contralateral prophylactic mastectomy.

The majority of male cases who developed BC were older than those in FBC. Previous research reported that MaBC tended to have a 1.75 times higher risk of distant metastasis than FBC (7% *vs.* 4%) (44, 45). Furthermore, patients with MaBC were likely to have a higher mutation rate of CHEK2 c.1100delC and BRCA2, which play a particularly prominent role in metastasis and the prognosis of disease, than those in FBC (11, 12, 46–49). In brief, MaBC patients were more likely to have poorer differentiated grade, were older, a higher node-positive, higher rates of lymphovascular invasion, and estrogen receptor (ER+) tumors. Therefore, there are differences in treatment procedures, for

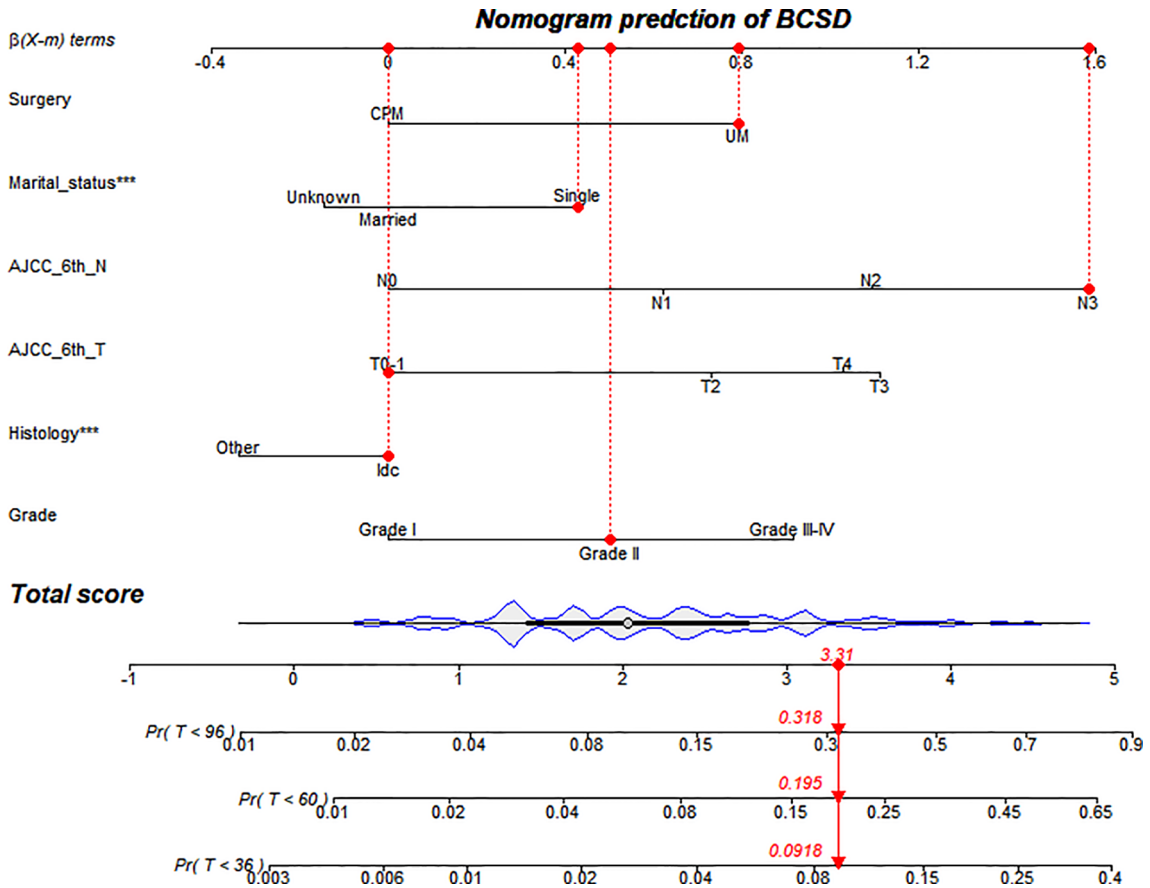

FIGURE 4 | Competing risks regression nomogram model for MaBC patients.

TABLE 5 | C-index, NRI, and IDI of the nomogram and AJCC-TNM stage system in BCSD prediction for MaBC patients.

	Training cohort		Validation cohort	
NRI (*vs.* the AJCC criteria-based tumor staging)	Estimate	95% CI	Estimate	95% CI
For 3-year BCSD	0.54	0.31-0.69	0.51	0.07-0.83
For 5-year BCSD	0.55	0.27-0.67	0.45	0.02-0.74
For 8-year BCSD	0.49	0.24-0.61	0.33	0.16-0.34
IDI (*vs.* the AJCC criteria-based tumor staging)				
For 3-year BCSD	0.02	0.01-0.03	0.02	0.003-0.04
For 5-year BCSD	0.03	0.01-0.04	0.04	0.01-0.07
For 8-year BCSD	0.04	0.02-0.06	0.04	0.004-0.04
C-index				
The nomogram	0.76	0.75-0.77	0.75	0.74-0.77
AJCC-TNM stage system	0.72	0.71-0.73	0.71	0.69-0.72

AJCC, American Joint Committee on Cancer; BCSD, breast cancer-specific death.

example chemotherapy/radiotherapy and the corresponding prognosis between MaBC and FBC.

Meanwhile, this study set up a nomogram model to predict BCSD in patients with MaBC. After integrating the demographic and clinicopathological characteristics, the nomogram model could be more precise than the conventional TNM stage system, such as the AJCC stage system. In the traditional sense, the AJCC-TNM stage system was the preferred alternative for predicting the prognosis of patients with carcinoma. In general, the stages of this system were strongly correlated with BCSD (50). Inevitably, patients at the same stage often had different prognoses. The underlying reasons might be the vagueness in the TNM-stage system and the variables which were not included in the sociodemographic characteristics, such as age, marital status, and so on. Actually, in our study, married patients with a well-differentiation level and T0-1 stage and N0 stage tumors tended to have better prognostic indicators for BCSD. These results are consistent with previous reports (18–20, 35, 46, 47) and indicate that both demographic and clinicopathological characteristics, such as marital status and tumor differentiation level, were objective and reliable prognostic indicators in men with breast carcinoma. Then, the NRI value

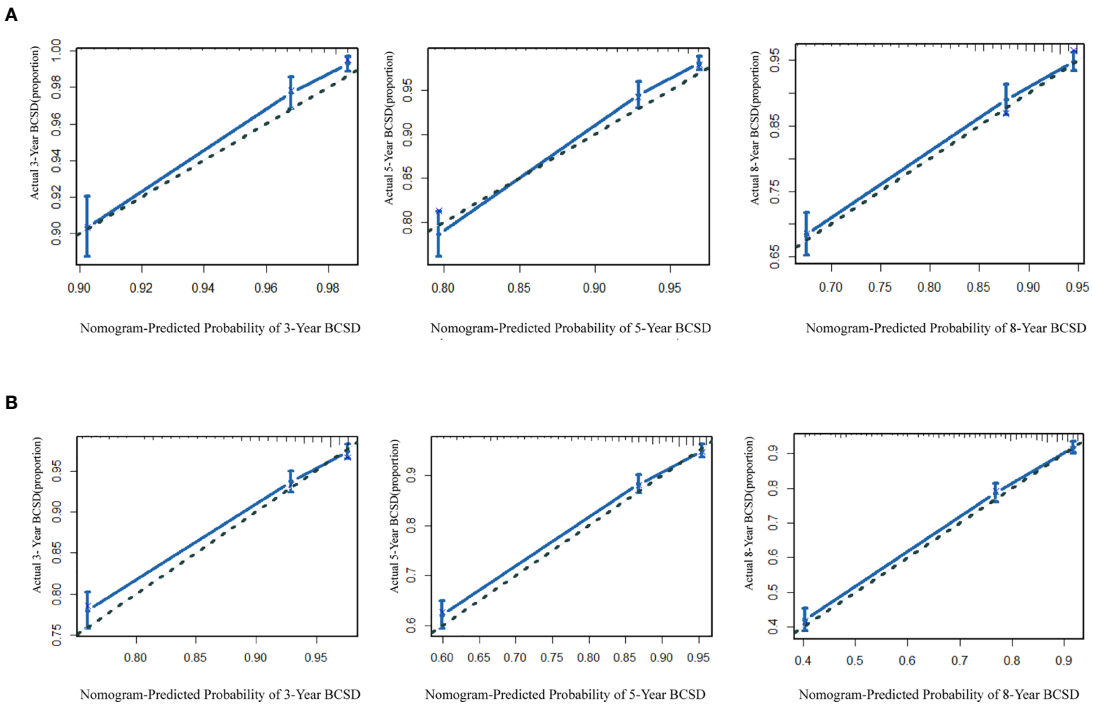

FIGURE 5 | **(A)** The calibration curve for predicting patient BCSD after three, five, and eight years in the training cohort; **(B)** the calibration curve for predicting patient BCSD after three, five, and eight years in the internal validation cohort.

and IDI value of the nomogram confirmed that the nomogram had better prediction power than the AJCC-TNM stage system. Furthermore, the favorable results were replicated well in the validation cohort. In summary, the nomogram could provide precise and personalized prediction of the cumulative risk in patients with MaBC after CPM.

Our subject indeed has limitations, as shown below: Firstly, studies that randomly assigned patients into different groups by treatment methods were needed. The retrospective study could not prove causation and may be subject to selection bias and uncontrolled confounding factors, even with the administration of competing risks regression models. Secondly, we were unable to avoid the possibility that the observed risks reduction might exclude the influence of potential confounders, such as family history, insurance coverage, comorbidities, health status, MRI application, patient anxiety, BRCA gene status, counseling, and so on. These data greatly impacted the clinical decisions and even breast cancer prognosis (18–20, 34–36, 46, 47). Thirdly, there was a big gap between CPM and UM that may have some bias to the data, and the study sample might be insufficient to uncover some differences in the abovementioned phenomenon. Next, the proportion of T1 stage (49.5%), T2 stage (41.1%), N0 stage (56.2%), and N1 stage (29.6%) may have been too high in our study, this statistical bias from the SEER database might lead to the result that the efficacy of radiotherapy and chemotherapy were limited in our study. Randomized controlled clinical and multicenter-clinical trials with long follow-up periods are still needed to further confirm this. Lastly, *P* value <0.05 was used to possess the statistics sense, and no adjustment was made for multiple analysis; the chance of falsely rejecting a null hypothesis may exceed 0.05.

CONCLUSION

The administration of CPM was associated with the decrease in risk of BCSD in patients with MaBC. The nomogram could provide precise and personalized prediction of the cumulative risk in patients with MaBC after CPM. Randomized controlled clinical and multicenter-clinical trials with long follow-up time are still needed to further confirm the effects of CPM on BCSD and the prediction efficacy of the nomogram.

DATA AVAILABILITY STATEMENT

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found below: https://seer.cancer.gov.

AUTHOR CONTRIBUTIONS

KL and BW drafted the manuscript and analyzed data, ZY, HC, and YL generated the figure, and RY performed the background research. CZ and JH edited the manuscript. All authors have read and approved the content of the manuscript.

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Real-Time *In Situ* Navigation System With Indocyanine Green Fluorescence for Sentinel Lymph Node Biopsy in Patients With Breast Cancer

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Background: The naked-eye invisibility of indocyanine green fluorescence limits the application of near-infrared fluorescence imaging (NIR) systems for real-time navigation during sentinel lymph node biopsy (SLNB) in patients with breast cancer undergoing surgery. This study aims to evaluate the effectiveness and safety of a novel NIR system in visualizing indocyanine green fluorescence images in the surgical field and the application value of combined methylene blue (MB) and the novel NIR system in SLNB.

Methods: Sixty patients with clinical node-negative breast cancer received indocyanine green (ICG) and MB as tracers. Two NIR system instruments, namely, lymphatic fluorescence imaging system (LFIS) designed by the University of Science and Technology of China and vascular imager by Langfang Mingde Medical Biotechnology Co., Ltd. (Langfang vascular imager), were used as navigation assistance to locate sentinel lymph nodes (SLNs). Excising the lymph nodes developed by both MB and ICG by two NIR systems or palpably suspicious as SLNs and undergoing rapid pathological examination.

Results: Both instruments exhibited 95% (57/60) success for real-time lymphatic fluorescent images. A total of 186 SLNs were identified, of which two were pathologically confirmed as lacking any lymph node tissue. SLN identification rate was 100% (184/184) for MB plus LFIS and 86.96% (160/184) for MB alone. The median number of SLNs identified by LFIS combined with MB was 3 (range of 1–8), which was significantly higher than that by MB alone at 2 (range 1–7) ($P<0.05$).

Conclusion: LFIS effectively detects SLNs in breast cancer, projects the fluorescence signals during surgery, and provides a continuous surgical navigation system without the need for a remote monitor. The ICG method navigated by combined LFIS and MB may be a promising alternative tracer for radioisotope in SLN mapping.

Clinical Trial Registration: This clinical trial was registered with the China Clinical Trial Center, registration number ChiCTR2000039542.

Keywords: breast cancer, sentinel (lymph) node biopsy, indocyanine green, real-time *in situ* navigation, false negative

BACKGROUND

Sentinel lymph node biopsy (SLNB) is the standard treatment for clinical axillary lymph node-negative breast cancer (1). Clinical studies and meta-analysis showed that the exemption from axillary lymph node dissection for sentinel lymph node (SLN)-negative patients does not affect their overall survival and saves them from its complications, such as upper limb lymphedema, numbness, and pain (2). Radioisotope (RI) and blue dye are SLNB tracers that are globally used but have some limitations. Blue dye has a long learning curve, requires practice to achieve high accuracy, has the risk of anaphylactic reactions, and is widely used in China but has unsatisfactory detection rate. Meanwhile, RI has a high detection rate. Dual localization with both tracers is considered the standard method (3, 4) with high detection rate and low false negative rate of 5%–10% (5, 6). However, RI requires the assistance of nuclear medicine department, and its widespread use is limited by exposure to RIs and high preservation.

Indocyanine green (ICG) has been introduced as a new SLNB tracer since 2005 (7). The NIR system can visualize the lymphatic flow and provide navigation for the surgeon to find and remove the SLNs. ICG has higher detection rate than traditional tracers RI and blue dye (8, 9). Recent studies and meta-analysis indicated that ICG and RI tracers show no statistically significant difference in SLN detection rate (10, 11). Although ICG has a high detection rate and short learning curve, the conventional NIR system need to be improved. Surgeons need to look at the remote monitors to identify the location of the fluorescent image because the fluorescent signal is invisible to the naked eye. The shadowless operating lamp must also be turned off to decrease the white-light contamination of images. This study introduced a novel NIR system that provides real-time operation navigation by producing fluorescent images that are directly visible in the operation field. SLNB was assisted by two NIR systems to verify the feasibility and effectiveness of lymphatic fluorescence imaging system (LFIS). In addition, the fluorescence localization effectiveness of ICG combined with MB was evaluated.

MATERIAL AND METHODS

Study Design

This clinical trial was a single-arm, prospective, multicenter study. Participating surgeons were well trained for sentinel lymph node biopsy.

Patients

Sixty female patients with early breast cancer and clinically confirmed negative axilla were recruited from the Department of Breast Surgery of the First Affiliated Hospital of Anhui Medical University of China Department of Tumor Surgery, The First Affiliated Hospital of Bengbu Medical College of China, and Department of Breast Surgery of Nantong Cancer Hospital of China between March 2018 and June 2018.

Inclusion criteria were as follows: 1) primary breast cancer confirmed by core needle biopsy or Mammotome biopsy; 2) no enlarged axillary lymph nodes as verified by palpation, mammography, or breast ultrasound examination; and 3) no distant metastasis.

Exclusion criteria were as follows: 1) pregnant or lactating, 2) primary breast cancer confirmed by open biopsy, 3) preoperative radiotherapy at the breast area or neoadjuvant chemotherapy, 4) history of the axillary surgery, and 5) allergy to iodine.

This study was approved by the Institutional Research Ethics Committee of the First Affiliated Hospital of Anhui Medical University, The First Affiliated Hospital of Bengbu Medical College of China and Nantong Cancer Hospital of China. And written informed consent was obtained from each subject. The study protocol was registered : (ChiCTR2000039542, Chinese Clinical Trial Registry).

Imaging System and Reagents

The two kinds of NIR system used in this study were LFIS by the University of Science and Technology of China and Jiangsu Xinmei Medical Engineering Technology Co., Ltd. (**Figure 1A**) and vascular imager by Langfang Mingde Medical Biotechnology Co., Ltd. (Langfang vascular imager) (**Figure 1B**). The fluorescence emission from the surgical site is acquired by the LFIS device, calibrated based on the detected working distance, and projected back to the surgical site for surgical guidance. This instrument has the updated version of handheld projective imaging device (12). The differences between Langfang vascular imager and LFIS is that the LFIS projects fluorescent images onto the skin surface. Under the Langfang vascular imager navigation, surgeons need to look at the remote monitors to identify the location of the fluorescent image because the fluorescent signal is invisible to the naked eye.

The tracers used were MB (JUMPCAN PHARMACEUTICAL GROUP CO., LTG.) and ICG (Eisai, Liaoning Pharmaceutical Co., Ltd.).

Preparation of ICG solution : Indocyanine green dosage form is powder, each containing 25mg. Dissolve with sterilization water of 10ml originally prepared by the manufacturer, and the mass concentration after dissolution is 2.5mg/ml. Then 0.2 mL of 2.5mg/mL indocyanine green was diluted to 1 mL (0.5mg/mL) with sterilized injection water as the mass concentration used.

In the studies on the influence of ICG concentration on the number of lymph node detection and lymphatic vessel development, the concentration varied from 0.5mg/ml to 2.5mg/ml, but the development effect of lymphatic vessel and lymph node was ideal.

SLNB Procedure

After general anesthesia was administered, the four sites of periareolar region were subcutaneously injected with 1 ml of 1% MB (**Figure 2A**), followed by 1 ml of ICG after 5 minutes. The areola area was then massaged. Real-time imaging of lymphatic drainage imagine in the outer upper quadrant of the

Abbreviations: NIR system, near-infrared fluorescence imaging systems; SLNB, sentinel lymph node biopsy; MB, methylene blue; RI, Radioisotope; BMI, Body Mass Index; FNR, false negative rate; LAA, Langer's axillary arch.

FIGURE 1 | Two NIR system. **(A)** Left one: Lymphatic Fluorescence Imaging System(LFIS) designed by university of Science and Technology of China. **(B)** Right one: Vascular imager by Langfang Mingde Medical Biotechnology Co.LTD (Langfang Vascular imager).

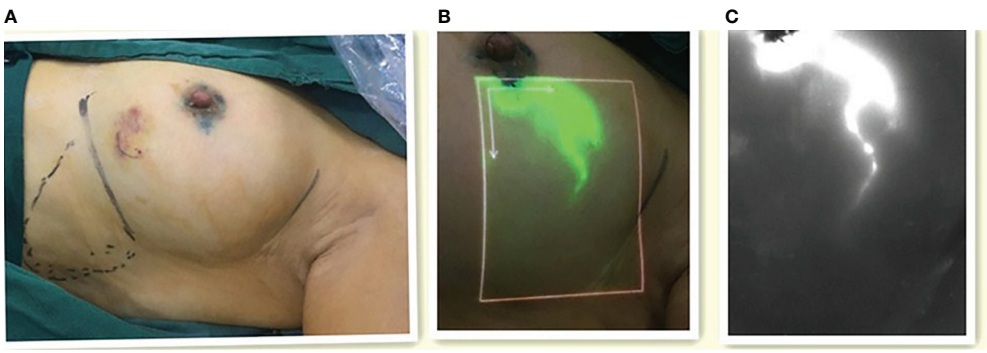

FIGURE 2 | The images of lymphatic drainage. **(A)** Left one: ICG was injected around the areola. **(B)** Middle one: The image of lymphatic drainage on the skin with the LFIS. **(C)** Right one: The image of lymphatic drainage on the monitor with the Langfang Vascular imager.

breast was performed using Langfang vascular imager and LFIS, and images of lymphatic drainage were captured (**Figures 2B, C**). SLNB incision was selected 2 cm away from where the fluorescence disappeared, and the consistency of incision location was evaluated. If the subcutaneous lymphatic flow is invisible or is discontinuous, then conventional incision (the external margin of the pectoralis major and the anterior margin of the latissimus dorsi) is chosen.

The fluorescent (ICG-positive) (**Figure 3**) and/or blue (MB-positive) lymph nodes were localized and excised similarly to the SLNs. The axilla was inspected for residual fluorescent with the Langfang vascular imager or blue nodes. Lymph node development was recorded, particularly whether the lymph node is MB-, LFIS+, and Langfang+ (**Figure 4**). All excised nodes underwent immediate and postoperative pathological examinations. Axillary lymph node dissection was conducted only on patients with positive SLNs.

The overall research process is shown in **Image 1**.

Statistical Analysis

SPSS statistical package version 21.0 was used for statistical analyses. Non-parametric Wilcoxon signed rank test was

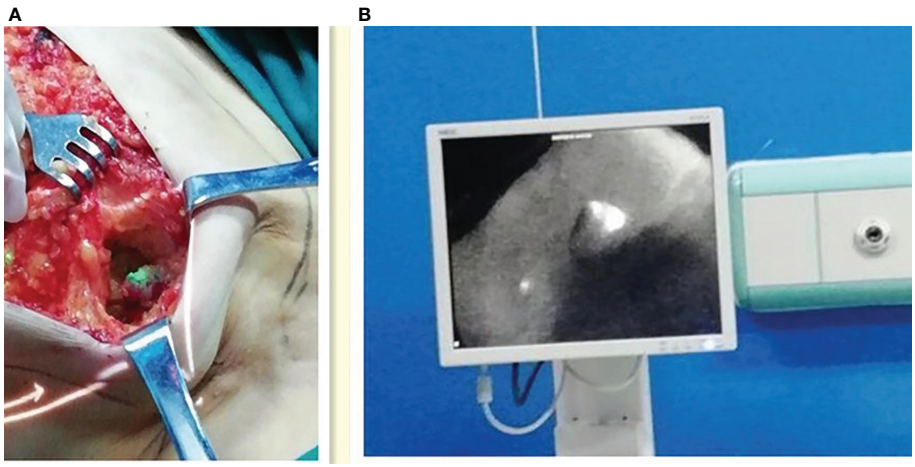

FIGURE 3 | Intraoperative fluorescence imaging of lymph nodes. **(A)** Left one: Intraoperative fluorescence imaging of lymph nodes with the LFIS. **(B)** Right one: Intraoperative fluorescence imaging of lymph nodes with the Langfang Vascular imager.

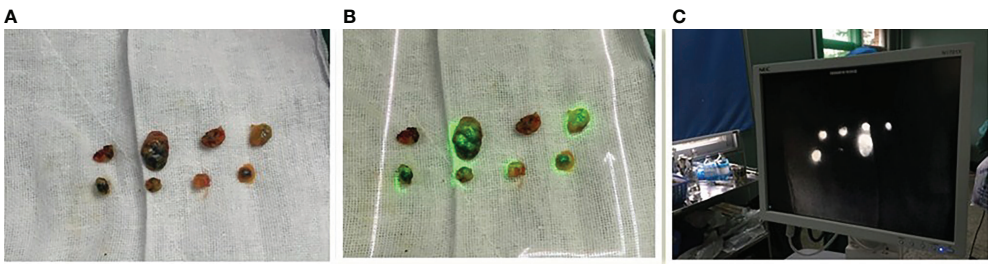

FIGURE 4 | Image of resected lymph nodes. **(A)** Left one: The MB lymph node. **(B)** Middle one: The ICG lymph nodes with the LFIS. **(C)** Right one: The ICG lymph nodes with the Langfang Vascular imager.

employed to compare the median number of SLNs between groups. A P-value<0.05 was considered statistically significant.

RESULTS

Patient Characteristics

Patient and tumor characteristics are shown in **Table 1**.

ICG Mapping

Among the 60 patients with SLN detected using ICG combined with MB, real-time lymph-vessel fluorescent images were observed in the skin of 57 patients by both instruments in the same position. Hence, the rate of real-time observation of skin lymphatic streams was 95%. The three patients with no substantial lymphatic streams on the skin underwent SLNB with conventional incision, and their fluorescent lymph nodes were found successfully. In one case, 2 SLNs were ICG positive and MB negative, and pathology revealed no lymph node tissues.

With the exclusion of the above case, 184 SLNs were obtained. **Table 2** shows that the detection rate of LFIS combined with MB sentinel node was 100% (184/184), and that of MB alone was 86.96% (160/184). The median number of SLNs identified by LFIS combined with MB was significantly higher (3, range 1–8) than by MB (2, range 1–7) (P <0.05).

Among the 60 patients, 10 has metastatic SLNs, and 15 out of 184 lymph nodes were positive. The trace situation of positive lymph nodes is shown in **Table 3**. The use of MB alone would have missed 20% of the positive axillae. Given the small number of cases, further clinical trials must be conducted for validation.

We analyzed the relationship between the number of sentinel lymph node biopsies and Body Mass Index (BMI). BMI was negatively correlated with the number of SLNs, and the correlation was weak.

Adverse Effects

No allergic reaction was observed from surgery to discharge. All 60 patients were followed up for 24 months and showed no adverse reactions such as skin lesions, necrosis, and infection at the ICG injection site.

TABLE 1 | Tumor and patients characteristics.

Factors	N	%
Total patients	60	
Age, median (range)	50(31-67)	
Body Mass Index	23.93(18.32-30.12)	51.67
<24	31	36.66
≥24	22	10.00
≥28	6	1.67
≥30	1	
Tumor stage	6	10
Tis	24	40
T1	28	46.67
T2	2	3.33
T3		
Histological grade	9	15
1	34	56.67
2	12	20
3	5	8.33
Unknown		
Patients with positive SLN	10	16.67

TABLE 2 | Detection rate of various methods.

	Number of SLNs identified and detection rate	Number of patients identified detection rate
(MB+) and (LFIS+)	184 (100%)	60(100%)
Only MB+	160 (86.96%)	58(96.7%)
Only LFIS+	177 (96.20%)	60(100%)
Langfang Vascular imager	174 (94.57%)	60(100%)

TABLE 3 | Metastatic SLNs and patients with metastatic SLNs detected by different methods.

	Number of detected positive nodes and detection rate	Number of patients detected positive node and detection rate
LFIS(+) and MB(+)	12(80%)	8(80%)
LFIS(+) and MB(+)	3(2%)	2(20%)
LFIS(-) and MB(+)	0(0)	0(0)
Total	15(100%)	10(100%)

DISCUSSION

This prospective and self-matching study aimed to compare LFIS with conventional NIR system and blue dye method to assess whether the former can be used as a reliable alternative and whether it is superior over blue dye method for early breast cancer. The Langfang vascular imager has been approved for clinical use. The researchers took into account that the new system (LFIS) was in the clinical validation stage, and compared the consistent development rate of subcutaneous lymphatic vessels and the detection rate of lymph nodes with Langfang vascular imager. So the two NIR systems were used in my study.

ICG has a short half-life in plasma. After injection, it can bind tightly to plasma proteins and immediately enter lymphatic vessels to flow to SLNs (13). Thus, ICG serves as a marker for a specific molecule or cell. SLNs in breast cancer regularly occur in specific areas. Thus, the precise location of incision can be readily chosen, and SLNs are easy to find under fluorescence guidance. The NIR fluorescence band of ICG is 700–900 nm, which is invisible to the naked eye. Therefore, the position and movement of these molecules and cells must be assisted by a NIR fluorescence imaging system to obtain the accurate location of lymphatic vessels and sentinel lymph nodes. Although the ICG fluorescence method is unique in surgical navigation and has high sensitivity, its application to current NIR systems encounters several technical issues that must be addressed. Companies like Hamamatsu Photonics and Novadaq have their own near-infrared fluorescent navigation systems. The two companies' instruments were similar to the Langfang vascular imager used in the study. This type of NIR system displays the fluorescence image on the mobile monitor, and the surgeon must alternately and repeatedly look at the surgical field and the remote monitor to confirm the site of the lymph nodes. With the fluorescence intensity image devoid of major anatomical landmarks, this phenomenon destroys the consistency and increases the complexity of the surgical procedure.

Our research team focuses on real-time in-situ surgical navigation. A Google-enhanced imaging system was developed in collaboration with the University of Science and Technology of China. When the surgeon wears Google Glasses, the fluorescent signal is projected onto the Google Glasses to achieve real-time display of approximate surgical field (14, 15). This study presents a novel NIR system called LFIS that can continuously and accurately project the fluorescence image on the surgical field to allow for a focused vision and shorten the operation time. The LFIS provides real-time navigation for SLNB and has two modes: projection mode and lighting mode, which shifts by pressing one button, thus limiting the need to switch the shadowless lamp. LFIS is comparable to conventional NIR systems in locating sentinel nodes. Owing to self-matching, quantitative comparison under short surgery duration is unavailable.

The detection rate of LFIS-guided ICG combined with MB (100%, 184/184) was better than that of MB alone (86.96% (160/184), and this finding was consistent with previous studies. The total number of LFIS positive (177) was higher than that of MB positive (160) and is possibly related to the affinity for the lymphatic system. The affinity of ICG is stronger than that of MB because of the molecular structure and diameter; the molecular mass of ICG (774.9) is larger than that of MB (319.9) (16).

ICG fluorescence imaging has been favored by researchers as a new SLN tracer method since 2005. Recent meta-analysis showed that ICG has SLN detection rate from 81.9% to 100% and sensitivity from 65.2% to 100%. No statistical difference in detection rate and sensitivity was found between ICG combined with RI tracer and ICG alone (17).

The key factor in evaluating the quality of SLNB is the false-negative rate. False negative means that metastatic lymph nodes are not detected, and the tumor stage is underestimated. This phenomenon leads to inadequate systemic treatment and increases the risk of local recurrence and distant metastasis. Another meta-analysis based on six studies reported 8% false negative rate when using ICG as a tracer (18). In the National

Surgical Adjuvant Breast and Bowel Project B-32 trial including 5611 patients with clinically negative axillary lymph nodes, a false negative rate of 9.8% is found when using combined blue dye and RI double tracer (4); this value was comparable to that of ICG. Findings about the comparability of false negative rate (FNR) between ICG and dual tracer of RI and blue dye are inadequate and thus require additional clinical trials for validation. On the basis of the above data, MB combined with ICG can be a new dual-tracer method to replace RI plus blue dye, especially for institutions without access to RI. This novel method have the following advantages over the gold standard: a) projection real-time navigation with advanced image processing for lymphatic visualization, b) no involvement of physicians from the nuclear medicine department prior to the operation, and c) easy transportation and preservation.

The median number of removed SLNs is 1.5–3.4 under the guidance of conventional NIR system with ICG fluorescence (11) and 3 under guidance of individual LFIS and conventional NIR system. The median number of SLNs excised by blue dye is 2, which is significantly lower than that by ICG methods ($P < 0.05$). Compared with blue dye, the NIR fluorescence imaging system shows sensitivity even at low concentrations that are visible to the naked eye (19) and detects more SLNs. The increase in the number of SLNs detected within the appropriate range can avoid excessive interference in the axillary tissue and enable an accurate and full evaluation of lymph node condition. Extracting only one SLN has a high risk of false negative. To date, 3–4 SLNs are needed to identify more than 97% positive lymph nodes. In combination with postoperative complications, the extraction of no less than 4 SLNs is currently recommended (20).

As for the result that ICG combined with MB is superior to MB alone, we believe that ICG and MB can complement each other. The ICG can show where the lymphatic vessels are going, and along the way we can find the sentinel lymph nodes, which have a navigation function. However, it is difficult to avoid the leakage of ICG after the removal of the first sentinel lymph node, resulting in the "pollution" of the fluorescent signal in the operative field, which increases the difficulty of subsequent lymph node biopsies. At this time, MB serves as a tracer for the naked eye to find blue-stained lymph nodes, providing further localization. In our study, 7 SLNs (3.8%) in the ICG + MB group were only blue, indicating that ICG alone may have resulted in partial lymph node escape.

In a case in this study, two SLNs were detected by the two fluorescence imaging systems but not by MB. These two lymph nodes were re moved and pathologically indicated as lacking lymph node tissues. This finding revealed the limitations of ICG as a tracer. The leakage of ICG caused by intraoperative lymphatic vessel damage and its high sensitivity resulted in the occurrence of non-lymph node fluorescence images in the operative field. This phenomenon is called "contamination", which may cause the difficulty of lymph node localization.

In this study, three patients had no percutaneous fluorescence signal and superficial lymphangiography but showed ICG lymph nodes as revealed by conventional incision. Body Mass Index (BMI) is negatively correlated with lymphatic vessels, and injection depth and fat thickness are the main factors affecting ICG sensitivity (21). However, no correlation was found between lymphatic vessels and the detection rate of fluorescent lymph nodes. In the three cases without lymphatic vessel images, fluorescent lymph nodes were observed through conventional incision. The surgeon's intuitive feeling is that the difficulty of SLNB is relatively high for obese patients. Hence, the difficulty of surgery must be quantified afterward, and the operation time should be measured.

In this study, the number of ICG lymph nodes was negatively and weakly correlated with BMI. In a similar study, patients with high BMI (≥ 22 Kg/m^2) have fewer removed SLNs than those with lower BMI, but no statistical difference was observed (22).

The advantage of the LFIS over the Langfang imager, devices from Hamamatsu Photonics and Novadaq is its in-situ projection navigation, while obtaining information on lymph node development and adjacent anatomy in the operative field. At the same time, the instrument cost is lower than the previous NIR fluorescence system, including the Langfang imager, devices from Hamamatsu Photonics and Novadaq. One weakness of the LFIs used in the study was that they projected light on the skin at a lower contrast than the screen-developed images of the three devices mentioned earlier, which could cause tiny details to be lost. To solve this problem, we can turn off the operating light during the operation, or increase the brightness of the projection in a subsequent product update.

About the use of near-infrared fluorescence in breast cancer and not just sentinel lymph node biopsy. The Langer's axillary arch (LAA) is a ventral extension of the anterior margin of the latissimus dorsi. Some breast cancer patients have this mutation, resulting in the failure of a posterior LAA lymph node biopsy or lymph node dissection (23). The LFIS may have great prospects for detecting and managing LAA axillary lymph nodes. Considering the tissue penetration of ICG fluorescence imaging, it is possible to detect the fluorescence signal of lymph nodes behind the LAA without truncation. Compared to radioisotope, ICG has a visual advantage, as the in-situ fluorescence signal of our new technology and the close combination of anatomical structures in the surgical field give surgeons a clearer navigation. If possible, we would like to carry out related studies.

This study has some limitations. First, in this study, ICG fluorescence assisted SLNB was not compared with gold standard method. Secondly, relatively small sample size cannot fully reflect the influencing factors of sentinel lymph node biopsy. For example, we do not have a large enough sample size to determine whether BMI is a factor in the number of sentinel lymph nodes guided by LFIS. But we introduced a new surgical navigation system. The study contributes to the growing evidence of the effectiveness of ICG and provided more opportunities for the use of ICG in SLNB. It is a limitation that this single arm design study also limited our opportunity to compare the quantitative timing of sentinel lymph node biopsies with the two NIR systems.

CONCLUSION

The novel real-time *in situ* navigation system is a promising instrument for SLNB in breast cancer. The lymphangiography

and SLN development of LFIS are consistent with those of the conventional NIR system. The combination of fluorescence by LFIS and MB may be alternative to the standard method of combined RI and blue dye because of its high detection rate, radiation-free, and operation fluency. This technique satisfies the surgeons' demand of navigation operation and can be used in various surgical fields.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Institutional Research Ethics Committee of the First Affiliated Hospital of Anhui Medical University (PJ2017-11-04). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

ZW, XY, and PL designed the experiment. ZW and JP analyzed the patient data and wrote papers. CH and YP recorded data. ZW, XY, and JW provided important information of writing and revising manuscript. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2021.621914/full#supplementary-material

Image 1 | Flow diagram for the progress of patients.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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REVIEW
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Evolving Trends in Surgical Management of Breast Cancer: An Analysis of 30 Years of Practice Changing Papers

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The management of breast cancer has evolved into a multidisciplinary evidence-based surgical speciality, with emphasis on conservative surgery. A number of landmark trials have established lumpectomy followed by radiation as the standard of care for many patients. The aim of this study is to construct a narrative review of recent developments in the surgical management of breast cancer and how such developments have impacted surgical practice. A comprehensive literature search of Pubmed was conducted. The latest search was performed on October 31st, 2020. Search terms "breast cancer" were used in combinations with specific key words and Boolean operators relating to surgical management. The reference lists of retrieved articles were comprehensively screened for additional eligible publications. Articles were selected and reviewed based on relevance. We selected publications in the past 10 years but did not exclude commonly referenced and highly regarded previous publications. Review articles and book chapters were also cited to provide reference on details not discussed in the academic literature. This article reviews the current evidence in surgical management of early-stage breast cancer, discusses recent trends in surgical practice for therapeutic and prophylactic procedures and provides commentary on implications and factors associated with these trends.

Keywords: breast cancer, breast cancer surgery, mastectomy, axilla, breast conserving therapy

INTRODUCTION

Breast surgery is a complex multi-disciplinary surgical specialty. The breast surgeon must diagnose and treat breast cancer in symptomatic patients and coordinate the timing of surgery as dictated by systemic and radiation therapies. Treatment varies on a case-by-case basis from breast conserving surgery to mastectomy to specialized oncoplastic techniques and reconstructive procedures. Since

the first Halsted radical mastectomy the range of surgical approaches has increased greatly. Following the introduction of the modified radical mastectomy it took almost 30 years for breast conserving surgery and adjuvant radiotherapy became an accepted standard of care (1).

Breast surgeons further challenged breast conserving surgery (BCS) in pursuit of improving cosmesis while maintaining oncological outcomes. This paradigm shift towards better cosmetic outcomes and quality of life led to the advent of oncoplastic surgery (2).

This paper will discuss the advances in the surgical management of breast cancer over the last 30 years while also providing an overview of emerging surgical options and the future they bring to the sphere of breast cancer management.

FROM MASTECTOMY TO BREAST CONSERVATION

Breast surgery has undergone significant changes over time. First, Halsted's radical mastectomy gained widespread acceptance as the standard of care up until 1960's. While this procedure improved local control, the extensive dissection of skin, breast, pectoralis muscles and axillary contents caused significant morbidity (3). Furthermore, to improve its curative potential some surgeons also excised the internal mammary nodes. This became known as an extended radical mastectomy. However this did not improve patient survival (4, 5).

To reduce morbidity, Patey introduced the modified radical mastectomy (MRM) excising the breast, pectoralis major fascia, and level I and II axillary lymph nodes (6). At the same time McWhirter introduced the simple mastectomy which combined surgery with radiotherapy. Several randomised controlled trials investigated survival outcomes of these two methods compared to Halsted's radical mastectomy. The National Surgical Adjuvant Breast and Bowel Project (NSABP) B-04 trial observed no significant improvement in survival for patients treated with Halsted radical mastectomy compared to less extensive surgery. NSABP B-04 also found the addition of local-regional radiation to total mastectomy had no significant advantage in overall survival (OS). Additionally, it found that in node negative disease, routine axillary lymph node dissection (ALND) is overly aggressive (7). As such, this trial heralded the move toward increasingly conservative surgical management of breast cancer along with introducing the first concept of multi-modality therapy.

The NSABP B-06 trial was the first trial to establish BCS as a feasible treatment option for early invasive breast cancer when used in conjunction with radiation (8). No significant difference in OS or disease-free survival (DFS) was found in patients receiving BCS with or without radiation compared to those receiving modified radical mastectomy. The rate of local regional recurrence (LRR) was significantly higher in those who underwent lumpectomy without radiation (8).

The Milan Cancer Institute (Milan I Study) further established BCS as the standard of care for early breast cancer (≤2cm in diameter). Despite higher local recurrence in the BCS group, there was no significant difference in long-term survival in those who underwent radical mastectomy compared to BCS and radiotherapy (1). **Table 1** outlines the landmark randomised controlled trials (RCT) in the surgical management of non-invasive and invasive breast cancer. **Figure 1** is a timeline of landmark trials in the surgical management of breast cancer.

BCS focuses on three primary aims; obtain tumour free margins, achieve a good cosmetic outcome, and at least equivalent survival to traditional mastectomy. As such the following contraindications must be considered before proceeding with BCS:

TABLE 1 | Landmark RCT in the surgical management of non-invasive and invasive breast cancer.

Trial Name	Study years	No. Participants	Population Characteristics	Mean follow-up (years)	Intervention	Primary outcome
NSABP B-04 (7)	1971-1974	1079	Arm 1: Clinically node negative Arm 2: node-positive disease	25	Radical mastectomy vs simple mastectomy and local nodal irradiation vs simple mastectomy with ALND	DFS: No significant difference RFS: No significant difference DDFS: No significant difference OS: No significant difference
NSABP B-06 (8)	1976-1984	2163	<4 cm invasive breast cancer with either negative or positive axillary lymph nodes	20	Lumpectomy and ALND with or without breast radiation vs modified radical mastectomy	DFS: No significant difference DDFS: No significant difference OS: No significant difference
MILAN I STUDY (1)	1973-1980	701	< 2cm and clinically node negative	20	Radical mastectomy vs breast-conserving surgery (quadrantectomy) followed by radiotherapy	OS: No significant difference LRR: cumulative incidence of recurrence after 20 years was 8.8% for the BCS group and 2.3% for the radical mastectomy group ($p < 0.001$)
NSABP B-17 (9–11)	1985–1990	818	Localized DCIS	12	Lumpectomy alone vs lumpectomy plus breast irradiation	OS: No significant difference Cumulative incidence of non-invasive ipsilateral breast cancer recurrence: Reduced with breast radiation from 14.6% to 8.0% ($p < 0.01$). Cumulative incidence of invasive ipsilateral recurrence: reduced from 16.8% to 7.7% ($p < 0.01$)

SLNB, sentinel lymph node biopsy; ALND, axillary lymph node dissectio; OS, overall survival; DFS, disease-free survival; RFS, recurrence free survival; DDFS, distant disease free survival; QOL, quality of life.

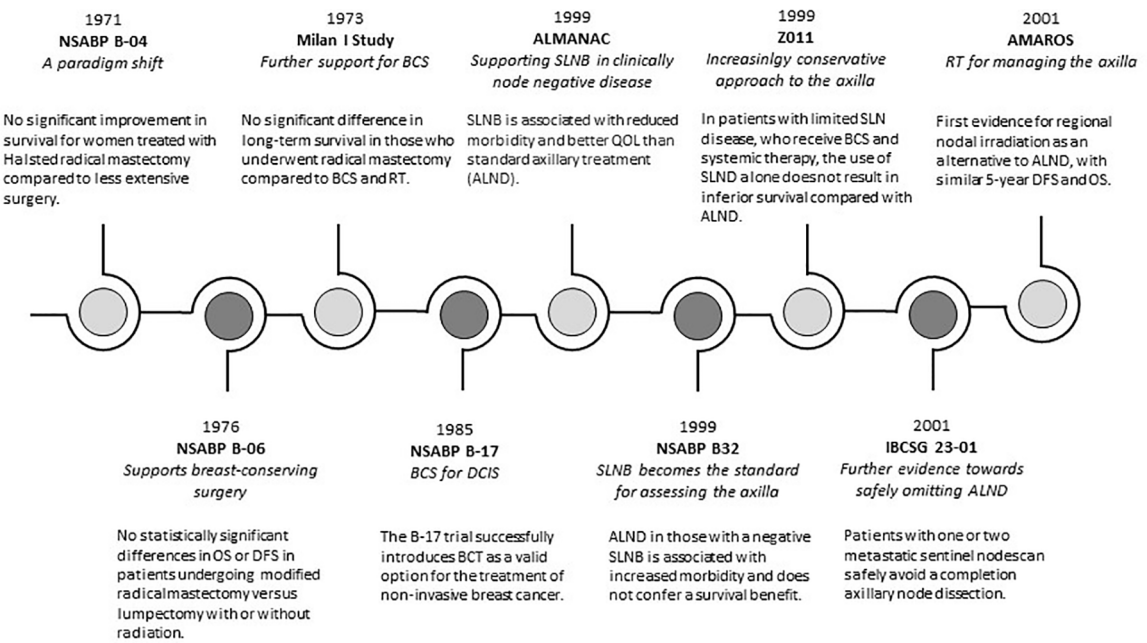

FIGURE 1 | A timeline of evolving trends in surgical management of breast cancer. OS, overall survival; DFS, disease free survival; BCS, beast conserving surgery; RT, radiotherapy; QOL, quality of life; SLNB, sentinel lymph node biopsy; ALND, axillary lymph node dissection.

-*Multicentric disease* - Two or more primary tumours in different quadrants of the breast such that they cannot be removed with a single excision

-Presence of *diffuse malignant-appearing calcifications* on imaging (mammogram or magnetic resonance imaging [MRI])

-*Previous history of chest radiotherapy* - which, when combined with the proposed treatment, would result in an excessively high total radiation dose to the chest wall

-*Pregnancy*

-*Persistently positive margins* despite attempts at re-excision

Furthermore, a consideration, but not an absolute contraindication to BCS is a large tumour in a relatively small breast. Neoadjuvant chemotherapy (NACT) is increasingly used in these patients for the purpose of downstaging the tumour and thus, making the patient eligible for BCS (12–14). Notably when compared to adjuvant chemotherapy, those receiving NACT do not benefit in terms of survival and local recurrence (12, 13, 15).

Local recurrence is a risk factor for distant metastasis (16). The local recurrence rate after BCS (2% at 10 years) is no longer considered higher than that after mastectomy (17, 18). Risk factors for local recurrence include young age, positive surgical margins, node positivity, estrogen receptor negativity, and absence of radiation therapy (19). Surgical margins are a controllable risk factor. Current recommendations for the adequacy of margins are based off a large meta analyses in 2014, which included 1506 ipsilateral breast tumour recurrences (IBTRs) (20). At a median follow-up of 79 months, the median prevalence of IBTR was 5.3%. A positive margin, defined as "ink on tumour", was associated with more than a two-fold increase in IBTR. Routine re-excision is not necessary for close positive margins (e.g. <1 mm), however clinical and pathological features should guide decisions to perform a second operation (21, 22). Positive margins are associated with a two-fold increase in LRR (20) and necessitate reoperation. Rates of reoperation vary from less than 10% to more than 50% (23–25).

INCREASING MASTECTOMY RATES

It was expected that rates of mastectomy would decrease with the availability of screening mammography. However, the effect of screening on surgical treatment has yielded conflicting results (26, 27). Increasing rates of prophylactic mastectomies may partially account for unchanged mastectomy rates, offsetting the benefits of advances in BCS (28). Improvements in reconstruction options have brought about an unanticipated increase in contralateral prophylactic mastectomy rates. A once disfiguring procedure, patients and surgeons are now more aware of symmetry and cosmesis post-surgery. Low satisfaction scores among patients undergoing unilateral mastectomy with implant-based reconstruction suggests cosmetic factors may be a driver of increasing contralateral prophylactic mastectomy rates (29, 30).

Furthermore, some patients with early-stage breast cancer who are suitable for BCS, choose to undergo mastectomy instead. While the reasons for this are unclear, they may in part be attributed to a fear of recurrence, thus triggering a move towards

more "aggressive" management approaches. However, it is important to note in young patients with early-stage breast cancer, BCS with adjuvant radiotherapy has comparable OS to mastectomy alone (31). This has been seen in a number of studies which have demonstrated improved OS and DFS in BCS compared to mastectomy (32–38). BCS may in fact have superior LRR compared to mastectomy due to a number of factors (39), including developments in radiation treatment planning which have resulted in increased coverage of residual breast tissue compared to techniques in original trials. Improvements in imaging modalities have resulted in more accurate selection of patients for BCS i.e. those without multicentric disease. Finally, with newer less invasive mastectomy techniques gaining popularity, it is conceivable that techniques such as nipple/skin sparing mastectomy are being adopted in patients that have less favourable tumour characteristics than those in the studies in which these approaches were initially assessed (40).

MANAGEMENT OF THE AXILLA

Management of the axilla has evolved in the last decade. Axillary nodal metastasis is a significant prognostic factor in breast cancer, influencing surgical and adjuvant treatment (41, 42). While the surgical approach to the axilla has become increasingly conservative, the optimal management of the axilla continues to be a controversial topic.

Traditionally all patients proceeded to ALND irrespective of nodal status (43). ALND is associated with significant morbidity including lymphedema, impaired shoulder movement and arm sensation, resulting in a considerable impact on quality of life (44, 45). The NSABP B32 trial randomized 5611 patients with clinically node-negative disease and a negative SLNB into two groups, ALND *versus* no further treatment. It found no significant difference in OS, DFS, or LRR between both groups. This demonstrated that ALND in those with a negative SLNB does not confer any survival benefit (46). SLNB was ultimately established as optimum standard for surgically assessing the axilla.

The extent of metastatic disease within the SLN is of prognostic importance. Nodal involvement is classified as macro-metastatic (>2mm), micro-metastatic (<2mm) or as isolated tumour cells (ITC). A systematic review found that the presence of micro-metastases is associated with decreased OS (47). The IBCSG 23-01 (48) and the AATRM 048 (49) trials, in which the majority of patients received adjuvant systemic therapy, demonstrated that ALND does not confer survival benefits in those with micro-metastatic nodal disease. As a result, many surgeons now omit ALND in patients with ITC or micro-metastatic disease on SLNB.

In cases of macro-metastatic disease, ALND has remained the standard of care (50). However, the ACOSOG Z0011 (51) questioned whether this represented overtreatment. In this phase 3 non-inferiority trial, 856 patients with T1 to T2 tumours with less than 2 positive SLNs were randomized to ALND *versus* no ALND, after breast conserving surgery (BCS), SLNB, and adjuvant whole-breast irradiation (WBI). The 5-year OS was higher in the SLNB group compared to those receiving ALND (92.5% *versus* 91.9% respectively). The 5-year DFS was also higher in the SLNB group (83.9%) compared to the ALND group (82.2%). While not significant, the 10-year LRR was 5.3% in the SLNB group, *versus* 6.2% in the ALND group. These results have been practice-changing for many surgeons. However, the Z0011 results have also added to the controversy surrounding optimal management of the axilla (52–54). This comes from the fact that Z0011 inclusion criteria were set at patients with tumours up to 5cm in size who underwent BCS and received WBI postoperatively. Furthermore, this study also failed to enrol the planned number of patients and thus did not have sufficiently high power to detect small differences between the groups.

As the approach to the axilla continues to evolve, the use of an oncologically safe alternative to ALND has been investigated. The AMAROS (55) trial included 4806 patients with T1 to T2, clinically node-negative invasive breast cancer and a positive SLNB. Patients were randomized to receive ALND or regional nodal irradiation (RNI). All underwent BCS followed by WBI, or mastectomy with or without chest wall irradiation. This trial provided evidence for regional nodal irradiation (RNI) as an alternative to ALND, with similar 5-year DFS and OS. The Edinburgh trials (56) randomized patients with N1 disease into ALND *versus* SLNB with RNI. This trial reported a significant difference in LRR, which was not seen in the AMAROS trial, concluding that there was no significant difference in OS between ALND and RNI. Now, several countries offer axillary radiotherapy as an alternative to ALND. The POSNOC trial aims to add to the evidence for radiotherapy in axillary management in patients with macro-metastatic nodal disease undergoing BCS and systemic therapy (57). **Table 2** outlines the landmark RCTs in the surgical management of the axilla.

Despite this shift towards a conservative approach, some studies have raised the possibility that failure to remove nodal disease could be harmful. Park et al. (59) suggest that the rate of axillary recurrence among patients with a positive SLNB who did not undergo ALND was 2.0% at 30 months *versus* 0.4% in those receiving ALND. Additionally, a retrospective review of 257,157 patients diagnosed with breast cancer in the Surveillance, Epidemiology, and End Results (SEER) database revealed decreased survival in patients with stage IIA or higher disease with increased number of positive nodes and increased ratio of positive to total nodes removed (60).

Considering the conflicting data, many ongoing trials aim to clarify the aforementioned studies and strengthen the rationale for omitting extensive axillary surgery. The SENOMAC trial (61) is comparing ALND *versus* no ALND after surgery with the primary endpoint being DFS at 5 years. Coming almost full circle, some clinicians are examining the utility of SLNB itself. For example there is a growing interest in omitting SLNB in early breast cancer patients with a clinically and radiologically negative axilla (62, 63). However, other studies caution that despite a radiologically negative axilla there is a risk of high nodal burden axillary metastasis, particularly in T2 tumours. As such these patients should continue to undergo SLNB (64). Surgeons await

TABLE 2 | Landmark RCT's in the surgical management of the axilla.

Trial Name	Study years	No. Participants	Population Characteristics	Mean follow-up (months)	Intervention	Primary outcome
Landmark RCT's in the surgical management of the axilla						
ALMANAC (58)	1999–2003	1031	Any tumor size and clinically node-negative breast cancer	12	ALND vs SLNB alone (if negative) or SLNB and ALND or axillary RT (if positive)	Arm and shoulder morbidity and QOL: SLNB was associated with reduced arm morbidity and better QOL.
NSABP B32 (46)	1999–2004	5611	<4 cm invasive breast cancer and clinically node-negative breast cancer	96	SLNB + ALND *vs* SLNB alone (if negative)	OS: No significant difference DFS: No significant difference Axillary recurrence: No significant difference
Landmark RCT's comparing ALND with no further treatment for patients with positive SLNB						
Z0011 (51)	1999–2004	856	T1-2 breast cancer, and 1-2 metastatic nodes by SLNB. All underwent lumpectomy and whole-breast irradiation	76	ALND vs No further axillary treatment	OS: No significant difference DFS: No significant difference
IBCSG 23-01 (48)	2001–2010	931	<5 cm invasive breast cancer and 1 or more micrometastatic sentinel nodes	60	ALND vs No further axillary treatment	OS: No significant difference DFS: No significant difference
Landmark RCT's comparing ALND with axillary radiotherapy for patients with positive SLNB						
AMAROS (55)	2001–2010	4805	T1-2 primary breast cancer and no palpable lymphadenopathy	73	ALND vs Axillary radiation	OS: No significant difference DFS: No significant difference Axillary recurrence: 0.43% ALND vs 1.19% axillary radiation

SLNB, sentinel lymph node biopsy; ALND, axillary lymph node dissection; OS, overall survival; DFS, disease-free survival; QOL, quality of life.

the results from two RCTs, both the SOUND trial (Sentinel Node Vs Observation after Axillary Ultrasound) (NCT02167490) and the Intergroup-Sentinel-Mamma (INSEMA) trial (NCT02466737) which examine the role of AUS and SLNB in early breast cancer. It is possible that these trials will help negate surgical biopsy requirements in select patient groups, therefore advancing conservative axillary management further (65, 66). Whether we can omit the ALND from the management of patients with breast cancer altogether remains to be seen. However, the trajectory to date has seen the management of the axilla evolve from a low threshold for performing ALND to an increasingly conservative one, consequently improving morbidity and patient outcomes.

ONCOPLASTIC SURGERY AND RECONSTRUCTION

The primary aim of breast cancer surgery is complete tumour excision. However, improved cosmetic outcomes achieved with breast reconstruction continues to positively affect patient quality of life (67). This has given rise to the concept of oncoplastic breast surgery, which aims to provide an acceptable breast appearance while maintaining oncological effectiveness.

A variety of oncoplastic procedures have been described, and location of cancer within the breast is a major determinant of procedure choice (68–70). A 2014 meta-analysis found that patients treated with oncoplastic resections had a lower rate of positive margins (12% versus 21%) and a lower rate of re-excisions (4% versus 15%). Although patients undergoing oncoplastic surgery had a higher rate of completion mastectomies compared with those who underwent BCS (7% vs 4%), oncoplastic resections produced a higher satisfaction with breast appearance then standar BCS (90% vs 83%) (71–73). Furthermore, patients who underwent oncoplastic resections developed fewer complications (16% vs 26%) and decreased rates of local recurrence (4% vs 7%) at 3-5 year follow up, demonstrating that the long-term outcomes of oncoplastic surgery are comparable, if not better than standard BCS (71).

One of the first oncoplastic procedures that came into practice was the skin-sparing mastectomy (SSM), in which the breast parenchyma is excised, and most of the breast skin envelope is maintained (74). SSM has become a popular choice of procedure for patients with DCIS, early stage breast cancer as well as high-risk patients opting for prophylactic mastectomy due to its excellent cosmetic outcomes and acceptable oncological safety profile when compared to conventional mastectomy without reconstruction. Another commonly performed procedure is the nipple sparing mastectomy (NSM), used for high-risk women undergoing prophylactic surgery and also in select patients undergoing therapeutic mastectomy (75). This procedure preserves the nipple-areolar complex but removes major ducts from within the nipple lumen (76). A meta-analysis in 2018 demonstrated comparable 5 year DFS and LRR between NSM and SSM (77). Equally in a 2015 meta-analysis the OS, DFS, and LR rates of NSM were comparable to modified radical mastectomy and SSM (78).

Breast reconstruction can be performed using several techniques including an expander/implant and/or autologous tissues. Opinion within the surgical community regarding

immediate breast reconstruction has evolved over time (79, 80). When planning the optimal reconstructive option, surgeons must consider patient-specific factors such as likelihood of postoperative radiation, prior breast radiation as well as patient preference. Typically, delayed reconstruction is indicated when there is impaired perfusion of the skin flaps post-mastectomy or when post-mastectomy radiotherapy will be needed (81). However, the absolute contraindication of immediate autologous reconstruction due to the challenges posed by post-mastectomy radiotherapy is increasingly being questioned. While radiotherapy after immediate autologous reconstruction had been thought to have a detrimental impact on flap outcome, several systematic reviews have shown no significant differences in measurable postoperative complications when comparing irradiated versus non-irradiated reconstructions. As such, immediate DIEP flap reconstruction in patients who need post-mastectomy radiation is an acceptable treatment option (82, 83). In the setting of inflammatory breast cancer where the presence of dermal lymphatic invasion often requires skin excision, a delayed reconstruction is more appropriate. However, often in cases of inflammatory breast cancer a decision is made not to proceed with reconstruction altogether.

RISK REDUCING SURGERY

A growing list of breast cancer susceptibility genes accompanies the ever-increasing amount of published clinical data. High-penetrance breast cancer susceptibility gene mutations associated with inherited breast cancer syndromes, such as BRCA1, BRCA2, PTEN (Cowden's syndrome), TP53 (Li Fraumeni syndrome), STK11 (Peutz-Jeghers syndrome), CDH1 (hereditary invasive lobular breast-diffuse gastric cancer) and those with an associated family history account for approximately 10% of breast cancers (84). BRCA1/2 mutations occur in 3-4% of all patients with breast cancer and in 10% of those with triple negative breast cancer (85, 86). Moderate penetrance breast cancer susceptibility gene mutations such as PALB2, CHEK2, ATM occur in 4-6% of breast cancer patients (85). Generally, it is advised that high-risk patients undergo more frequent screening, use of imaging modalities and consider prophylactic risk reducing surgery. Recently published guidelines offer recommendations on the management of breast cancer in patients with germline mutations in BRCA1/2, PALB2, CHEK2 and ATM (87).

Bilateral prophylactic mastectomy reduces the risk of breast cancer by 95% in patients with BRCA 1&2 mutations, and by 90% in those with a strong family history of breast cancer (88). Prophylactic mastectomy may be performed using many of the techniques described. Contralateral prophylactic mastectomy is considered for patients with a high lifetime risk for developing contralateral breast cancer, such as BRCA mutations, strong family history, or young patients with aggressive disease (87). Bilateral prophylactic salpingo-oopherectomy can reduce the risk of ovarian cancer by approximately 80% and the risk of all-cause mortality by 68% (89). Decisions regarding prophylactic mastectomy must be individualized for every patient. Benefits of the reduced anxiety relating to developing breast cancer must be balanced against risks of surgery, complications from reconstructive surgery as well as any potential adverse feelings relating to body image.

As family history breast clinics are further incorporated into routine clinical practice worldwide and as next-generation sequencing continues to become more accessible, it is expected that there will be an increase in the number of BRCA1/2 mutations diagnosed each year and at an earlier age. Thus, forward planning by policy makers for the provision of all aspects of patient management, including genetic counselling, surgery, radiotherapy, and oncological therapy, are required.

NOVEL THERAPEUTICS

Interventional Radiology (IR)

The use of IR-guided cryoablation as a minimally invasive technique to treat primary breast tumours is being explored (90). Through repetitive freezing/thawing cycles or rapidly decompressing argon gas, cryoablation results in cell injury and coagulative necrosis (91). Some studies have demonstrated feasibility of cryoablation for early breast cancer treatment (92, 93). Ongoing trials are investigating complete response rate and local recurrence without subsequent surgery (FROST trial – NCT01992250; Ice3 trial – NCT02200715). This emerging modality may be most useful in those with significant co-morbidities who are less suitable for surgical resection. Other image-guided ablation techniques include radiofrequency ablation, microwave ablation, high-intensity focused ultrasound, laser ablation and irreversible electroporation (94).

Neoadjuvant Chemotherapy and Non Operative Strategies

Neoadjuvant treatments are increasingly being used in high-risk breast cancers such as triple negative and Her2 positive breast cancer. Neoadjuvant therapies are offered in patients at high risk of recurrence, in locally advanced disease, and to downstage the tumour to allow for BCS. Achieving a pathological complete response (pCR) is associated with improved event free survival and overall survival, particularly in triple negative and Her2 positive breast cancer (95, 96).

Patients who achieve a partial or complete response pose a clinical dilemma in applying established surgery and radiotherapy treatment protocols. Patients who demonstrate a good clinical response to neoadjuvant treatment may benefit from de-escalation strategies in the adjuvant setting based on the degree of neoadjuvant response. Optimal methods to accurately detect a complete pathological response and the oncological safety in de-escalation strategies are currently the focus of a number of trials.

One such de-escalation strategy is to provide BCS for patients previously deemed unresectable or unsuitable for BCS. In an era of targeted therapy, increased rates of pCR in the breast have been observed. However advances in response to systemic

therapy have not been matched with increased rates of BCS. It would be expected that those who achieve a complete response would be more likely to undergo BCS. However meta-analysis of RCT assessing eligibility for BCS following neoadjuvant chemotherapy found no association between rates of BCS and pCR (97). The inability to accurately detect viable tumour following neoadjuvant chemotherapy may contribute to the decision of the surgeon to perform a less radical procedure.

De-escalation of axillary management after neoadjuvant chemotherapy has also been explored following high rates of nodal pCR in patients who have histologically confirmed nodal disease (98, 99). Due to the increased likelihood of false negative sentinel node biopsy following neoadjuvant chemotherapy, de-escalation of axillary clearance to sentinel lymph node biopsy alone following neoadjuvant chemotherapy in patients who were previously clinically node positive should only be considered if 3 or more negative nodes have been retrieved.

Whether surgery can be omitted in patients receiving neoadjuvant treatment who obtain a pCR, is under investigation. A trial (NCT02945579) is evaluating patients with HER2 positive or triple negative breast cancer who forgo surgery after systemic neoadjuvant therapy.

There is currently no evidence to suggest that avoidance of surgery in patients who have a pCR is oncologically safe. Analysis of the NSABP B-18 and B-27 trials observed LRR of 6-9% in patients who had a pCR following neoadjuvant chemotherapy and BCS or mastectomy (100).

Until such a time as the accuracy of imaging and core needle biopsies can reliably determine pCR surgery with histological assessment of the resected specimen is likely to remain a corner stone of effective treatment, accurate assessment of pCR, and reduction of local regional recurrence.

FUTURE PERSPECTIVE ON BREAST CANCER SURGERY

Surgical innovation continues to drive advances in the management of breast cancer. Artificial intelligence (AI) technology and machine learning algorithms applied to diagnostic imaging and analysis of large clinical and genomic datasets in predicting response to treatment have been shown to improve patient outcomes (101–104). Once healthcare practitioners have overcome the fear of the unknown and data scientists and AI experts become more incorporated into healthcare, the future of surgical breast cancer management may change rapidly. Capabilities for storing vast amounts of data for imaging analysis can be applied to a multitude of areas from digital pathology to surgical planning. Digitization of breast cancer pathology with whole slide imaging has enabled the use of artificial intelligence machine learning algorithms to be applied to digital pathology. These advances in computer aided diagnostics have the potential to replace some of the expensive multi-gene assays (105, 106). Machine learning for image analysis will act as an adjunct to enhance human reporting, increase accuracy, and improve outcomes by predicting the likelihood of recurrent disease and dictating the optimum surgical intervention. AI have also been used to aid surgical planning using MRI based 3D reconstructions of the tumour within the breast (107).

Technological advancements in the surgical management of non-palpable breast lesions such as wire-free radar technology to provide real-time surgical guidance during breast surgery have demonstrated efficacy and are oncologically safe (108, 109). The emergence of imaging and probe-based devices to detect differences between normal and cancerous tissue have the potential to improve margins, reduce re-operation rates and avoid current labour-intensive intraoperative margin assessment techniques such as frozen section and specimen radiology. The intelligent knife (iKnife) utilizes rapid evaporative ionisation mass spectrometry of aerosol generated by electrocautery of tissue. This technique provides a rapid and effective method for identification and characterization of neoplastic tissue, guides resection *in vivo* and improves the quality of the surgical resection (110, 111). A future surgical model may include SLNB and axillary dissection with real time diagnosis for presence of axillary disease.

CONCLUSION

Advances in the surgical management of breast cancer have favoured an increasingly conservative approach. This article reviews the current evidence in surgical management of early-stage breast cancer, discusses recent trends in surgical practice for therapeutic and prophylactic procedures and provides commentary on implications associated with these trends.

AUTHOR CONTRIBUTIONS

Literature research – SK, MF. Manuscript Preparation – SK, MF. Manuscript Review – SK, MF, AH. All authors contributed to the article and approved the submitted version.

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Metastatic Pattern Discriminates Survival Benefit of Type of Surgery in Patients With *De Novo* Stage IV Breast Cancer Based on SEER Database

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Background: The role of surgery and surgery type in *de novo* stage IV breast cancer (BC) is unclear.

Methods: We carried out a retrospective cohort study that included the data of 4,108 individuals with *de novo* stage IV BC abstracted from SEER (Surveillance, Epidemiology, and End Results) data resource from 2010 to 2015. The patients were stratified into the non-surgery group, breast-conserving (BCS) surgery group, and mastectomy group. Inverse probability propensity score weighting (IPTW) was then used to balance clinicopathologic factors. Overall survival (OS), as well as the breast cancer-specific survival (BCSS), was assessed in the three groups using Kaplan–Meier analysis and COX model. Subgroups were stratified by metastatic sites for analysis.

Results: Of the 4,108 patients, 48.5% received surgery and were stratified into the BCS group (574 cases) and mastectomy group (1,419 cases). After IPTW balance demographic and clinicopathologic factors, BCS and mastectomy groups had better OS (BCS group: HR, 0.61; 95% CI: 0.49–0.75; mastectomy group: HR, 0.7; 95% CI: 0.63–0.79) and BCSS (BCS group: HR, 0.6; 95% CI, 0.47–0.75; mastectomy group: HR, 0.71; 95% CI, 0.63–0.81) than the non-therapy group. Subgroup analyses revealed that BCS, rather than mastectomy, was linked to better OS (HR, 0.66; 95% CI: 0.48–0.91) and BCSS (HR, 0.63; 95% CI: 0.45–0.89) for patients with bone-only metastasis. For patients with viscera metastasis or bone+viscera metastases, BCS achieved similar OS (viscera metastasis: HR, 1.05; 95% CI: 0.74–1.48; bone+viscera metastases: HR, 1.01; 95% CI: 0.64–1.61) and BCSS (viscera metastasis: HR, 0.94; 95% CI: 0.64–1.38; bone+viscera metastases: HR, 1.06; 95% CI: 0.66–1.73) in contrast with mastectomy.

Conclusions: Local surgery for patients with distant metastasis (DS) exhibited a remarkable survival advantage in contrast with non-operative management. BCS may have more survival benefits for patients with *de novo* stage IV BC with bone-only metastasis than other metastatic sites. Decisions on *de novo* stage IV BC primary surgery should be tailored to the metastatic pattern.

Keywords: SEER, IPTW, *de novo* stage IV BC, surgery, metastatic patterns

INTRODUCTION

There is an ongoing epidemic of breast cancer (BC) among women all over the world, and to date, it is a universally acknowledged fact that this disease is the most frequent form of cancer Lands far and near (1, 2). About 3%−8% of BC cases are detected in stage IV (3), and BC with distant metastasis (DM) is generally incurable, with a median overall survival (OS) of 2–3 years (4, 5). Given its poor prognosis, treating primary tumors in *de novo* stage IV BC remains a vital position. Treatment aims to relieve the symptoms, enhance the quality of life (QOL), as well as prolong survival (6). Advancements in systemic treatment have remarkably improved metastatic disease control along with survival (7, 8). Nonetheless, the role of surgery and surgery type in *de novo* stage IV BC treatment is unclear, and the consensus is lacking.

Numerous retrospective studies have illustrated that local surgery improves the prognoses of patients with BC with DMs (9, 10). However, three prospective randomized trials have generated controversial findings. MF07-01 trial updated their data at a median follow-up of 40 months, and a remarkably different improvement in OS was observed in favor of performing surgery (11). However, the Indian Tata Memorial, as well as ABCSG-28 POSYTIVE trials, found no association between prognosis and surgery (12, 13). Moreover, some studies suggest that surgery may even accelerate metastatic growth, adversely affecting survival (14, 15). These inconsistent outcomes are attributed to differences in metastatic patterns, which affect prognosis (11, 16–18). Thus, individualized clinical strategies are needed for *de novo* stage IV BC.

Here, we explored the survival benefits of primary surgery and surgery scheme in *de novo* stage IV BC categorized by metastatic profiles. We followed a large cohort of *de novo* stage IV BC from the population-based SEER data resource (Surveillance, Epidemiology, and End Results) from 2010 to 2015.

MATERIALS AND METHODS

Data Resource

The recent version of SEER 18 registries Custom Data (with additional treatment fields) was employed as a data resource for this retrospective longitudinal study. This database is comprised of 18 population-based cancer registries, representing about 26% of the USA population (19). SEER*-Stat V.8.3.8 (https://seer.cancer.gov/seerstat/) (Information Management Service, Inc.) was employed in generating case listing. The approved guidelines were followed in all the procedures. This study was granted approval by the ethics committee of the First Affiliated Hospital of Xi'an Jiaotong University. The consent of the participants is not required to access and use SEER data.

Patient Cohort

Cases of 14,968 individuals who had been diagnosed with stage IV BC from January 1, 2010, to December 31, 2015, were identified in the SEER data resource. According to the SEER program, diagnosis of metastases in the first 4 months of diagnosis is defined as initial stage IV BC. The demographic along with the clinicopathologic variables contained sex (female), tumor T stage, age, tumor N stage, race, histology, tumor grade, radiotherapy, type of surgery, breast subtype, chemotherapy, survival months, the status of DS, vital status, cause of death, breast-adjusted American joint committee on cancer (AJCC) sixth tumor node metastasis (TNM) stage, and marital status.

After the first selection, participants were excluded based on the following criteria: (1) patients with multiple primary tumors, (2) follow-up autopsy type or death certificate, (3) not receiving any non-surgical treatment (chemotherapy or radiotherapy), (4) unknown metastatic sites, (5) unknown breast subtype, (6) aged <18 years old, (7) missing surgical records, (8) patients without metastasis or with brain metastasis, and (9) survival time of <6 months.

About 4,108 patients with stage IV BC were enrolled. To estimate the impact of surgery on prognosis, the enrolled dataset was stratified into three groups based on operation selection: non-surgery group, breast-conserving surgery (BCS) group, and mastectomy group. Based on SEER Program Coding and Staging Manual, 2016, local tumor destruction, partial mastectomy, and subcutaneous mastectomy were regarded as BCS. Extended radical mastectomy, simple mastectomy, modified radical mastectomy, as well as radical mastectomy, were regarded as mastectomy. And "No radiation and/or cancer-directed surgery" was regarded as no radiotherapy. "No/Unknown" chemotherapy records were regarded as no chemotherapy. To evaluate surgical options for different metastatic sites, the patterns were categorized into bone-only, viscera, and bone+viscera. The screening process is outlined in **Figure 1**.

Endpoints

The patients whose data were used in this study had been followed up until November 2015. OS was the primary index, which was defined as the time beginning the diagnosis date to the date of death due to any cause, while the secondary outcome measurements were breast cancer-specific survival (BCSS), defined as the time beginning the diagnosis date to the date of death from BC.

STATISTICAL ANALYSIS

All statistical analyses were implemented in R V. 3.6.3 (https://www.r-project.org). Clinicopathologic and demographic factors were compared between non-surgery, BCS, and mastectomy groups with the chi-square test or Fisher's exact test, as appropriate. Inverse probability propensity score weighting (IPTW) (20–22) was employed to balance clinicopathologic and demographic characteristics among the above-mentioned groups. Propensity scores were calculated based on race, tumor grade, histology, tumor T stage, non-surgical treatment, tumor N stage, metastatic organs, breast subtype, age, and marital status using a generalized boosted model (GBM) for receipt of different surgeries (22, 23). Propensity score weighted log-rank tests along with Cox proportional hazard model were used to compare OS and BCSS among the three groups. OS and BCSS HR with 95% CI were determined from multivariable models corrected for baseline characteristics of the patients. Metastatic pattern subgroups were analyzed similarly.

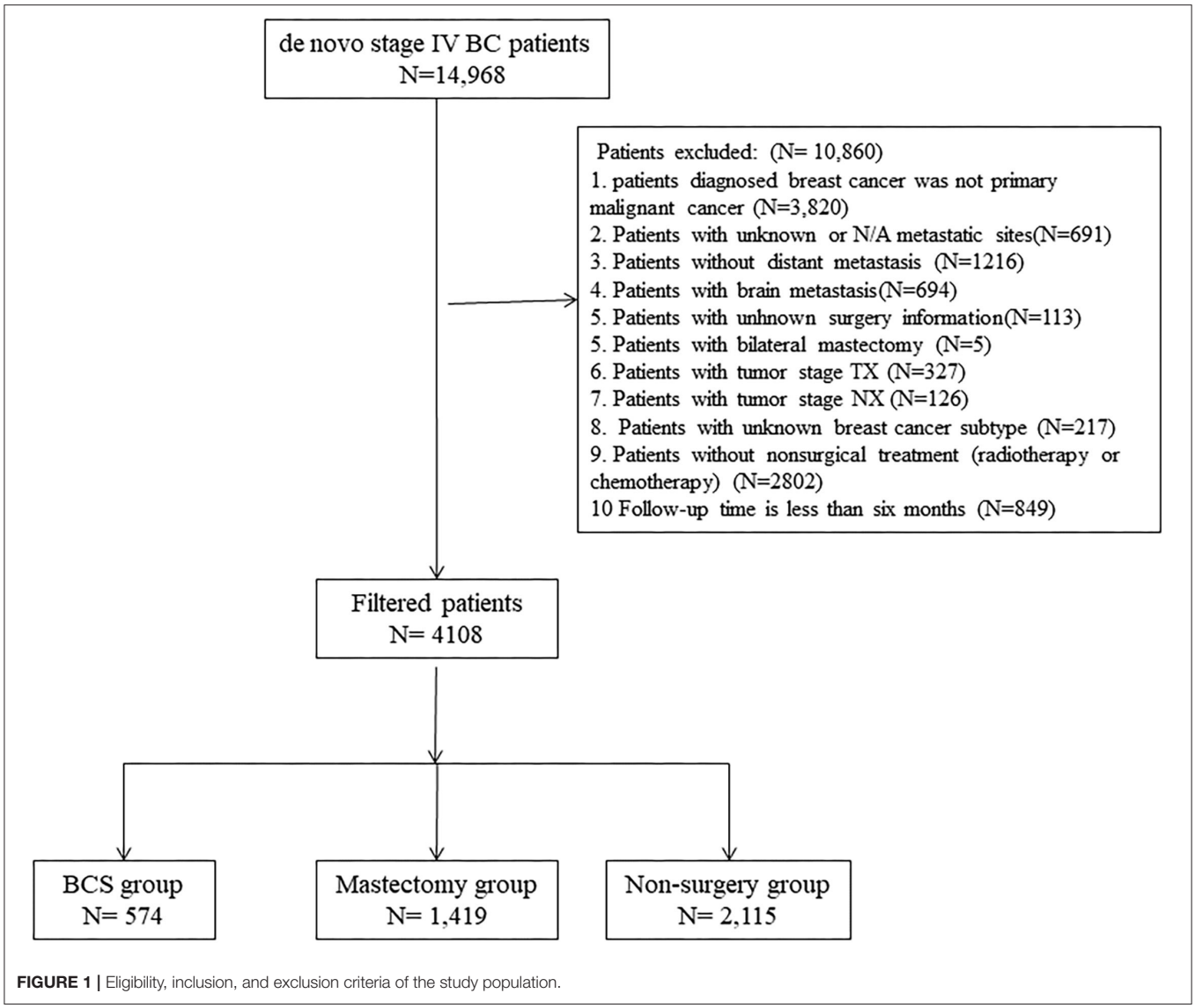

FIGURE 1 | Eligibility, inclusion, and exclusion criteria of the study population.

RESULTS

Baseline Characteristics

A total of 4,108 individuals with *de novo* stage IV BC were eligible for analyses. Of these, 51.5% were non-surgical. Of the 48.5% who received surgery, 574 and 1,419 belonged to the BCS and mastectomy groups, respectively. Of these patients, 54.5% had poorly differentiated or undifferentiated BC (grade III or IV), 82.9% had infiltrating duct carcinoma, 35.9% had T2 stage BC, 48.8% had N1 stage BC, 68% had received chemotherapy only, 45.4% had bone-only metastasis, 51.3% had Luminal A BC, 73.1% were white, and 48.6% were married. By comparing non-surgery (BCS) and mastectomy groups, remarkable differences ($p = <0.05$) were found in grade, stage, histology, T-stage, N-stage, non-surgical treatment, metastatic sites, molecular subtype, age, and marital status. Detailed information is shown in **Table 1**. Balance in patient features was attained after adjustments of the propensity score for predicting the average treatment impact (**Table 2**).

Kaplan–Meier Analysis of OS and BCSS After IPTW

About 51.3% (1,941/4,108) of the patients in this cohort study died after a median follow-up time of 27 months from diagnosis. Of these, 91.3% (1,771/1,941) were BC-specific deaths, while 8.7% (170/1,941) were due to other causes. After weighing inverse propensity score, the 3 year OS rate was 50.4, 65, and 61.5% in the non-surgery, BCS, and mastectomy group, respectively. The 5 year OS rate was 26.8, 44.6, and 40.5% in the non-surgery, BCS, and mastectomy group, respectively. The 3 year BCSS rate was 52.3, 66.3, and 62.7% in the non-surgery, BCS, and mastectomy group, respectively. The 5 year BCSS rate was 29, 48.8, and 42.9% in the non-surgery, BCS, and mastectomy

TABLE 1 | The baseline characteristics of patients with different surgery procedures in the SEER database.

ITEMS	Total	BCS	Mastectomy	Non-surgery	*P-value*
	N (%)	*N* (%)	*N* (%)	*N* (%)	
	4,108 (100)	574 (14)	1,419 (34.5)	2,115 (51.5)	
Age	55.32 (13.05)	56.28 (12.79)	54.71 (13.28)	55.47 (12.94)	0.04
Grade					<0.001
I–II	1,869 (45.5)	255 (44.4)	574 (40.5)	1,040 (49.2)	
III–IV	2,239 (54.5)	319 (55.6)	845 (59.5)	1,075 (50.8)	
Histology					<0.001
Infiltrating duct carcinoma	3,404 (82.9)	490 (85.4)	1,126 (79.4)	1,788 (84.5)	
Other	704 (17.1)	84 (14.6)	293 (20.6)	327 (15.5)	
T_stage					<0.001
T1	443 (10.8)	112 (19.5)	102 (7.2)	229 (10.8)	
T2	1,474 (35.9)	321 (55.9)	481 (33.9)	672 (31.8)	
T3	811 (19.7)	70 (12.2)	319 (22.5)	422 (20.0)	
T4	1,380 (33.6)	71 (12.4)	517 (36.4)	792 (37.4)	
N_stage					<0.001
N0	718 (17.5)	152 (26.5)	150 (10.6)	416 (19.7)	
N1	2,005 (48.8)	237 (41.3)	571 (40.2)	1,197 (56.6)	
N2	628 (15.3)	100 (17.4)	328 (23.1)	200 (9.5)	
N3	757 (18.4)	85 (14.8)	370 (26.1)	302 (14.3)	
Non-surgical treatment					<0.001
Chemotherapy	2,795 (68.0)	225 (39.2)	659 (46.4)	1,911 (90.4)	
Radiotherapy	363 (8.8)	119 (20.7)	147 (10.4)	97 (4.6)	
Radiotherapy+Chemotherapy	950 (23.1)	230 (40.1)	613 (43.2)	107 (5.1)	
Metastatic sites					<0.001
Bone+viscera	1,110 (27.0)	91 (15.9)	251 (17.7)	768 (36.3)	
Bone_only	1,867 (45.4)	325 (56.6)	747 (52.6)	795 (37.6)	
Viscera	1,131 (27.5)	158 (27.5)	421 (29.7)	552 (26.1)	
Molecular subtype					0.001
HER2-enriched	489 (11.9)	57 (9.9)	174 (12.3)	258 (12.2)	
Luminal A	2,106 (51.3)	317 (55.2)	729 (51.4)	1,060 (50.1)	
Luminal B	948 (23.1)	117 (20.4)	293 (20.6)	538 (25.4)	
Triple-negative	565 (13.8)	83 (14.5)	223 (15.7)	259 (12.2)	
Race					
White	3,004 (73.1)	430 (74.9)	1,041 (73.4)	1,533 (72.5)	0.49
Unwhite	1,104 (26.9)	144 (25.1)	378 (26.6)	583 (27.5)	
Marital status					0.009
Married	1,996 (48.6)	306 (53.3)	716 (50.5)	974 (46.1)	
Single	1,930 (47.0)	242 (42.2)	639 (45.0)	1,049 (49.6)	
Unknown	182 (4.4)	26 (4.5)	64 (4.5)	92 (4.3)	

HER2, human epidermal growth receptor 2; BCS, breast-conserving surgery.

group, respectively. Compared to non-surgery patients, BCS and mastectomy recipients had significantly higher OS (BCS group: 95% CI: 0.49–0.75, $p = <0.001$, HR, 0.61; mastectomy group: HR, 0.7, 95% CI: 0.63–0.79, $p = <0.001$) and BCSS (BCS group: HR, 0.6, 95% CI: 0.47–0.75, $p = <0.001$; mastectomy group: HR, 0.71, 95% CI: 0.63 0.81, $P < 0.001$) in patients with stage IV BC (**Figures 2A,B**).

Univariate Along With Multivariate Cox Regression Model Analysis of MaBC Patients After IPTW

Univariate Cox analysis revealed that age, tumor grade, race, T-stage, type of surgery, non-surgical treatment, molecular subtype, metastatic pattern, and marital status were remarkably linked to OS and BCSS (**Table 3**). To identify independent predictors for OS and BCSS, multivariate Cox proportional hazard regression analysis was conducted. After adjusting clinical factors and considering propensity score in the Cox proportional hazard regression models, we found that relative to non-surgery patients, patients in BCS group and mastectomy group exhibited better OS (BCS group: HR, 0.59, 95% CI: 0.47–0.75, $p = <0.001$; mastectomy group: $p = <0.001$, HR, 0.68, 95% CI: 0.59–0.77) and BCSS (BCS group: HR, 0.58, 95% CI: 0.45–0.75, $p = <0.001$; mastectomy group: HR, 0.69, 95% CI: 0.6–0.79, $p = <0.001$). Additionally, age, grade, tumor grade, T-stage, non-surgical treatment, metastatic pattern, and molecular subtype were also independent predictive factors for OS and BCSS.

TABLE 2 | The baseline characteristics of patients with different surgery procedures in the SEER database after IPTW.

ITEMS	Total	BCS	Mastectomy	Non-surgery	*P-value*
	N (%)	*N* (%)	*N* (%)	*N* (%)	
	4,108	574	1,419	2,115	
Age	55.32 (13.05)	56.28 (12.79)	54.71 (13.28)	55.47 (12.94)	0.04
Grade					0.12
I–II	1,866 (45.4)	256 (44.6)	617 (43.5)	993 (46.9)	
III–IV	2,242 (54.6)	318 (55.4)	802 (56.5)	1,122 (53.1)	
Histology					<0.001
Infiltrating duct carcinoma	3,430 (83.5)	490 (85.4)	1,172 (82.6)	1,768 (83.6)	
Other	678 (16.5)	84 (14.6)	247 (17.4)	347 (16.4)	
T_stage					0.28
T1	427 (10.5)	64 (11.2)	141 (9.9)	222 (10.5)	
T2	1,439 (35)	221 (38.5)	499 (35.2)	719 (34)	
T3	803 (19.5)	98 (17)	294 (20.7)	411 (19.4)	
T4	1,439 (35)	191 (33.3)	485 (34.2)	763 (36.1)	
N_stage					0.51
N0	698 (17)	96 (16.7)	235 (16.6)	367 (17.4)	
N1	2,038 (49.6)	285 (49.6)	683 (48.1)	1,070 (50.6)	
N2	622 (15.1)	94 (16.3)	229 (16.2)	299 (14.1)	
N3	751 (18.3)	100 (17.4)	272 (19.2)	379 (17.9)	
Non-surgical treatment					0.003
Chemotherapy	2,845 (69.3)	378 (65.8)	945 (66.6)	1,522 (72)	
Radiotherapy	357 (8.7)	55 (9.5)	129 (9.1)	173 (8.2)	
Radiotherapy+Chemotherapy	907 (22)	142 (24.7)	345 (24.3)	420 (19.8)	
Metastatic sites					0.28
Bone+viscera	1,115 (27.1)	157 (27.4)	358 (25.2)	600 (28.4)	
Bone_only	1,835 (44.7)	249 (43.3)	646 (45.5)	940 (44.4)	
Viscera	1,158 (28.2)	168 (29.3)	415 (29.3)	575 (27.2)	
Molecular subtype					0.74
HER2-enriched	494 (12)	73 (12.7)	172 (12.1)	249 (11.8)	
Luminal A	2,052 (50)	274 (47.7)	713 (50.2)	1,065 (50.4)	
Luminal B	978 (23.8)	147 (25.7)	322 (22.7)	509 (24)	
Triple-negative	585 (14.2)	80 (13.9)	213 (15)	292 (13.8)	
Race					0.6
White	3,014 (73.4)	431 (75.1)	1,038 (73.1)	1,545 (73.1)	
Unwhite	1,094 (26.6)	143 (24.9)	381 (26.9)	570 (26.9)	
Marital status					0.71
Married	2,010 (48.9)	290 (50.4)	703 (49.5)	1,017 (48.1)	
Single	1,910 (46.7)	259 (45.1)	650 (45.9)	1,010 (47.7)	
Unknown	181 (4.4)	26 (4.5)	66 (4.6)	89 (4.2)	

HER2, human epidermal growth receptor 2; IPTW, inverse probability propensity score weighting; BCS, breast-conserving surgery.

Subgroup Analysis After IPTW

To explore the influence of metastatic pattern on the choice of surgical strategy for *de novo* stage IV BC, subgroup analyses were performed after IPTW (**Tables 4**, **5**). This analysis showed that relative to mastectomy recipients with bone-only metastasis, BCS recipients had better OS (95% CI: 0.48–0.91; $p = <0.001$; HR, 0.66) and BCSS ($p = 0.01$; HR, 0.63; 95% CI, 0.45–0.89), while non-surgery patients had poorer OS (HR, 1.73; 95% CI, 1.4–2.14; $p = 0.01$) and BCSS (HR, 1.65; 95% CI, 1.33–2.06; $p = <0.001$). Moreover, BCS recipients had similar OS relative to mastectomy recipients with viscera metastasis or bone+viscera metastases (viscera metastasis: HR, 1.05, $p = 0.81$; 95% CI, 0.74–1.48, bone+viscera metastases: HR, 1.01, 95% CI, 0.64–1.61, $p = 0.96$) and BCSS (viscera metastasis: HR, 0.94, 95% CI, 0.64–1.38, $p = 0.75$; bone+viscera metastases: 95% CI, 0.66–1.73, $p = 0.8$, HR, 1.06,), while non-surgery patients had worse OS (viscera metastasis: HR, 1.35, 95% CI, 1.06–1.73, $p = 0.02$; bone+viscera metastases: HR, 1.33, $p = 0.02$, 95% CI, 1.04–1.7) and BCSS (viscera metastasis: HR, 1.32, $p = 0.04$, 95% CI, 1.02–1.7,; bone+viscera metastases: HR, 1.37, $p = 0.02$, 95% CI, 1.06–1.77).

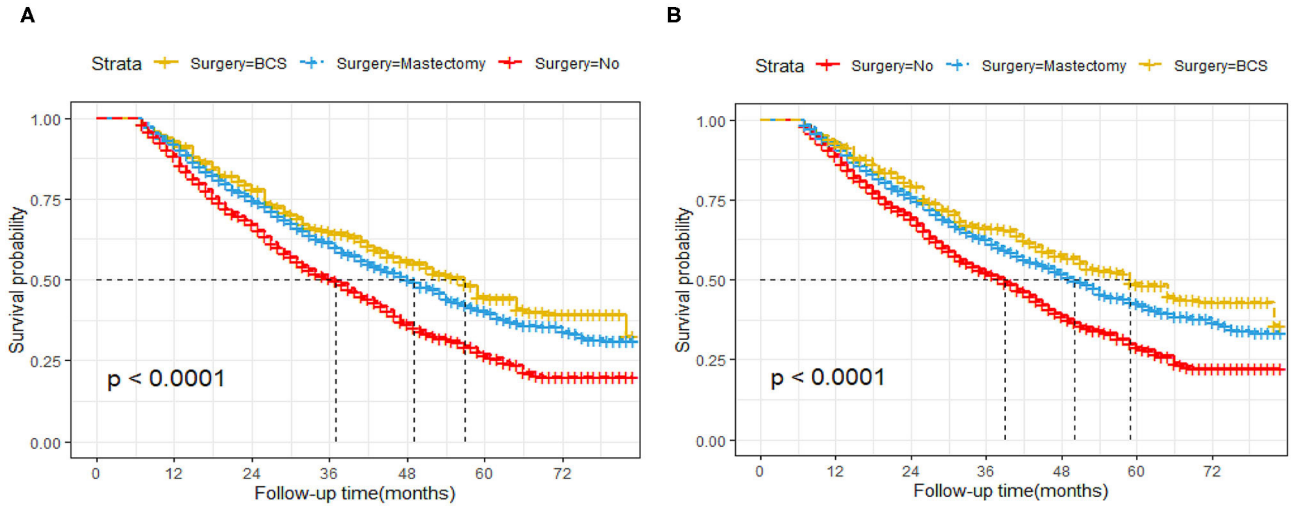

FIGURE 2 | Kaplan–Meier survival analysis for patients with *de novo* stage IV Breast Cancer after IPTW. **(A)** Overall survival curves. **(B)** Breast cancer-specific survival curves.

DISCUSSION

In this large population-based cohort study, the role of surgery for patients with BC remained ambiguous, with no consensus; hence, we employed the SEER population database from 2010 to 2015. We find that the BCS and mastectomy group (surgery groups) had a better prognosis than the non-surgery group. Furthermore, we find that a personalized scheme for *de novo* stage IV BC surgery can be based on different metastatic patterns. Our study shows that BCS offers a significant survival improvement over mastectomy for patients with bone-only metastasis, but not for those with other metastatic patterns. For the first time, this is the largest population-based study to compare survival rates between non-surgery, BCS, and mastectomy individuals with *de novo* stage IV BC.

In our study, surgery was linked to improved BCSS and OS, which were objective, credible, and accurate indexes for patients with BC. *L*og-rank test analysis uncovered significant improvements in BCSS and OS in surgery groups, but not in the non-surgery group. To reduce estimation bias and then study further the efficiency of surgery on BCSS and OS in individuals with stage IV BC, multivariate Cox regression and IPTW analyses were conducted. After adjusting and balancing demographic, clinicopathologic, and therapeutic variables by weighing inverse propensity scores, we found that surgery could prolong BCSS and OS. A previous study based on the SEER database (1998–2011) suggested a survival benefit with a surgical procedure (median OS, 34 months for surgery vs. 18 months for non-surgery), but the data about HER2 status in this study was incomplete (24). However, other recent studies based on the SEER database (2010-2015), the information about HER2 status was integral, also proposed that surgery could improve OS and BCSS in patients with stage IV BC (25, 26). Moreover, one research based on the NCDB database also highlighted that surgery could benefit patients with stage IV BC. In this large cohort, an improved OS was found in the surgery group compared with the non-surgery group even after propensity score matching (HR = 0.68, 95% CI [0.63–0.72], p < 0.001) (27). The above-mentioned findings are in consistent with the previous studies showing that surgical procedure has a key role in *de novo* stage IV BC therapy (17, 25, 26, 28, 29) as surgery may substantially reduce overall tumor burden and improve survival by activating immune responsiveness (30, 31). But other studies held different opinions. A retrospective control study from Massachusetts General Hospital demonstrated no difference in survival between the surgery group and non-surgery group (median OS of 2.4 vs. 2.36 years). The researchers considered that this conclusion was correlated with lead-time bias. Meanwhile, a case-matched study suggested that survival was similar between the above-mentioned groups. So the results were potentially confounded by selection bias and system error.

Due to these biases, randomized clinical trials were designed. MF07-01 trial was a prospective, multicenter, randomized trial to figure out the impact of breast surgery on the prognosis of patients with *de novo* stage IV BC (11). In this study, one group received surgery plus systemic therapy after primary surgery and the other group only received systemic therapy. Surgery might not obtain a survival advantage after 3 years of follow-up, but after 5 years of follow-up, patients receiving surgery could attain a better prognosis. However, TATA, TBCRC 013, and POSYTIVE clinical trials suggested that surgery had a similar prognosis in patients with *de novo* stage IV BC compared with non-surgery (12, 13, 32). Moreover, the Eastern Cooperative Oncology Group (ECOG) 2018 suggested that there were no statistically significant differences in OS and progression-free survival (PFS) between the surgery and palliative groups, while the rate of local recurrence was significantly higher in the palliative care group than in the surgery group (3 year recurrence rate 25.6% vs.

TABLE 3 | Multivariate analysis of prognostic factors of BCSS and OS in metastatic breast cancer after IPTW.

ITEMS	OS						BCSS					
	Univariate analysis			Multivariate analysis			Univariate analysis			Multivariate analysis		
	HR	95% CI	*P-value*	HR	95% CI	*P-value*	HR	95% CI	*P-value*	HR	95% CI	*P-value*
Age	1.01	1.008–1.02	<0.001	1.01	1.002–1.02	0.005	1.02	1.01–1.03	<0.001	1.02	1.01–1.03	0.02
Grade												
I–II		As reference			As reference			As reference			As reference	
III–IV	1.69	1.46–1.95	<0.001	1.58	1.34–1.86	<0.001	1.75	1.5–2.04	<0.001	1.63	1.38–1.94	<0.001
Histology												
Infiltrating duct carcinoma		As reference						As reference				
Other	0.98	0.81–1.18	0.8				1.01	0.83–1.23	0.96			
T_stage												
T1		As reference			As reference			As reference			As reference	
T2	1.26	1.01–1.58	0.04	1.21	0.96–1.52	0.11	1.32	1.04–1.67	0.02	1.26	0.99–1.6	0.06
T3	1.55	1.21–1.99	<0.001	1.31	1.02–1.69	0.04	1.66	1.29–2.16	<0.001	1.39	1.07–1.81	0.01
T4	1.82	1.43–2.33	<0.001	1.51	1.18–1.94	0.001	1.91	1.47–2.48	<0.001	1.57	1.21–2.04	0.001
N_stage												
N0		As reference						As reference				
N1	1.07	0.88–1.32	0.5				1.1	0.89–1.35	0.38			
N2	1.27	0.99–1.61	0.05				1.3	1–1.68	0.05			
N3	1.17	0.93–1.46	0.18				1.2	0.94–1.53	0.14			
Type of surgery												
Non-surgery		As reference			As reference			As reference			As reference	
BCS	0.61	0.49–0.75	<0.001	0.59	0.47–0.75	<0.001	0.6	0.47–0.75	<0.001	0.58	0.45–0.75	<0.001
Mastectomy	0.7	0.63–0.79	<0.001	0.68	0.59–0.77	<0.001	0.71	0.63–0.81	<0.001	0.69	0.6–0.79	<0.001
Non-surgical treatment												
Chemotherapy		As reference			As reference			As reference			As reference	
Radiotherapy	0.86	0.71–1.04	0.11	0.99	0.79–1.25	0.97	0.87	0.71–1.07	0.18	1.03	0.81–1.31	0.83
Radiotherapy+Chemotherapy	0.8	0.67–0.94	0.007	0.84	0.7–1.01	0.07	0.79	0.67–0.94	0.01	0.84	0.69–1.02	0.08
Metastatic pattern												
Bone+viscera		As reference			As reference			As reference			As reference	
Bone_only	0.55	0..45–0.66	<0.001	0.55	0.46–0.66	<0.001	0.53	0.44–0.63	<0.001	0.54	0.45–0.65	<0.001
Viscera	0.83	0.68–1.01	0.06	0.68	0.55–0.84	<0.001	0.81	0.66–1.01	0.05	0.67	0.54–0.84	<0.001
Molecular subtype												
HR–/HER2– (Triple-negative)		As reference			As reference			As reference			As reference	
HR–/HER2+ (HER2-enriched)	0.26	0.2–0.36	<0.001	0.27	0.2–0.36	<0.001	0.26	0.19–0.36	<0.001	0.27	0.2–0.36	<0.001
HR+/HER2– (Luminal A)	0.32	0.27–0.39	<0.001	0.41	0.33–0.51	<0.001	0.32	0.27–0.39	<0.001	0.42	0.33–0.52	<0.001
HR+/HER2+ (Luminal B)	0.21	0.16–0.27	<0.001	0.21	0.17–0.28	<0.001	0.2	0.16–0.27	<0.001	0.21	0.16–0.27	<0.001
Race												
Unwhite		As reference			As reference			As reference			As reference	
White	0.82	0.71–0.95	0.008	0.93	0.79–1.09	0.37	0.83	0.71–0.97	0.02	0.94	0.79–1.12	0.51
Marital status												
Married		As reference			As reference			As reference			As reference	
Single	1.24	1.07–1.44	0.005	1.12	0.96–1.31	0.14	1.24	1.06–1.45	0.01	1.14	0.97–1.34	0.12
Unknown	1.16	0.87–1.54	0.3	1.1	0.83–1.45	0.51	1.13	0.83–1.52	0.45	1.07	0.8–1.43	0.66

BCSS, breast cancer-specific survival; OS, overall survival; HR, hazard ratio; CI, confidence interval; HER2, human epidermal growth receptor 2; BCS, breast-conserving surgery; IPTW, inverse probability propensity score weighting.

10.2% in the surgery group) (33). In addition, the SUBMIT study (NCT01392586) is a randomized clinical trial that could provide evidence about the impact of surgery in patients with BC with metastatic disease, but it was stopped because of low accrual rate (34).

Based on BC heterogeneity, previous studies have been inconsistent. Past studies have proposed that different metastatic patterns have different biological effects on BC and prognoses may differ with metastatic pattern (17, 35, 36). It was recognized that the most frequent metastasis sites are bones, viscera, and

TABLE 4 | Multivariate analysis of prognostic factors of OS for specific sites of metastases after IPTW.

Metastatic sites	Only_bone			Viscera			Bone+viscera		
	HR	**95% CI**	***P-value***	**HR**	**95% CI**	***P-value***	**HR**	**95% CI**	***P-value***
Age	1.01	1.005–1.02	0.04	1.01	0.99–1.02	0.06	1.01	1.002–1.02	0.02
Grade									
I–II		As reference			As reference			As reference	
III–IV	1.37	1.11–1.69	0.003	1.66	1.23–2.23	<0.001	1.66	1.24–2.23	<0.001
T_stage									
T1		As reference			As reference				
T2	1.52	1.05–2.22	0.03	1.06	0.73–1.55	0.74			
T3	1.87	1.25–2.79	0.002	1.06	0.71–1.59	0.78			
T4	1.85	1.25–2.74	0.002	1.33	0.87–2.01	0.18			
N_stage									
N0		As reference							
N1	1.22	0.89–1.67	0.22						
N2	1.6	1.12–2.29	0.01						
N3	1.61	1.15–2.24	0.005						
Type of surgery									
Mastectomy		As reference			As reference			As reference	
Non-surgery	1.76	1.43–2.15	<0.001	1.37	1.09–1.73	0.01	1.39	1.1–1.75	0.006
BCS	0.66	0.48–0.91	<0.001	0.98	0.69–1.4	0.93	1.02	0.72–1.43	0.93
Molecular subtype									
HR–/HER2– (Triple-negative)		As reference			As reference			As reference	
HR–/HER2+ (HER2-enriched)	0.14	0.1–0.25	<0.001	0.34	0.22–0.52	<0.001	0.33	0.22–0.51	<0.001
HR+/HER2– (Luminal A)	0.38	0.28–0.52	<0.001	0.51	0.37–0.7	<0.001	0.49	0.36–0.67	<0.001
HR+/HER2+ (Luminal B)	0.22	0.14–0.33	<0.001	0.19	0.13–0.27	<0.001	0.19	0.13–0.26	<0.001
Race									
Unwhite		As reference							
White	0.84	0.66–1.08	0.17						
Marital status									
Married		As reference			As reference				
Single	1.2	0.96–1.48	0.1	1.15	0.89–1.49	0.28			
Unknown	0.89	0.54–1.47	0.65	1.44	0.99–2.09	0.06			

OS, overall survival; HR, hazard ratio; CI, confidence interval; HER2, human epidermal growth receptor 2; BCS, breast-conserving surgery; IPTW, inverse probability propensity score weighting.

bone+viscera. Bone-only metastases are most common and have the best prognosis (18, 37, 38). These reports were mirrored in our study, where 45.4% of the cohort had bone-only metastasis at primary diagnosis and had a 59.4% survival rate, which was higher than in other groups (viscera: 51%, bone+ viscera: 43.3%). Metastasis site is influenced by BC subtype (39, 40). For example, despite aggressive systemic treatment, HER2-positive, as well as triple-negative, cancers have a high risk of visceral metastasis, while luminal A tumors tend to metastasize to bones (37, 41). We find that 55% of the cohort with luminal A BC had bone-only metastasis, 47% of the HER2-enriched BC cohort, and 48.7% of the cohort with triple-negative BC had viscera metastasis.

Some SEER-based studies suggest that BCS plus radiotherapy had a better prognosis in contrast with mastectomy (42–44), while these studies were conducted on patients with early-stage BC. However, we found that BCS was equally remarkable for individuals with BC, with bone-only metastasis, because patients with BC with bone-only metastasis received radiotherapy or radiotherapy plus chemotherapy were highest among our cohort. Furthermore, relative to mastectomy recipients, BCS may have cosmetic benefits and is safe, and decreases anxiety, psychological morbidity, and depression, improving body image and self-esteem (45–47). In our cohort, the median BC survival time for individuals with BC, with bone-only metastasis, was 31 months, higher than in the viscera and bone+viscera metastases group (both 25 months). Thus, the absence of breasts after a mastectomy had a remarkable influence on the QOL of patients, all the time reminding them that they are patients with BC. Thus, BCS may be recommended for individuals with BC with bone-only metastasis, which provides considerable survival benefits and is more acceptable to patients.

Interestingly, BCS had similar effects on OS and BCSS in patients with viscera and bone+viscera metastases relative to mastectomy, even after combined COX multivariate proportional hazard and IPTW analyses. Breast subtypes were correlated with the choice of surgery type (48, 49). Luminal

TABLE 5 | Multivariate analysis of prognostic factors of BCSS for specific sites of metastases after IPTW.

Metastatic sites	Only_bone			Viscera			Bone+viscera		
	HR	**95% CI**	***P-value***	**HR**	**95% CI**	***P-value***	**HR**	**95% CI**	***P-value***
Age	1.01	0.99–1.02	0.14	1.01	0.99–1.02	0.06	1.01	0.99–1.02	0.11
Grade									
I–II		As reference			As reference			As reference	
III–IV	1.36	1.09–1.69	0.005	1.66	1.21–2.27	0.002	1.92	1.34–2.73	<0.001
T_stage									
T1		As reference			As reference				
T2	1.54	1.04–2.27	0.03	1.2	0.79–1.8	0.39			
T3	1.91	1.25–2.89	0.003	1.22	0.79–1.88	0.38			
T4	1.76	1.17–2.67	0.007	1.48	0.95–2.33	0.08			
N_stage									
N0		As reference							
N1	1.22	0.87–1.7	0.25						
N2	1.63	1.12–2.38	0.01						
N3	1.63	1.15–2.3	0.006						
Type of surgery									
Mastectomy		As reference			As reference			As reference	
Non-surgery	1.69	1.37–2.09	<0.001	1.33	1.04–1.69	0.02	1.38	1.09–1.75	0.007
BCS	0.62	0.44–0.87	0.006	0.89	0.61–1.31	0.56	1.03	0.63–1.69	0.9
Molecular subtype									
HR–/HER2– (Triple-negative)		As reference			As reference			As reference	
HR–/HER2+ (HER2-enriched)	0.13	0.1–0.25	<0.001	0.34	0.22–0.53	<0.001	0.28	0.16–0.49	<0.001
HR+/HER2– (Luminal A)	0.37	0.27–0.51	<0.001	0.53	0.38–0.74	<0.001	0.37	0.22–0.63	<0.001
HR+/HER2+ (Luminal B)	0.2	0.13–0.31	<0.001	0.19	0.13–0.28	<0.001	0.21	0.12–0.37	<0.001
Race									
Unwhite		As reference							
White	0.87	0.67–1.12	0.28						
Marital status									
Married		As reference			As reference				
Single	1.21	0.96–1.62	0.1	1.18	0.9–1.55	0.22			
Unknown	0.92	0.54–1.57	0.76	1.52	1.03–2.23	0.03			

BCSS, breast cancer-specific survival; HR, hazard ratio; CI, confidence interval; HER2, human epidermal growth receptor 2; BCS, breast-conserving surgery; IPTW, inverse probability propensity score weighting.

A and luminal B BC are linked to good prognosis, while Her2-enriched and triple-negative BC have a poor prognosis (37, 40, 50, 51). Meanwhile, the prognosis of patients with bone metastasis was significantly better than that of patients with viscera or bone+viscera metastasis. Herein, patients in the viscera metastasis group had 13.1% Her2-enriched and 10.7% triple-negative, patients in bone+viscera metastasis group had 20.3% Her2-enriched and 24.3% triple negative, and the above-mentioned two groups were both more than bone-only metastasis group. Because patients without bone-only metastasis had shorter survival, BCS had a limited impact on our analysis. Furthermore, individuals with hormone receptor-positive tumors are sensitive to endocrine treatment, while those with HER2-enriched or triple-negative BC lack effective therapeutic targets (52, 53). Meanwhile, we also compared prognosis among three surgery methods based on different molecular subtypes. BCS recipients had similar OS and BCSS relative to mastectomy recipients, but non-surgery patients had a worse effect, regardless of subtype (**Supplementary Tables 1, 2**). Due to the limited number of patients enrolled in our study, subgroup analysis of metastasis type and molecular typing could not be carried out simultaneously.

Moreover, despite different metastasis patterns, the tumor grade and the molecular subtype were prognostic factors that influenced the survival of patients with *de novo* stage IV BC. Meanwhile, age at diagnose was significantly correlated only with better OS and the threshold value of BCSS. The above-mentioned results were consistent with previous studies investigating prognostic factors in metastatic BC (36, 54, 55). But tumor T stage and tumor N stage had only impacted the patients with bone metastasis in our study. BC was a systemic disease, which had different tumor burdens depended on different biological characteristics. In our study, the absolute survival benefit was observed for women with small primary breast tumors as previous meta-analysis and retrospective study reported (56, 57) because patients with a lower disease burden

could have greater benefit from surgery. Patients with a higher disease burden could have had more challenging local control and may have done poorly on this basis. We hypothesized that the size of the primary lesion and the number of lymph node metastasis in patients with stage IV BC with bone metastasis had a great impact on the systemic tumor burden of the patient. Surgical resection could reduce the burden of the local tumor to improve OS and BCSS. But for patients with visceral or multiple metastases, local lesion size and number of lymph node metastasis had little influence on systemic tumor burden, local surgery had a limited impact. Thus, the notion that the T stage and N stage in the stage IV setting could impact survival is plausible, especially in patients with bone metastasis.

This was a comprehensive study of how the benefits of different surgery types vary by metastatic pattern in stage IV BC. However, it has some limitations. First, in our studies, patients needed to be randomized into different groups according to the treatment. Retrospective studies could not be the cause and may be influenced by selection bias and uncontrolled confounding factors, especially metastatic site and non-surgical treatment, even with IPTW administration. Second, due to the lack of information on endocrine, anti-HER2, denosumab or zoledronic acid therapy, family history, patient anxiety, BRCA gene status, and other variables in the SEER database, we were unable to control for these potential modifiers. These factors greatly influence clinical decisions and even prognosis. Third, there was a big gap among the three groups, which may introduce bias to the data, and the sample size was not sufficient to uncover modest differences. Fourth, the SEER data resource only contained data on four site-specific DS sites at primary diagnosis. Thus, we could not obtain details on other DS sites. Lastly, $p < 0.05$ was statistically significant, and the chance of falsely rejecting a null hypothesis may exceed 0.05.

CONCLUSION

Our research show that survival benefit from the type of surgery used on *de novo* stage IV BC differs by metastatic pattern. Local surgery for individuals with DS offered a remarkable survival advantage in contrast with non-surgical management, and BCS is the top selection for individuals with bone-only metastasis. Surgical decisions on patients with *de novo* stage IV BC should be customized to metastatic profile. The mechanisms underlying bone, viscera, bone+viscera, or first BC metastasis need investigation.

DATA AVAILABILITY STATEMENT

Publicly available datasets were analyzed in this study. This data can be found here: https://seer.cancer.gov.

AUTHOR CONTRIBUTIONS

KL and CZ drafted the manuscript and analyzed the data. YY, LN, and WZ generated the figure. BW performed the background research. GG and JH edited the manuscript. All authors have read and approved the content of the manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fsurg.2021.696628/full#supplementary-material

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A Retrospective Study of Latissimus Dorsi Flap in Immediate Breast Reconstruction

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Background: There are many different methods used for immediate breast reconstruction, but the advantages and disadvantages between distinct methods are not reported and compared directly.

Methods: We collected the data of patients who underwent breast reconstruction from 2010 to 2015 and classified a total of 103 patients into three groups: i) skin- or nipple-sparing mastectomy with implant and partial latissimus dorsi flap (MIPLD); ii) skin- or nipple-sparing mastectomy with the whole latissimus dorsi flap (MWLD); and iii) breast-conserving surgery and partial latissimus dorsi flap (BCSPLD). The outcome, safety, and cosmetic outcome of the latissimus dorsi muscle flap with or without implant were reported and compared.

Results: The procedures were successful in all cases. None of the patients had severe complications. The 5-year distant metastasis-free survival is 94.2%. All the patients exhibited good arm and back function. Based on the evaluation of the BREAST-Q score, the cosmetic outcome of Satisfaction with Breasts was excellent or good in 97.8% of the cases.

Conclusions: MIPLD, MWLD, and BCSPLD stand for three distinct methods for immediate breast reconstruction with good outcome and aesthetic effect. They were safe, were easy to perform, and provided quick recovery and good quality of life.

Therefore, these three breast reconstructive methods are worthy of widespread use in clinical practice and provide different ways to reconstruct the breast according to the patients' conditions and preferences.

Keywords: breast cancer, latissimus dorsi (LD) flap, implant, breast reconstruction, outcome

INTRODUCTION

Breast cancer is the most common malignancy for women. The treatment of choice for early-stage breast cancer is surgery (1). Among all the surgical methods, modified mastectomy is adopted most commonly in China; however, it has been found to have negative psychological effects on women's emotion and affects their quality of life. Therefore, it is vital to consider other surgical approaches such as breast reconstruction and oncoplastic conservation surgery.

The latissimus dorsi flap is widely used in breast reconstruction, including the whole latissimus dorsi muscle flap and partial latissimus dorsi muscle flap combined with implant or without implant. The advantage of the whole latissimus dorsi muscle flap, compared with rectus abdominis muscle breast reconstruction, is that it provides better postoperative appearance, requires lesser surgery time, results in lesser injury, and is easier to perform (2). However, the whole latissimus dorsi flap is obtained by making a 20-cm-long rectangular or transverse skin incision on the back, and patients are required to change their position one or two times during a single procedure. Therefore, using the partial latissimus dorsi muscle flap combined with implant is also a good way to reconstruct the breast and does not need the change of position during operation. Covering the implant and reconstructing the breast with partial latissimus dorsi muscle flap or whole latissimus dorsi flap are considered as safe and reliable, especially in the case of breast cancer patients who have indications of neoadjuvant or adjuvant radiotherapy (3, 4).

However, there are still some patients who are reluctant to undergo breast removal or other methods such as implantation or acellular dermal matrix (ADM) for breast reconstruction even when they have a big lump in their breasts. So they may choose oncoplastic conservation surgery. As we know, some oncoplastic surgery techniques have been used widely in breast-conserving surgery. However, in some cases, partial latissimus dorsi muscle flap can also have a role in filling the large defect, especially for those who have small-size breast such as cup A, are reluctant to receive other artificial materials, and have tumor–breast ratio that is more than 1/8.

Therefore, breast reconstruction and oncoplastic conservation surgery using distinct latissimus dorsi muscle flap offer a good quality of life and help women to better integrate themselves into society and have normal life after the surgery.

At our institution, we have been using latissimus dorsi muscle flap with or without implant for breast reconstruction since 2010. We collected the data of patients who underwent breast reconstruction from 2010 to 2015 and classified a total of 103 patients into three groups: i) skin- or nipple-sparing mastectomy with implant and partial latissimus dorsi flap (MIPLD), 51 cases; ii) skin- or nipple-sparing mastectomy with the whole latissimus dorsi flap (MWLD), 19 cases; and iii) breast-conserving surgery and partial latissimus dorsi flap (BCSPLD), 33 cases. We report the outcome, safety, and cosmetic outcome of the latissimus dorsi muscle flap with or without implant, and we compare the advantages and disadvantages of these three methods in immediate breast reconstruction.

PATIENTS AND METHODS

Patients

The patient group included 103 women with breast cancer who underwent unilateral skin-sparing or nipple-sparing mastectomy or breast-conserving surgery with or without implant plus the whole or partial latissimus dorsi muscle flap for immediate breast reconstruction at Hubei Cancer Hospital, Tongji Medical College, Huazhong University of Science and Technology, from January 2010 to May 2015.

Of the 103 patients, 70 underwent skin- or nipple-sparing mastectomy and immediate breast reconstruction, while the other 33 patients received breast-conserving and oncoplastic surgery using partial latissimus dorsi muscle flap.

Preparation for the Procedure and Data Collection

All procedures were performed by the same surgical team at the Department of Breast Surgery. Core needle biopsy or lumpectomy was performed in all the patients to confirm that they had invasive breast cancer or ductal carcinoma *in situ*. Further, their informed consent was obtained before the surgery was performed.

The following data of breast were collected and used to select the appropriate implant: degree of convexity, height and width of the base, thickness of subcutaneous fat, spacing between nipples, and spacing between the collarbone and nipple.

Surgery Protocol

Skin- or Nipple-Sparing Mastectomy

All the patients underwent the surgery in the supine position under general anesthesia. First, 1 ml of methylene blue trihydrate was administered in the area around the nipple–areola complex and breast tumor, both subcutaneously and intramammarily; and then sentinel lymph lode biopsy was conducted after 10–15 min. The number of sentinel lymph lodes sampled was three to five in each patient. According to the tumor size, area, and concealment required, a 4- to 5-cm-long incision was made with a skin thickness of 0.5 cm, for mastectomy. The adipose layer, 0.5-cm glandular tissue under the nipple, and pectoral fascia

were conserved. If the intraoperatively obtained frozen biopsy sample of the glandular tissue under the nipple was not indicative of cancer, the nipple–areola complex was conserved. If the sample did have evidence of cancer, the complex was excised. Axillary lymph node dissection was only performed in patients with positive sentinel lymph nodes. Additionally, the subscapular blood vessels were preserved, and the thoracodorsal nerve, long thoracic nerve, and intercostobrachial nerve were left intact.

Breast-Conserving Surgery

Patients who were eligible for breast-conserving surgery and had the desire to conserve their breast underwent breast-conserving schedule. Some patients with big lump and residual cavity that could not be covered by the adjacent mammary gland required the filling of more tissues such as partial latissimus dorsi flap. Before surgery, we put a cushion underneath their back, so that patients did not need to change their position when we harvested the partial latissimus dorsi muscle flap. Comparable latissimus dorsi tissue was harvested according to the breast residual cavity, rotated to the chest, and then sutured with the surrounding tissue.

Selection of the Partial and Whole Latissimus Dorsi Muscle Flap With Pedicle

For partial latissimus dorsi flap, a 5-cm vertical skin incision was made along the mid-axillary line from the third intercostal space, in order to free the latissimus dorsi muscle flap along the surface and anterior area. Based on the orientation of the thoracodorsal vessels, a fan-shaped flap was selected, while avoiding any impact on the thoracodorsal nerve. During the selection of the fan-shaped flap, the anterior serratus branch of the thoracic dorsal vessels can be left intact, in order to preserve the function of the anterior serratus muscle. Furthermore, the size of the flap was flexible, and it could be enlarged (if required) by including some of the surrounding fascia at the distal end and avoiding the tissue around the pedicle so as to facilitate movement, extension, and rotation of the flap.

For whole latissimus dorsi flap, an 8-cm skin incision was made at the back, and patients had to change their position to the lateral position after completing breast surgery. We harvested the whole dorsi muscle flap without tension. And then the flap was rotated to the anterior chest wall through the tunnel and was sutured with the surrounding tissue for breast reconstruction.

Placement of the Implant

The implants used ranged from 160 to 400 cm^3 (median, 280 cm^3) in volume and were either moderate-profile or high-profile, smooth, round, silicone-gel implants (Hideo Medical Equipment Corp., Wuhan, China). The implant (Sumei) was soaked in 200 ml of saline containing gentamicin (160,000 U) for 20 min before the surgery. The area between the pectoralis major and pectoralis minor was opened (while preserving the medial and lateral pectoral nerves) up to the level of the third rib, medial to the parasternum. The attachment point of the inferior pectoralis major was detached, and the implant was placed. The exposed area of the implant was measured.

Coverage of the Implant

The partial latissimus dorsi muscle flap was rotated so that it covered the anterior and inferior portions of the implant *via* the lateral subcutaneous tunnel of the breast and was sutured with the surrounding tissue. The flap was sutured along the inframammary fold, and the whole exposed implant was covered and left intact. A negative pressure drainage system was applied, and the wound was sutured.

Postoperative Care and Evaluation of Cosmetic Outcome

The patients were encouraged to relax their arm on the operated side and do a little functional exercise 1 day after the procedure. They were prescribed ceftazidime injection liquid (1.0 g, twice a day) for 3 days, and the drainage system was removed when the drained volume was less than 15 ml. Systematic treatment was chosen based on the postoperative pathological report of each patient.

The cosmetic outcome was evaluated by BREAST-Q (5, 6), for both breast cancer and breast reconstruction. The modules included Satisfaction with Breasts, Psychosocial Wellbeing, Sexual Wellbeing, and Physical Wellbeing Chest. The Satisfaction with Breasts was evaluated as follows: excellent (score 81–100), the reconstructed breast had high symmetry with the normal breast, and the patient was highly satisfied; good (score 61–80), the reconstructed breast was symmetrical with the normal breast, and the patient was satisfied; average (score 31–60), the reconstructed breast was not symmetric with the normal breast, and the patient was dissatisfied; and bad (score 0–30), the reconstructed breast showed severe deformation.

RESULTS

Of the 103 patients, 51 underwent MIPLD, 19 patients received MWLD, and the other 33 patients received BCSPLD. The median age of the patients was 41 years (27–57 years). Ten patients had ductal carcinoma *in situ*, and 93 patients had invasive breast carcinoma: 49 patients had the luminal A subtype; 11, luminal B1 (non-HER2 positive) subtype; 16, luminal B2 (HER2 positive) subtype; 9, HER-2-positive subtype; and 18, triple-negative subtype (**Table 1**). The cosmetic outcome was evaluated by the BREAST-Q at 1 year after operation, and the BREAST-Q reconstruction module demographics were also collected (**Table 2**).

The procedures were successful in all cases. None of the patients had severe complications. Only two patients had hematoma and seroma, and one patient experienced nipple superficial erosion. One month after the conservative treatment, all signs of discomfort disappeared (**Table 3**). The median follow-up time was 69 months, and there was no local recurrence. However, metastasis occurred in six patients, who had triple-negative breast cancer (lung metastasis in three patients, and both lung and liver metastases in the other three patients) (**Table 1**). The 5-year distant metastasis-free survival is 94.2%. All the patients exhibited good arm and back function.

TABLE 1 | Characteristics of patients.

Items	MIPLD* N = 51	MWLD* N = 19	BCSPLD* N = 33
Age			
≤43	28 (54.9%)	14 (73.7%)	15 (45.5%)
>43	23 (45.1%)	5 (26.3%)	18 (54.5%)
Pathology			
Ductal carcinoma *in situ*	5 (9.8%)	4 (21.1%)	1 (3.0%)
Invasive carcinoma	46 (90.2%)	15 (78.9%)	32 (97.0%)
Stage			
0	5 (9.8%)	4 (21.1%)	1 (3.0%)
1	16 (31.4%)	2 (10.5%)	12 (36.4%)
2	25 (49.0%)	6 (31.6%)	18 (54.5%)
3	5 (9.8%)	7 (36.8%)	2 (6.1%)
Radiotherapy			
No	46 (90.2%)	5 (26.3%)	0 (0)
Yes	5 (9.8%)	14 (73.7%)	33 (100%)
Subtype			
Luminal A	26 (51.0%)	5 (26.2%)	18 (54.5%)
Luminal B1	5 (9.8%)	3 (15.8%)	3 (9.1%)
Luminal B2	7 (13.7%)	4 (21.1%)	5 (15.2%)
HER2 positive	4 (7.9%)	3 (15.8%)	2 (6.0%)
TNBC	9 (17.6%)	4 (21.1%)	5 (15.2%)
Outcome			
Local recurrence	0	0	0
Distant metastasis	2 (3.9%)	2 (10.5%)	2 (6.1%)
Neither	49 (96.1%)	17 (89.5%)	31 (93.9%)
BMI			
<30	13 (25.5%)	10 (52.6%)	30 (90.9%)
≥30	38 (74.5%)	9 (47.4%)	3 (9.1%)
Tobacco			
Yes	0 (0)	0 (0)	0 (0)
No	51 (100%)	19 (100%)	33 (100%)
Breast cup size			
≤A	4 (7.8%)	(42.1%)	19 (57.6%)
B	30 (58.8%)	7 (36.8%)	11 (33.3%)
C	17 (33.4%)	4 (21.1%)	3 (9.1%)
≥D	0 (0)	0 (0)	0 (0)
Diabetes			
Yes	1 (2.0%)	0 (0)	0 (0)
No	50 (98%)	19 (100%)	33 (100%)

**MIPLD, skin- or nipple-sparing mastectomy with implant and partial latissimus dorsi flap; MWLD, skin- or nipple-sparing mastectomy and the whole latissimus dorsi flap without implant; BCSPLD, breast-conserving surgery and partial latissimus dorsi flap without implant; Luminal B1, Luminal B (non-HER2 positive); Luminal B2, Luminal B (HER2 positive); TNBC, triple-negative breast cancer; BMI, body mass index.*

Based on the evaluation of the BREAST-Q score, the Satisfaction with Breasts was excellent in 67 patients, good in 34 patients, and average in two patients. The Psychosocial Wellbeing was excellent in 61 patients, good in 29 patients, and average in four patients. The Sexual Wellbeing was excellent in 68 patients, good in 22 patients, and average in four patients. The Physical Wellbeing Chest was excellent in 69 patients, good in 28 patients, and average in three patients. Further, seven and six patients did not finish the Psychosocial Wellbeing module and Sexual Wellbeing module, respectively, due to personal reasons. Thus, the cosmetic outcome of Satisfaction with Breasts was excellent or good in 97.8% of the cases (**Table 4**). We also showed the images of the three cases, and each stands for one kind of surgical method (**Figures 1**–**3**).

TABLE 2 | BREAST-Q reconstruction module demographics.

Items	Number (%)
BMI	
<30	53 (51.5)
≥30	50 (48.5)
Bra size	
<A	15 (14.6)
A	16 (15.5)
B	48 (46.6)
C	24 (23.3)
D	0 (0)
>D	0 (0)
Education	
Lower than high school	22 (21.5)
High school	28 (26.9)
College	37 (36.4)
Higher than college	16 (15.2)
Employment	
Full time	32 (31.4)
Part-time	28 (26.7)
Student	14 (13.9)
Retired	16 (15.2)
Others	13 (12.8)
Annual gross household income	
≤¥24,000	32 (31.4)
>¥24,000	71 (68.6)
Marital status	
Married	74 (72.0)
Unmarried	12 (11.8)
Others	17 (16.2)

BMI, body mass index.

DISCUSSION

In this study, we have evaluated the outcome of three surgical methods for immediate breast reconstruction, which are MIPLD, MWLD, and BCSPLD.

In these three methods, MIPLD used both latissimus dorsi flap and implant for immediate breast reconstruction. MWLD and BCSPLD methods did not use the implant and used only latissimus dorsi flap for immediate breast reconstruction. In these two methods without implant, no extra material was required, and cosmetic satisfaction was high among the patients. The aesthetic effect of Satisfaction with Breasts was excellent or good in 97.8% of the cases, and these two methods were particularly suitable for those who were reluctant to use ADM and biological patch (7). Indeed, BCSPLD method is not a commonly used method, and not all the patients who underwent breast-conserving surgery need the latissimus dorsi muscle flap, especially with the development of oncoplastic surgery in breast cancer (8). However, for those who have small-size breasts such as cup A, have tumor–breast ratio of more than 1/8, and are reluctant to receive other artificial materials, we can use partial latissimus dorsi muscle flap to repair well the defect.

In this study, 70 patients received skin- or nipple-sparing mastectomy. As for this kind of surgery, the oncological safety is a controversial subject. Some doctors used 2 mm as the cutoff value for the distance from tumor to the dermis by preoperative ultrasound measurements (9), and others adopted 10 mm as the cutoff value for the distance from tumor to the nipple–areola complex by

TABLE 3 | Complications of three different surgery procedures.

Complications	MIPLD	MWLD	BCSPLD
Acute surgical complication			
Bleeding	0	0	0
Hematoma	0	0	1
Seroma	0	1	0
Infection	0	0	0
Nipple superficial erosion	1	0	0
Nipple necrosis (overall)	0	0	0
Nipple partial loss	0	0	0
Nipple total loss	0	0	0
Skin flap/wound edge necrosis (overall)	0	0	0
Require debridement	0	0	0
Conservative treatment	1	1	1
Secondary touch-up procedure			
Scar revision	0	0	0
Release of capsular contracture	0	0	0
Nipple revision/reconstruction	0	0	0
Convert implant to DIEP flap	0	0	0
Change implant	0	0	0
Remove prosthesis	0	0	0

MIPLD, skin- or nipple-sparing mastectomy with implant and partial latissimus dorsi flap; MWLD, skin- or nipple-sparing mastectomy and the whole latissimus dorsi flap without implant; BCSPLD, breast-conserving surgery and partial latissimus dorsi flap without implant; DIEP, deep inferior epigastric perforator.

preoperative MRI (10). In our study, we used 2 and 10 mm as the distance from tumor to the dermis and the distance from tumor to the nipple–areola complex separately.

TABLE 4 | BREAST-Q reconstruction module scores.

Items and score	Number (%)
Satisfaction with Breasts	
0–30[a]	0
31–60[b]	2 (2.2)
61–80[c]	34 (33.2)
81–100[d]	67 (64.6)
None*	0
Psychosocial Wellbeing	
0-30[a]	2 (2.1)
31–60[b]	4 (4.3)
61–80[c]	29 (28.0)
81–100[d]	61 (59.2)
None*	7 (6.4)
Sexual Wellbeing	
0–30[a]	3 (3.1)
31–60[b]	4 (4.3)
61–80[c]	22 (21.6)
81–100[d]	68 (66.0)
None*	6 (5.8)
Physical Wellbeing Chest	
0–30[a]	3 (3.3)
31–60[b]	3 (3.1)
61–80[c]	28 (26.7)
81–100[d]	69 (66.9)
None*	0

All the questionnaires were completed 1 year after operation.

** Patients who did not complete the questionnaire due to personal reasons.*

[abcd] *Cosmetic results.*

[a] *Bad: score 0–30.*

[b] *Average: score 31–60.*

[c] *Good: score 61–100.*

[d] *Excellent: score 81–100.*

For the MIPLD method, the patients are in the supine position throughout the surgery and is not required to change their position when compared with that in the whole latissimus dorsi flap for breast reconstruction. Similarly, Kim reported that compared with the whole latissimus dorsi flap, the partial latissimus dorsi flap was associated with fewer aesthetic defects, a lower degree of dysfunction in the latissimus dorsi, and a lower rate of seroma formation owing to removal of lesser tissue and lesser dead space formation (11). Gust et al. also reported the use of the latissimus dorsi flap with a tabbed expander in the lateral position without the need for intraoperative change in the position of the patient. Direct-to-implant reconstruction, however, requires confirmation of the symmetry between the reconstructed implant and the normal breast with the patient in the sitting position, as this cannot be achieved with the patient in the lateral position (12). Bittar et al. also reported elevating the latissimus dorsi flap with an anterior approach successfully; however, their incision technique was different from ours (13).

Another advantage of this partial latissimus dorsi muscle flap is that the flap length and width are adjustable. This eliminates concerns about selection of the improper implant. Further, if the length of the flap is found to be sufficient, the anterior serratus branch of the thoracic dorsal vessels can be preserved. This can help to avoid atrophy of the anterior serratus muscle and protect its function.

Overall, the therapeutic benefits are commendable, and the cosmetic outcome is satisfactory. Additionally, the 5-year distant metastasis-free survival is 94.2%, which is consistent with the findings reported in the literature (14). Park et al. (15) reported that the 5-year recurrence-free survival in the reconstructed group was 96.2% and that in the non-reconstructed group was 96.4%, and there was no statistical significance in the two groups.

And in this study, we used BREAST-Q to evaluate the aesthetic effect and quality of life for patients. The response rate was 100% in Satisfaction with Breasts module and Physical Wellbeing Chest module. However, in the modules of Psychosocial Wellbeing and Sexual Wellbeing, there were some patients who did not complete their questionnaires. Therefore, we should pay more attention to patients' psychosocial and sexual education. The overall response rate in our study was 87.4%, which was comparable with the review literature that showed 82% response rate (6). Our study showed that BREAST-Q was a good method for the outcome evaluation of breast reconstruction and breast cancer so far.

There are some limitations in our study. First, our sample size is small; we may need more samples to verify the advantage of these three procedures. Second, there are two incisions in the skin for these three methods. As the development of modern technologies, the latissimus dorsi muscle flaps can also be harvested by modern techniques such as endoscopic and robotic procedure with little scar and good appearance (16–19). But these two modern techniques are not widely used especially in developing countries, and there is a long learning curve.

In conclusion, MIPLD, MWLD, and BCSPLD stand for three distinct methods for immediate breast reconstruction with good outcome and aesthetic effect. They were safe and easy to perform and provided quick recovery and good quality of life. Therefore, these three breast reconstructive methods are worthy of widespread use in

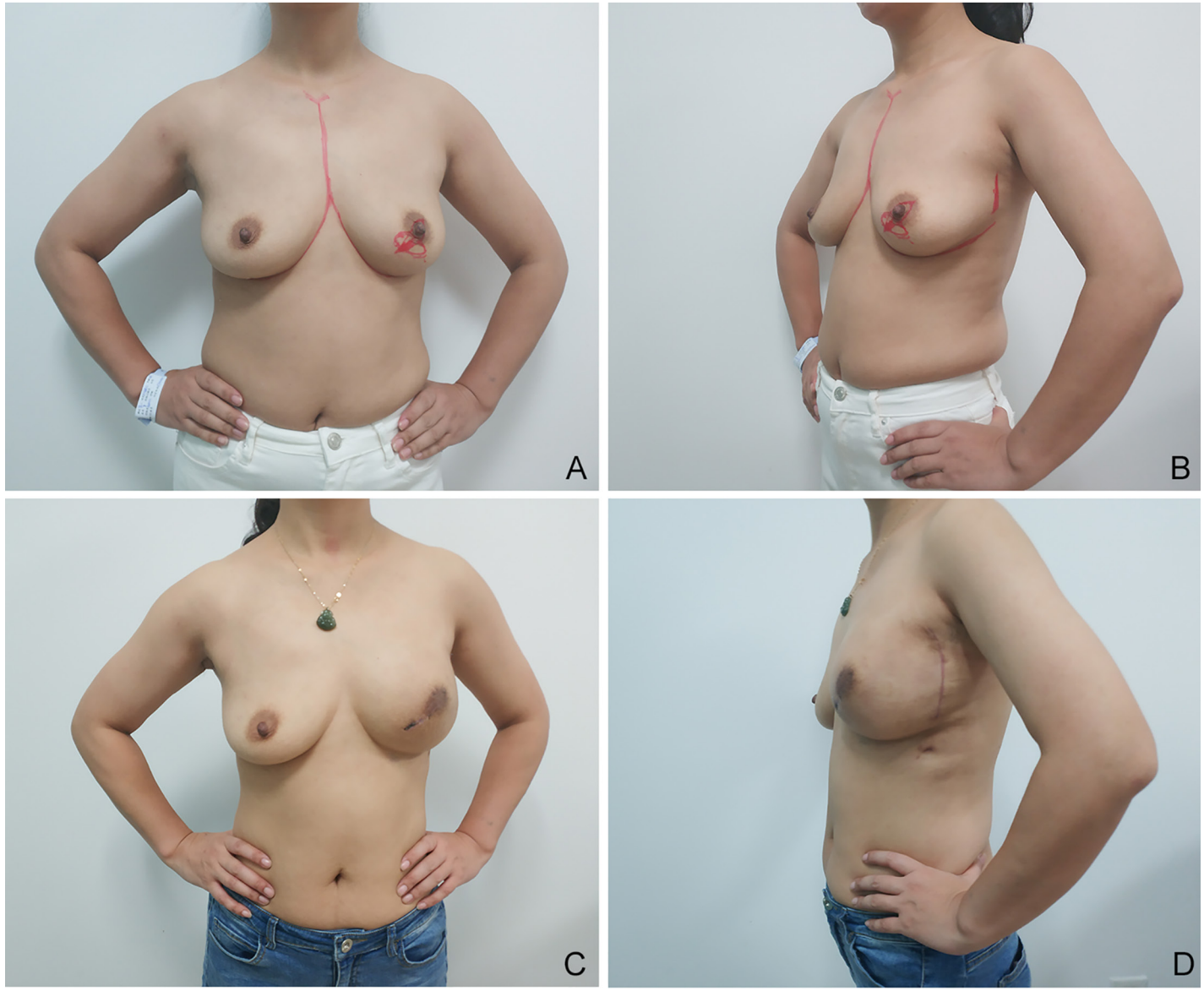

FIGURE 1 | Images of a 30-year-old patient, which were obtained 1 year after left breast nipple-sparing mastectomy with a 280-cm^3 Sumei high-profile implant and partial latissimus dorsi muscle flap (MIPLD) for breast reconstruction. Note the adequate coverage of implant and acceptable inframammary fold. Appropriate volume is evident at the superior and inferior poles and laterally. **(A)** Frontal view before surgery; **(B)** lateral view before surgery; **(C)** frontal view after surgery; and **(D)** lateral view after surgery.

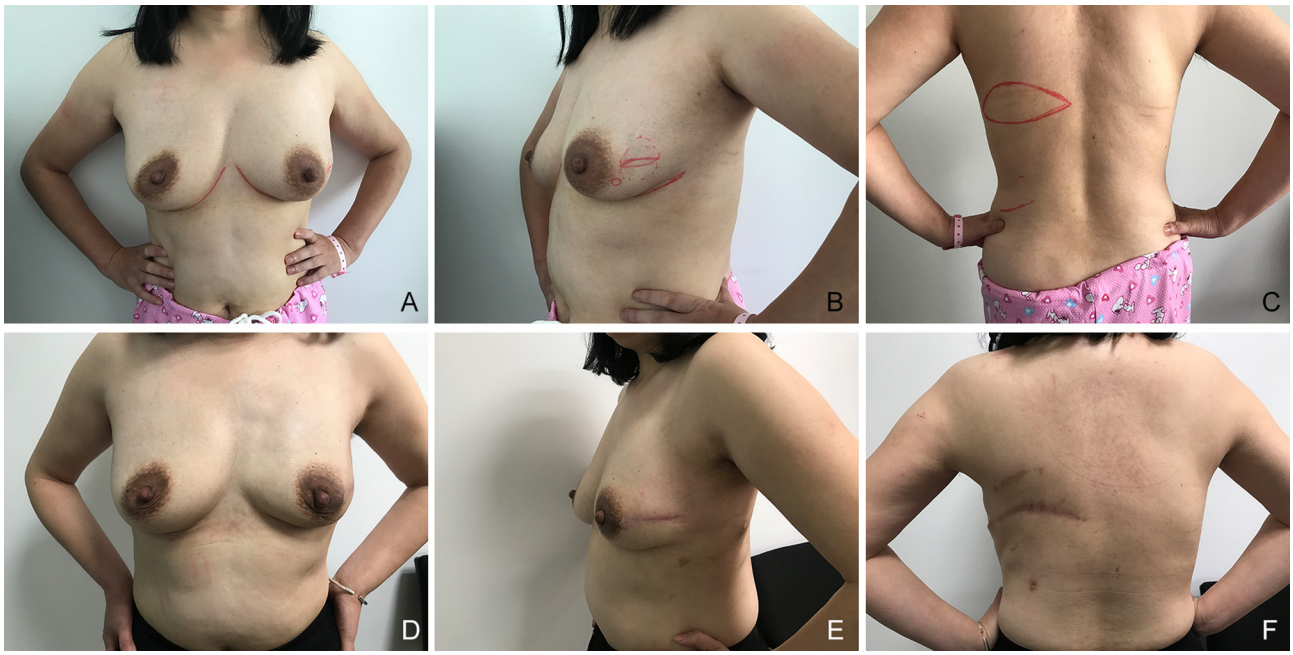

FIGURE 2 | Images of a 50-year-old patient, which were obtained 1 year after left breast nipple-sparing mastectomy with whole latissimus dorsi muscle flap (MWLD) for breast reconstruction. **(A)** Frontal view before surgery; **(B)** lateral view before surgery; **(C)** back view before surgery; **(D)** frontal view after surgery; **(E)** lateral view after surgery; **(F)** back view after surgery.

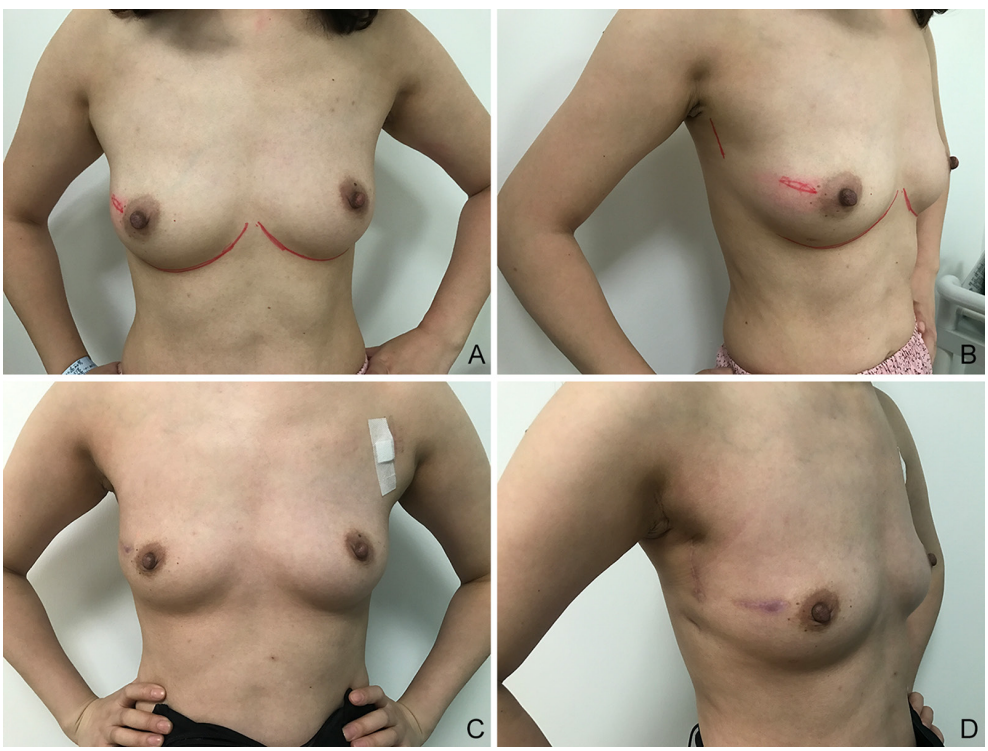

FIGURE 3 | Images of a 36-year-old patient, which were obtained 1 year after right breast-conserving surgery with partial latissimus dorsi flap (BCSPLD) for breast reconstruction. **(A)** Frontal view before surgery; **(B)** lateral view before surgery; **(C)** frontal view after surgery; **(D)** lateral view after surgery.

clinical practice and provide different ways to reconstruct the breast according to the patients' conditions and preferences.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Hubei Cancer Hospital Ethics Committee. It is a retrospective study, so written informed consent was included in the patient record and saved in our hospital. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

XW and HZ had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. HZ and GZ contributed equally as co-first authors. Study concept and design: all authors. Acquisition, analysis, or interpretation of data: all authors. Drafting of the manuscript: HZ and GZ. Critical revision of the manuscript for important intellectual content: HZ and GZ. Statistical analysis: HZ and GZ. Administrative, technical, or material support: all authors. Study supervision: XW, HZ, and GZ. All authors contributed to the article and approved the submitted version.

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frontiers in Oncology

CASE REPORT
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Primary Giant Cell Tumor of the Breast With Pulmonary Metastasis: A Case Report and Review of the Literature

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Giant cell tumor of soft tissue (GCT-ST) is an extremely rare tumor that is similar in morphology and immunohistochemistry to giant cell tumor of the bone. Almost 80% of these tumors occur in the upper and lower extremities, and the breast is a very rare location. Here, we report a case of a 65-year-old female patient with a small mobile palpable lump in the left breast. Although the left breast tumor was considered malignant on preoperative imaging, no evidence of malignant tumor was found by ultrasound-guided core needle biopsy (CNB). Subsequently, the left breast tumor was confirmed as a malignant tumor by intraoperative rapid pathological examination. The initial treatment of the tumor was wide local excision and sentinel lymph node biopsy, and it was confirmed to be GCT-ST by histopathology and immunohistochemistry. Despite surgical treatment achieving clear surgical margins, the patient experienced lung metastases within a year of her initial treatment. Fortunately, the patient underwent surgical treatment of lung metastases, and at the last follow-up, the patient was still alive. This is the first case of a primary soft tissue tumor of the breast that has undergone surgical intervention after lung metastasis. This case report highlights the complexity of the clinical diagnosis and treatment of GCT-ST arising from the breast. Surgery may be another good treatment when the patient develops lung metastases.

Keywords: giant cell tumor of soft tissue, breast tumor, diagnosis, treatment, prognosis

INTRODUCTION

Giant cell tumor of soft tissue (GCT-ST) is a rare tumor. In 1972, Slam and Sissons (1) first reported 10 cases of a type of tumor that originated in the soft tissue but resembled giant cell tumor of the bone in morphology and considered it benign. In the same year, Guccion and Enzinger (2) described 32 cases of such tumors rich in giant osteoclast cells, which have aggressive histological manifestations and biological behavior; however, later, it was found that these tumors were similar to the recognized "malignant fibrous tissue cell tumor". At present, GCT-ST is considered to be a

type of tumor with low malignant potential. The 2013 edition of the World Health Organization (WHO) classifies it as an intermediate-type fibrous tissue cell tumor (occasionally metastatic type).

GCT-ST usually occurs in the superficial and deep soft tissues of the extremities. It is extremely rare for this type of tumor to arise in the breast, and there are fewer than 10 cases of GCT-ST of the breast. Previous research shows that GCT-ST may have a benign clinical course when treated adequately by complete excision. Therefore, in clinical diagnosis and treatment, local recurrence or distant metastasis is extremely rare. In this case report, we introduced a unique case of GCT-ST arising from the breast with lung metastasis. After surgical intervention, the patient was still alive at the last follow-up. In addition to this, a review of the literature is presented.

CASE PRESENTATION

On May 6, 2016, a 65-year-old woman was admitted to the hospital with a complaint of a recently self-detected left breast mass without nipple discharge or skin changes. She had no previous history of breast disease but had a history of hysterectomy for uterine leiomyoma. There was a palpable, firm, non-tender, 2-cm mass in the upper inner quadrant of the left breast, and the contralateral breast was unremarkable in the physical examination findings. Ultrasonography revealed an irregular shape, unclear borders, and a 2-cm mass in the upper inner quadrant of the left breast. The right breast and both axillary regions showed no evidence of disease (**Figure 1**). On magnetic resonance imaging (MRI), the breast mass on the left was found to be lobulated with smooth edges. Compared with normal glandular tissue, this lesion appeared homogeneously isointense on T1-weighted imaging (T1WI). After the injections of the contrast agent, the enhancement of all masses was rapid and heterogeneous. On T2-weighted imaging (T2WI), the mass had extensive high T2WI signals, demonstrating washout kinetics. In addition, left axillary lymphadenopathy with preserved fatty hilum and regular cortex was observed in this patient (**Figure 2**). As for mammograms, the patient refused to undergo mammography examination because she had been examined in other hospitals a year ago. However, the relevant image data have been lost. At the same time, we found no abnormal changes in internal organs by chest X-ray and abdominal color Doppler ultrasound for the patient.

Histological analysis of the needle biopsy specimen showed breast tissue with mammary duct ectasia. On May 11, 2016, a biopsy of the left breast mass was performed. The intraoperative rapid pathological examination indicated a spindle cell tumor. At the same time, the patient underwent wide local excision and sentinel lymph node biopsy, which was finally diagnosed as giant cell tumor of breast soft tissue (**Figure 3A**). On gross examination, the tumor was a well-circumscribed, solid, grayish pink mass measuring 2.5 cm × 2.0 cm × 1.5 cm in maximum dimension. Microscopically, this tumor was composed of round or oval mononuclear cells and numerous osteoclast-like multinucleated giant cells (**Figure 3A**). The mononuclear cells had basophilic cytoplasm with small nucleoli, multinucleated giant cells had irregular cell borders. Adjacent benign breast parenchyma had ductal epithelial proliferation. In addition, the surgical margins were free of tumor, and the sentinel lymph nodes were negative.

Immunohistochemically, the tumor showed a strong positive reaction in the giant cells to the histiocytic marker CD68 (**Figure 3B**) and a positive reaction in the mononuclear component to antibodies against vimentin and CD163 (**Figure 3C**). The tumor was negative for progesterone receptor (PR) (**Figure 3D**) and estrogen receptor (ER) (**Figure 3E**), and the Ki-67 labeling index was 30% (**Figure 3F**). The tumor was also negative for cytokeratin and epithelial markers (AE1/AE3, CK7, CK5/6). Based on this disease having a benign clinical course, the patient did not undergo adjuvant treatment after the operation. However, she was then asked to attend routine follow-up every year.

Unfortunately, on May 10, 2017, the patient attended the follow-up clinic and underwent a chest CT examination, which revealed a shallow lobulated nodule with uneven density and containing calcification in the upper lobe of the left lung. The largest cross section was approximately 1.1 cm × 1.0 cm (**Figure 4**). These special imaging examinations suggest that hamartomas and metastases need to be differentiated. No other signs of metastasis were found on other systemic examinations. On May 18, 2017, this patient underwent a wedge resection of the upper lobe of the left lung. Histologically, the tumor was composed of monotonous monocytes mixed with many osteoclast-like giant cells. There are small necrosis and hemorrhage areas in the cell area (**Figure 5A**). Immunohistochemistry for CD68 was strongly positive in the tumor and stained the multinucleated cells more strongly than the mononuclear component (**Figure 5B**). A Ki-67 antibody stained approximately 15%, the tumor was focally positive for CD163 and for S-100 protein (**Figures 5C, D**). Knowledge of the patient's history of breast tumor and comparing the histology of the lung lesion with the original breast tumor helped the pathologist confirm that the lung nodule was a breast-derived metastasis. Starting on June 28, 2017, the patient received four cycles of systemic adjuvant chemotherapy (epirubicin and ifosfamide, a course of 21 days). As of this report, the disease had no progress, and the patient was still alive and underwent regular follow-up exams. The disease development process and the treatment line are shown in **Table 1**.

DISCUSSION

GCT-ST is an uncommon kind of soft tissue tumor, although previous studies have found that GCT-ST is genetically distinct from GCT-B (3), its histological and immunohistochemical similarities with GCT of bones. Clinically, it is considered a tumor of low malignant potential, with a tendency for local recurrence while rarely metastasizing. It occurs at any age, but it usually occurs in patients aged 40–60 years without gender difference (4). The tumor usually involves the superficial and deep soft tissues of the limbs, trunk, and head and neck. However,

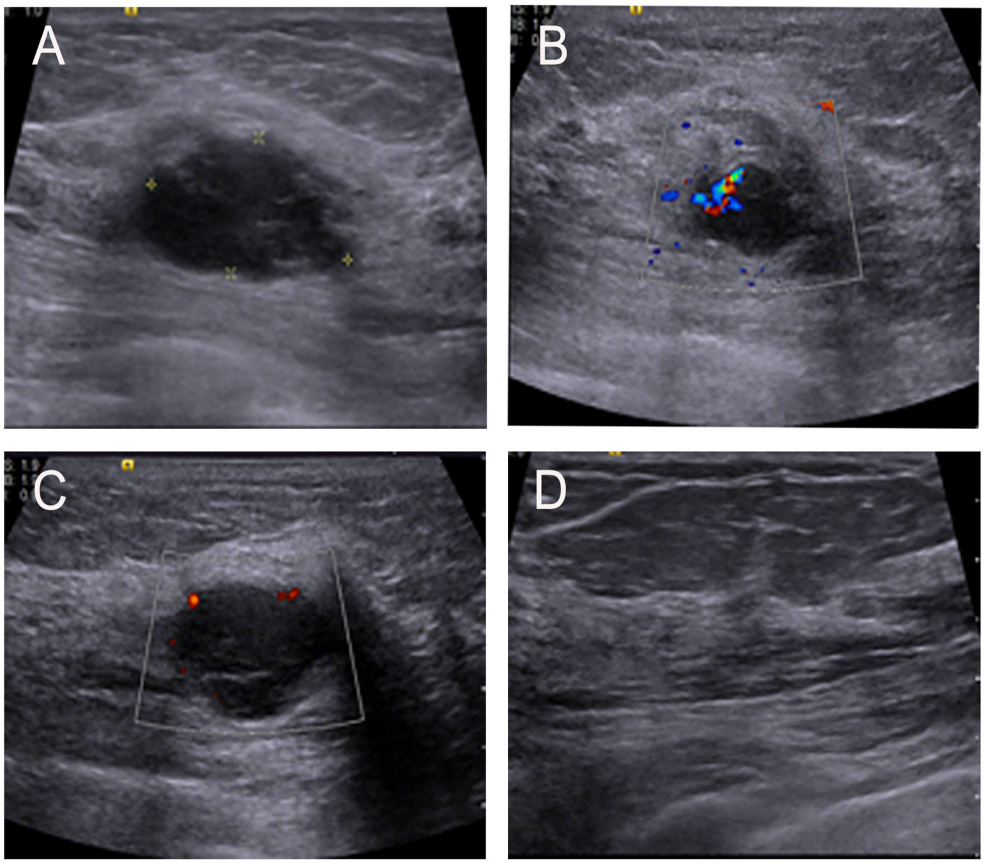

FIGURE 1 | **(A)** Ultrasonographic image showing a low echo mass in the upper inner quadrant of the left breast and with an irregular shape and uneven internal echogenicity. **(B, C)** Color-flow Doppler image showing small amount of blood flow signals inside and vessels in rim. **(D)** No enlarged lymph nodes were found in the armpit.

GCT-ST in the female breast is exceedingly rare; to the best of our knowledge, only nine cases have been reported in the literature, and information from each case report is summarized in **Table 2** (5–13). Eight of the nine patients were female. The median age of the diagnosis was 58.1 years with a range of 36–74 years. Tumors ranged in size from 2.5 to 13 cm with a median size of 4.7 cm. The first symptom of the nine patients was a breast mass, of which one was accompanied by nipple discharge (7). All patients underwent surgery, only one patient had features of lung metastasis and a fatal outcome (10). Our case is different from previous case reports. Although the patient developed lung metastasis, she achieved a good prognosis after surgical intervention and systemic adjuvant chemotherapy and was still alive.

The imaging characteristics of GCT-ST arising from the breast have not been well described due to its uncommonness. However, some nonspecific imaging features of this disease have been described. It may present as a solid and cystic mass or hypoechoic mass with sharp or obscured margins on sonography (5, 6). It can appear as an irregular mass with circumscribed, microlobulated, obscured margins on mammography. To the best of our knowledge, the magnetic resonance imaging (MRI) characteristics of GCT-ST arising from the breast have only been published in three reports (5–7). Luangxay et al. (5) and Terada et al. (6) found that the masses appeared indistinct or irregularly on MRIs surrounded by a non-mass-enhanced segmental lesion. In our study, the mass appeared lobulated, on T2WI, demonstrating extensive hyperintensity. In addition, the mass demonstrated washout kinetics. These nonspecific and highly mimicked imaging features of malignant tumors make the diagnostic process challenging through clinical features or imaging findings only. Our case appropriately reflects the difficulty of diagnosis. The preoperative core needle biopsy (CNB) showed no evidence of malignancy. Later, the frozen section during the operation only suggested breast cancer, and no signs of giant cell tumors of breast soft tissue were found. Finally, combining the characteristics of histopathology and immunohistochemistry, the patient was finally diagnosed with a giant cell tumor of the breast soft tissue.

In addition, the second challenge in our case is the differential diagnosis of the solitary lung nodule. Radiologists consider the solitary lung nodule to be a benign lesion based on the imaging characteristics, but at the same time, they also remind us of the

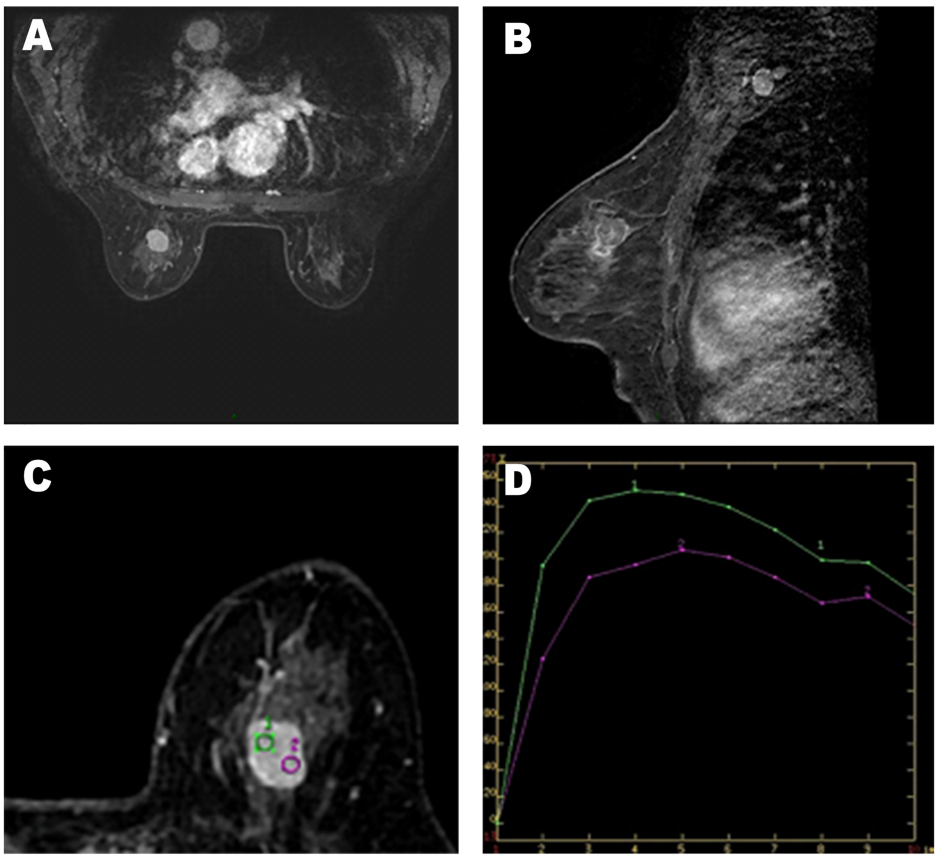

FIGURE 2 | **(A–C)** Axial and sagittal contrast-enhanced MR image shows rapid and heterogeneous tumor enhancement. **(D)** Dynamic contrast-enhanced magnetic resonance imaging (MRI) demonstrated a time–signal intensity curve (TIC) with a rapid rise to a peak (after the administration of the contrast material), followed by a slow-out at the mass.

possibility of this nodule being a metastatic tumor. Based on such results, we were faced with whether to continue with follow-up or surgical treatment. Michaels et al. (14) stated that a solitary pulmonary nodule appearing in a patient with breast cancer is not always suggestive of metastatic disease, as more than 50% of the nodules may have etiologies such as primary lung tumor or other benign lesions, while emphasizing that histological confirmation is necessary. Traditionally, a bronchoscopic biopsy is an important means to obtain histology. However, this histology specimen is often equivocal. Finally, we chose surgical resection of solitary pulmonary nodules to offer diagnostic confirmation and local control of the disease. Given the difficulty of the diagnosis of this disease, it is particularly important for pathologists to exclude other giant cell-rich lesions through histology and immunohistochemistry before making a diagnosis, such as giant cell tumor of tendon sheath (GCT-TS), plexiform fibrohistiocytic tumor (PFT), or other benign reactive processes containing abundant osteoclast-like giant cells. Here, we compared the differences of these three common tumors (GCT-TS, GCT-ST, and PFT) in terms of biological behavior, histology, immunohistochemistry, and treatment methods and presented them in the form of **Table 3**. Microscopically, the tumor cell composition of GCT-ST is simple, containing only osteoclast-like giant cells and monocytes. In contrast, the tumor cells of GCT-TS show obvious morphological variation, and the degree of variation depends on the number of osteoclast-like giant cells, monocytes, foam cells, and the degree of interstitial vitreous change. Second, there was only one type of monocyte in GCT-ST, but GCT-TS contained two types of monocytes: small mononuclear histiocytes and large synovial-like monocytes, sometimes in the form of dendrites. Third, among GCT-ST cases, the mitotic figures were visible, ranging from 1 to 30 per 100 high-power fields (HPF). Atypia, pleomorphism, and necrosis are rarely found in tumor cells. In addition, metaplastic bone formation can be seen in about half of GCT-ST cases. These histological differences between GCT-TS and GCT-ST help us make a correct diagnosis. Immunohistochemically, the multinucleated giant cells were strongly positive for CD163 or CD68, while monocytes were only weakly expressed. Basal cytokeratins (CKs) and myoepithelial markers (p63, S-100 protein) are not expressed, and occasionally they may be focally positive. Furthermore, we compared the results of postoperative pathology between the metastatic and primary lesions and found that the histological features of metastatic tumor closely resembled those of the primary tumor. At the same time,

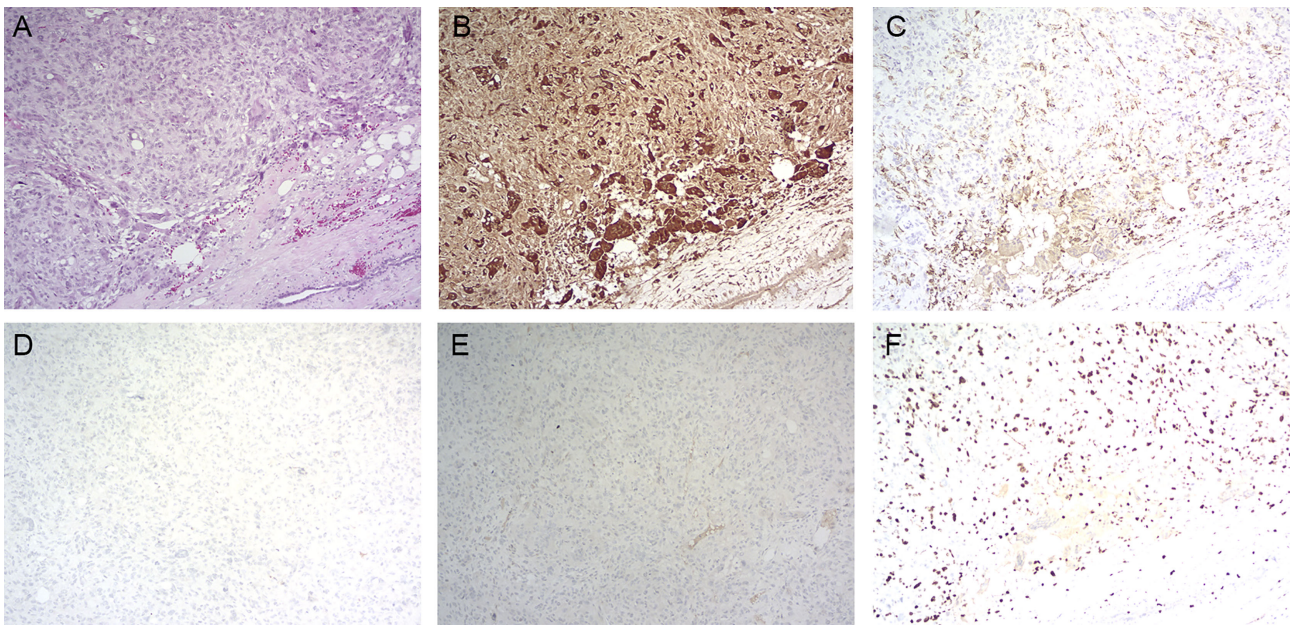

FIGURE 3 | Histopathology of primary tumor. **(A)** Hematoxylin and eosin staining (magnification: ×100); **(B)** immunohistochemistry for CD68 (magnification: ×100); **(C)** immunohistochemistry for CD163 (magnification: ×100); **(D)** immunohistochemistry for PR (magnification: ×100); **(E)** immunohistochemistry for ER (magnification: ×100); **(F)** immunohistochemistry for KI-67 (magnification: ×100).

we noticed that both the Ki-67 index and mitotic figures of the metastatic tumor were higher than those of the primary lesion, which may indicate that the metastatic tumor had a greater likelihood of malignant behavior than the primary tumor. We tried to identify pathological factors suggestive of tumor metastasis, but unfortunately, no useful information was found.

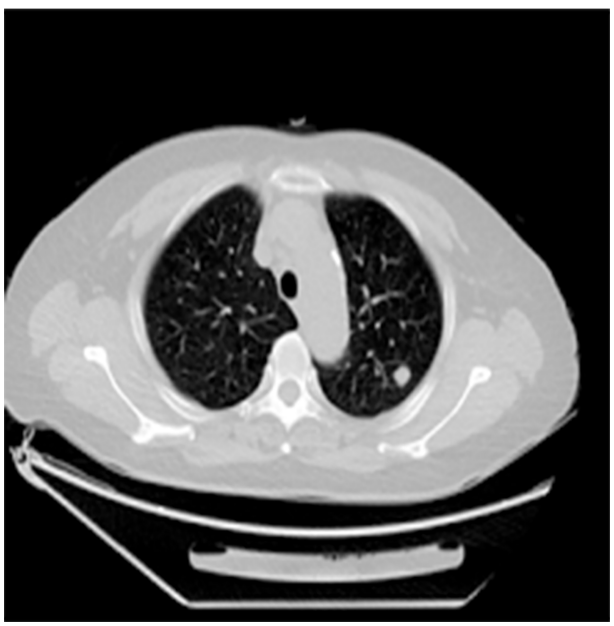

FIGURE 4 | Chest CT showed that a soft tissue nodule in the left upper lobe with lobulated contours, inhomogeneous density, and calcifications is visible inside, and the largest cross-sectional dimension of the mass was 1.0 cm × 1.1 cm.

For soft tissue giant cell tumors, the vast majority of GCT-STs have a benign clinical course and sometimes lead to local recurrence but rarely to distant metastasis. Oliveira et al. (4) reported 22 cases of GCT-ST, of which 16 cases were followed up after surgical treatment, and only one patient experienced local recurrent disease, developed pulmonary metastasis, and died of the tumor. In the same year, O'Connell et al. (15) reported 11 cases of GCT-ST with an average follow-up of 24 months, and no recurrence or metastasis was found. According to the newly revised classification of soft tissue tumors by the World Health Organization (WHO), the local recurrence rate of soft tissue giant cell tumors is 12% in the clinical follow-up period of 34–45 months. Metastasis and death are rare, so they defined these tumors as "intermediate (occasionally metastatic)". For soft tissue giant cell tumors that occurred in the breast, in light of previous reports, only May et al. (10) reported on a patient with GCT-ST caused by breast trauma who developed lung metastases and died 10 months after the initial presentation. The pathological features of this case are as follows: the mitotic index was 5 per 10 HPF, and the Ki-67-positive rate was approximately 35%. Moreover, monocytes and osteoclast giant cells were only mildly pleomorphic. In the case presented in our study, our patient achieved a fairly good outcome after surgery and systemic adjuvant chemotherapy. We tried to find any reason for the different course of disease between the two cases, and we noticed some differences between the two cases. First, the etiology is different. The tumor in our case appeared without

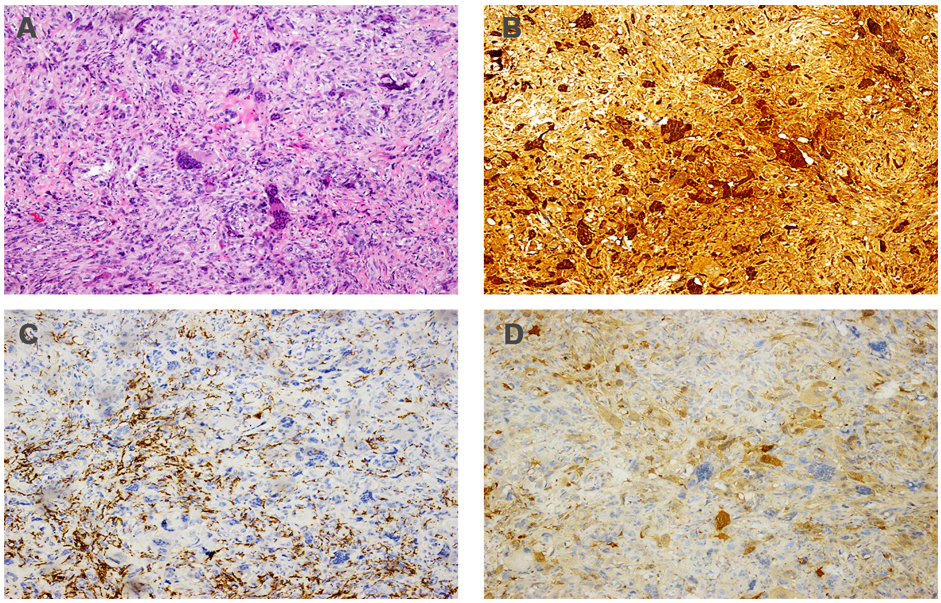

FIGURE 5 | Histopathology of metastatic lesion. **(A)** Hematoxylin and eosin staining (magnification: ×100); **(B)** immunohistochemistry for CD68 (magnification: ×100); **(C)** immunohistochemistry for CD163 (magnification: ×100); **(D)** immunohistochemistry for S-100 (magnification: ×100).

obvious cause, rather than after a chest trauma. Second, the proportion of Ki67 was lower in the presented case than in that case reported by May et al. (10) (30% *vs.* 35%). In addition, the entire treatment process was different. In that case reported by May et al. (10), when a lung nodule was found and suspected to be a metastatic lesion, the histological evaluation of the lung lesion was not performed, and there was no follow-up surgery and adjuvant treatment. Perhaps it is based on these factors that led to the completely different outcomes of the two patients.

There is no consensus on the optimal management for patients with GCT-ST of the breast; surgical treatment ranges from local excision and lumpectomies to modified and radical mastectomies. Reviewing previous reports on nine cases of GCT-ST of the breast, all nine patients underwent surgical treatment: one patient had excisional biopsy only, one patient underwent wide local excision, and the remaining seven patients underwent mastectomy. Among these patients, three patients received sentinel lymph node biopsy (5, 6, 12) and two patients had axillary lymph node dissection (7, 13). All five of these had no axillary lymph node metastasis. In our case, the patient underwent wide local excision and sentinel lymph node biopsy. The vast majority of these patients have an excellent prognosis, so a conservative surgical resection with free surgical margins may be an appropriate treatment strategy, and axillary lymph node dissection or sentinel node biopsy may not be necessary in some cases. However, the lack of large studies and long-term follow-ups makes it difficult to confirm the safety of this operation. Currently, there is no report in the literature about the choice of adjuvant therapy, and whether adjuvant therapy can improve the outcomes of patients with GCT-ST of the breast after lung metastasis is unknown. This type of tumor belongs to the category of soft tissue tumors. Although its biological behavior is completely different from that of soft tissue sarcoma, it has a greater possibility of malignant behavior with lung metastasis. Therefore, we refer to the treatment guidelines for soft tissue sarcoma when formulating this treatment plan. The patient received four cycles of systemic adjuvant chemotherapy (epirubicin and ifosfamide).

TABLE 1 | Disease development process and the treatment line.

Time	Disease development	Treatment
2016.05.06	Self-detected left breast mass	Hospitalization
2016.05.08	None	Core needle biopsy
2016.05.11	None	WLE+SLNB
2017.05.10	A left lobe nodule	Chest CT examination
2017.05.18	Tumor progression (lung metastasis)	Wedge resection of the upper lobe of the left lung
2017.06.28	Lung metastasis	Chemotherapy (four cycles)[#]
As of this report, the disease has no progress and the patient was still alive		

WLE, wide local excision; SLNB, sentinel lymph node biopsy.
[#]*Epirubicin and ifosfamide.*

TABLE 2 | Case reports of GCT-ST of the breast.

First author	Published year	Age/ Sex	Laterality	Tumor size (cm)	Tumor distribution	Symptoms	Imaging findings			Preoperative diagnosis	Treatment	Prognosis
							Ultrasonography	Mammography	MRI			
Luangxay et al. (5)	2020	59/F	Left	3	Retroareolar region	A solid and cystic mass	A mixed solid and cystic mass	A microlobulated mass	A mixed solid and cystic irregular mass surrounded with a non-mass enhancement	Intracystic carcinoma	TM+SLNB	8 months, no recurrence
Terada et al. (6)	2019	74/F	Right	2.5	Upper outer quadrant	A tender lump	An irregular-shaped and hypoechoic mass with a suspicion of a spread to the nipple inside the duct	An indistinct mass	An indistinct mass surrounded with a non-mass enhanced segmental lesion	Suspected malignant tumor	TM+SLNB	12 months, no recurrence or metastasis
Sawa et al. (7)	2019	45/F	Left	5	Central portion	A rapidly enlarging lump and bloody nipple discharge	A mainly well-circumscribed mass. Internal echoes are heterogeneous and hypervascular	Not mentioned	A high-intensity area suggestive of hemorrhaging on T1- and T2-weighted images along with a fibrous capsule	Suspected GCT-ST	TM+ALND	Disease-free for 5 years
Gaspar et al. (8)	2017	36/F	Right	7	Upper quadrant	A rapidly increasing lump	Not mentioned	A well-defined hyperdense mass	Not mentioned	Suspected phyllodes tumor	WLE	12 months, no recurrence or metastasis
Romics et al. (9)	2009	50/F	Left	2.5	Upper outer quadrant	A discrete swelling lump	A slightly irregular, hypoechoic area	A dense, well-defined opacity mass	Not mentioned	OGCT of the soft tissue of the breast	Excisional biopsy	Not mentioned
May et al. (10)	2007	60/F	left	3	Inner quadrant	A cystic mass, History chest trauma in a motor vehicle accident	A well-demarcated cystic mass with mixed echogenicity	A well-demarcated cystic mass with mixed echogenicity	Not mentioned	Suspected organizing hematoma	Partial resection and total mastectomy	10 months, die of lung metastasis
Shousha and Sinnett (11)	2004	59/F	Left	3.7	Not mentioned	An alarming increase in mass	A well-circumscribed lesion presents entirely within the pectoralis major	A well-circumscribed lesion presents entirely within the pectoralis major	Not mentioned	GCT-ST	TM	2 years, no recurrence or metastasis
Fukunaga (12)	2002	68/F	Right	2.5	Outer and lower quadrant close to the nipple	A small mass	An intracystic papilloma	An intracystic papilloma	Not mentioned	Intracystic papilloma	TM+SLNB	22 months, no recurrence or metastasis
Lucas et al. (13)	1981	72/ M	Right	13	Medial to and above the nipple	A rapidly enlarging lump	Not mentioned	Not mentioned	Not mentioned	Not mentioned	TM+ALND	6 months, no recurrence or metastasis

MRI, magnetic resonance imaging; BCS, breast-conserving surgery; ALND, axillary lymph node dissection; SLNB, sentinel lymph node biopsy; MT, Mastectomy; WLE, wide local excision; GCT-ST, Giant cell tumor of soft tissue; OGCT, osteoclast-like giant cell tumor.

TABLE 3 | Comparison of three different types of tumors.

	PFT	GCT-TS	GCT-ST
Biological behavior	A rare, low-to-intermediate grade, soft tissue tumor	A rare, locally aggressive, mesenchymal neoplasm	A tumor of low malignant potential, with a tendency to local recurrence while rarely metastasizing
Another name	Plexiform fibrous histiocytoma tumor (PFHT)	Pigmented nodular tenosynovitis (PVNS)	Soft tissue osteoclastoma
Etiology and pathogenesis	Unknown	Injury and bleeding, lipid metabolism disorders, tumor formation, and inflammatory reactions are the most likely causes	Unknown, it is rarely seen in patients with Paget's disease and post-traumatic bone
Age distribution	An average age of presentation at around 14.5 years	①L–GCT-TS, mainly 30–50 years old ②D-GCT-TS, less than 40 years old	Mainly 40–60 years old
Gender distribution (female: male)	2.5–6.0:1	①L–GCT-TS, F:M = 3:2 ②D-GCT-TS (PVNS), F>M	No gender difference in incidence
Disease site	The spine, distal femur, proximal tibia, and distal radius	①L–GCT-TS, finger/toe joints ②D-GCT-TS, big joints (knee, ankle)	Superficial and deep soft tissues of the limbs, trunk, and head and neck
Main symptoms	A slow-growing painless lump	①L–GCT-TS, A painless lump of gradually increasing size with a long course of disease (<3 cm in diameter); ②D-GCT-TS (PVNS), Swelling (86%), pain (82%), stiffness (73%), restricted movement (64%), joint instability (64%)	A gradually growing and painless mass with symptoms appearing in an average of 6 months
Imaging findings	A low echo mass with clear boundary, irregular shape, uniform internal echo, and abundant blood flow signals in color Doppler flow imaging (CDFI)	①L-GCT-TS, A soft tissue mass with a clear boundary that grows close to or surrounding the tendon sheath; ②D-GCT-TS, a diffuse thickening of the synovial membrane/multiple soft tissue mass with an unclear boundary	①Peripheral calcification of the tumor; ②A solid, heterogeneous, frequently hemorrhagic mass on computed tomography and magnetic resonance imaging
Histopathologically	①These tumors consist of three cell types, osteoclast-like multinucleated giant cells; mononuclear cells, and spindle-shaped, fibroblast-like stromal cells; ②Mitosis activity is usually less than 3/10 HPF	Proliferation of synovial-like mononuclear cells, variable numbers of multinucleate osteoclast-like cells form cells, macrophage foam cells, some of which contained iron deposits	A mixture of round and oval mononuclear cells and multinucleated osteoclast-like giant cells (OGCs) with a blood vessel-rich stroma, mitotic activity is seen on monocytes (range 1–30 MF/10HPFs)
Immunohistochemistry	Mononuclear and osteoclast-like multinucleated giant cells, CD68(+), CD163 (+); spindle cells, vimentin (+), α-SMA (), and SA (+)	Osteoclast-like multinucleated giant cells, CD68(+), CD45(+); Mononuclear cells, CD68 (focal+), HHF35(+)	Osteoclast-like multinucleated giant cells, vimentin (+), CD68(+++), CD163(+), SMA (-), desmin (-), Mononuclear cells, vimentin (+), CD68 (focal+), SMA (+), p63(+), desmin (-)
Treatment method	①Surgical therapy; ②Radiotherapy	①Surgical therapy (Arthroscopy, open surgery); ②Targeted therapy: pexidartinib; ③Radiotherapy (teletherapy, brachytherapy)	Surgical intervention
Prognosis	Local recurrence rate, 35%; rare metastases	①L–GCT-TS, local recurrence rate, 10%–14%; ②D-GCT-TS, local recurrence rate, 9%–25%	Local recurrence rate,12%~24%; occasionally lung metastases

PFT, plexiform fibrohistiocytic tumor; GCT-ST, giant cell tumor of the soft tissue; GCT-TS, giant cell tumor of tendon sheath; PVNS, pigmented villonodular synovitis.

As of the date of follow-up, no progress was found. Because of the possibility of local recurrence and distant metastasis, long-term follow-up is necessary. Whether there are other relevant specific treatment measures or prognostic factors or clinicopathologic factors that suggest tumor metastasis is currently unknown.

CONCLUSION

This is the first case of a primary soft tissue tumor of the breast that has undergone surgical intervention after lung metastasis and also got a good outcome.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors without undue reservation.

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

WZ: article writing. XK: performed image acquisition. YQ: performed image acquisition. XW, and QL: data collection. YF, YS, and JW: revised and improved the article. All authors contributed to the article and approved the submitted version.

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SYSTEMATIC REVIEW
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Complication Differences Between the Tumescent and Non-Tumescent Dissection Techniques for Mastectomy: A Meta-Analysis

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Purpose: We conducted a systematic literature search and pooled data from studies to compare the incidence of complications between the tumescent and non-tumescent techniques for mastectomy.

Methods: We searched PubMed, Embase, BioMed Central, Ovid, and CENTRAL databases for studies comparing the two mastectomy techniques up to November 1st, 2020. We used a random-effects model to calculate odds ratios (OR) with 95% confidence intervals (CI).

Results: Nine studies were included with one randomized controlled trial (RCT). Meta-analysis indicated no statistically significant difference in the incidence of total skin necrosis (OR 1.18 95% CI 0.71, 1.98 I^2 = 82% p=0.52), major skin necrosis (OR 1.58 95% CI 0.69, 3.62 I^2 = 71% p=0.28), minor skin necrosis (OR 1.11 95% CI 0.43, 2.85 I^2 = 72% p=0.83), hematoma (OR 1.19 95% CI 0.80, 1.79 I^2 = 4% p=0.39), and infections (OR 0.87 95% CI 0.54, 1.40 I^2 = 54% p=0.56) between tumescent and non-tumescent groups. Analysis of studies using immediate alloplastic reconstruction revealed no statistically significant difference in the incidence of explantation between the two groups (OR 0.78 95% CI 0.46, 1.34 I^2 = 62% p=0.37). Multivariable-adjusted ORs on total skin necrosis were available from three studies. Pooled analysis indicated no statistically significant difference between tumescent and non-tumescent groups (OR 1.72 95% CI 0.72, 4.13 I^2 = 87% p=0.23).

Conclusion: Low-quality evidence derived mostly from non-randomized studies is indicative of no difference in the incidence of skin necrosis, hematoma, seroma, infection, and explantation between the tumescent and non-tumescent techniques of mastectomy. There is a need for high-quality RCTs to further strengthen the evidence.

Keywords: breast cancer, mastectomy, epinephrine, lignocaine, complications, skin necrosis

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INTRODUCTION

Since the first description of the tumescent dissection mastectomy method by Worland (1) in 1996, the technique has gained popularity for both breast cancer and esthetic surgical procedures (2, 3). Tumescent dissection involves an injection of a very dilute solution of local anesthetic with epinephrine and a crystalloid into the subcutaneous tissues of the breast (4) using multiple small stab punctures. The solution is injected just before the initial incision thereby creating tension between the anatomical planes and hydro-dissecting the tissues. The space created by the solution enhances visibility and ease of dissection, and allows the surgeon to distinguish between the subcutaneous and glandular tissues (5). Dissection can be easily carried out using sharp scissors obviating the need for electrocautery near the skin flaps which might lead to soft tissue damage by the dissipating thermal energy (6). The epinephrine in the mixture causes vasoconstriction, which is further enhanced by the tamponading effect of the high volume infiltration on the subdermal vessels (7). Another potential advantage is the analgesic effect offered by the local anesthetic which has been confirmed by researchers (8, 9).

However, despite the technique's benefits, the risk of skin flap necrosis with the use of the tumescent solution is disconcerting to many surgeons. Skin flap necroses after mastectomy are a serious complication leading to patient dissatisfaction and increased healthcare costs (10). More importantly, they can cause a delay in the initiation of adjuvant therapies after surgery thereby affecting patient outcomes (11). In this context, clarifying the impact of the tumescent dissection technique vis-a-vis the standard surgical technique on the incidence of postsurgical complications in patients undergoing mastectomies is important. In a systematic review and meta-analysis by Siotos et al (3), authors found that the use of the tumescent technique in mastectomies is associated with a significantly increased risk of skin necrosis. However, as pointed out in the study itself, they were only able to pool data from five studies. Thus, we conducted an updated systematic literature search and pooled data from studies to strengthen the published evidence by comparing the incidence of complications between the tumescent and non-tumescent surgical techniques for mastectomies.

MATERIALS AND METHODS

Search Strategy

Two independent reviewers carried out a comprehensive electronic search of PubMed, Embase, BioMed Central, Ovid, and CENTRAL databases without language restrictions. The search was conducted from the inception of these databases to the 1st of November, 2020. Various combinations of the following search terms were included in the database search: "breast surgery", "mastectomy", "hydrodissection", "tumescent", "lignocaine", "epinephrine" and "local anaesthetic". The two researchers reviewed the titles and abstracts of the articles after the database search to identify the relevant articles. They evaluated the full-text of these articles for final inclusion in the study; selection process disagreements were resolved by discussion. Finally, we also performed a manual search of the bibliography of studies meeting the inclusion criteria and of previous reviews on the topic for any missed references. We followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) statement guidelines during the conduct of this review (12), and we present the search strategy and results in **Supplementary Table S1** accordingly.

Inclusion and Exclusion Criteria

We defined the inclusion and exclusion criteria of the review *a priori* based on the PICOS (Population, Intervention, Comparison, Outcome, Study type) framework as follows:

Population: Studies conducted on adult women undergoing mastectomy with or without immediate reconstruction.

Intervention: Use of tumescent dissection technique.

Comparison: Use of non-tumescent technique (defined as the standard surgical technique with electrocautery and/or harmonic scalpel).

Outcomes: Studies reporting data on complications (including skin necrosis, hematoma, infections, seroma, *etc*) after the relevant surgical procedures.

Study type: Randomized controlled trials (RCTs), prospective or retrospective cohort studies.

Our exclusion criteria were the following: 1) Studies on other patients (not undergoing mastectomy). 2) Non-comparative studies. 3) Studies lacking relevant outcomes. 4) Case reports and review articles.

Data Extraction and Quality Assessment

We prepared a data extraction form beforehand to process relevant data. Information Two authors independently sourced the information, and they extracted the name of the first author, publication year, study type, study location, surgery type, non-tumescent technique used, sample size, number of breasts in the population, age of patients, proportion of smokers, proportion of diabetics, use of radiation therapy, mastectomy weight, follow-up length, and study outcomes. The outcomes of interest were the incidences of total skin necrosis, major skin necrosis, minor skin necrosis, hematoma, seroma, infections, and explantation or conversion to autologous reconstruction in cases of alloplastic reconstruction. We defined major skin necrosis as full-thickness necrosis requiring intervention in the operating room and minor skin necrosis as partial necrosis needing only local wound care. Our definition of hematoma included only those requiring surgical evacuation, and that of infections included only those requiring intravenous antibiotics with or without hospital readmission.

We assessed the quality of the studies included using the Cochrane Collaboration risk assessment tool for RCTs (13) and the risk of a bias assessment tool for non-randomized studies (RoBANS) (14). We evaluated selection of participants, confounding variables, intervention measurements, blinding of outcome assessment, incomplete outcome data, and selective outcome reporting for each study.

Statistical Analysis

We carried out our pooled analysis using "Review Manager" (RevMan, version 5.3; Nordic Cochrane Centre [Cochrane Collaboration], Copenhagen, Denmark; 2014). On account of the inherent heterogeneity of the included studies, we chose a random-effects model for the meta-analysis of all outcomes. We calculated odds ratios (ORs) with 95% confidence intervals (CIs) to compare complications between the tumescent and non-tumescent surgical techniques. We pooled the incidence of complications per breast rather than per patient. We carried out a sub-group analysis based on the use of immediate reconstruction after the mastectomies. We also extracted the multivariable-adjusted ORs of the outcomes, if available, from the included studies. We pooled variable data if reported by at least three of the studies using the generic inverse variance model. We used the I^2 statistic to assess heterogeneity and classified it as low (I^2 values between 25% and 50%), medium (values between 50% and 75%) or high (values higher than 75%). We avoided using funnel plots to assess publication bias because each meta-analysis was based on data from more than 10 studies.

RESULTS

Figure 1 shows the PRISMA flow-chart. We included nine studies in the review (15–23). **Table 1** presents their characteristics. Seven studies were retrospective, one prospective, and one an RCT. Most studies were carried out in the USA. All the patients underwent immediate reconstruction in all but in two studies. In the study of Abbott et al (21), 65.7% of patients in the tumescent group and 57.8% of patients in the non-tumescent group underwent immediate reconstruction. In the trial of Lautrup et al (15), none of the patients underwent immediate reconstruction. Two studies reported the use of a harmonic scalpel in the non-tumescent group. In the study of Khavani et al (20), the use of pre-and post-surgery radiation therapy was significantly higher in the non-tumescent group than in the tumescent group. Complication data per breast were available for all studies except for that by Gipponi et al (17), which reported data per patient. Therefore, we excluded this study from the meta-analysis. In that study, the authors reported a significantly higher incidence of minor skin necrosis in the tumescent group (2/15 patients) than in the non-tumescent group (7/15 patients) (p=0.45) without major skin necroses. In addition, they found no significant differences in the incidences of hematoma or wound infection between the two groups (17).

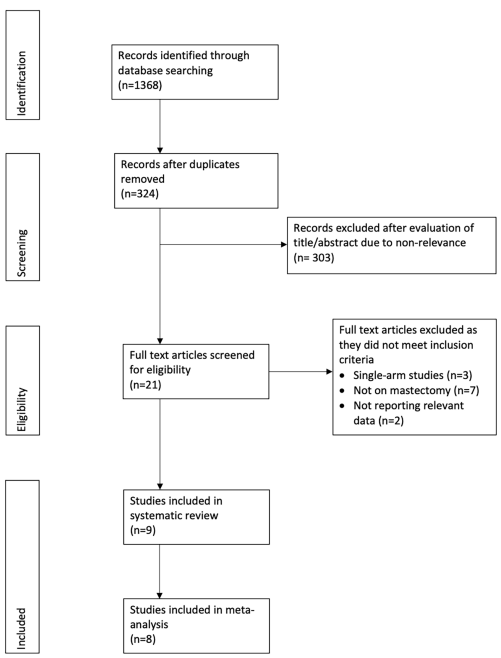

FIGURE 1 | Study flowchart.

Meta-Analysis

We pooled the data on total skin necrosis from eight studies. Our meta-analysis results indicated no significant differences in the incidences of total skin necrosis between tumescent and non-tumescent groups (OR, 1.18; 95% CI, 0.71 to 1.98; I^2 = 82%; p=0.52). Our subgroup analysis based on the use of immediate reconstruction, showed similar results for all sub-groups (**Figure 2**). The incidences of major skin necrosis (OR, 1.58; 95% CI, 0.69 to 3.62; I^2 = 71%; p=0.28) and of minor skin necrosis (OR, 1.11; 95% CI, 0.43 to 2.85; I^2 = 72%; p=0.83) were also similar amongst the two study groups. The results were similar for studies using immediate reconstruction and for the study by Abott et al (21) reporting on a mixed population of patients with or without immediate reconstruction (**Figures 3**, **4**).

We found no statistically significant differences in the incidence of hematoma requiring re-intervention between the tumescent and non-tumescent groups (OR, 1.19; 95% CI, 0.80 to 1.79; I^2 = 4%; p=0.39). The results were similar on the sub-group analysis based on the use of immediate reconstruction (**Figure 5**). A meta-analysis of studies using immediate reconstruction with mastectomy indicated no significant differences in the incidence of seroma between two study groups (OR, 0.84; 95% CI, 0.51 to 1.38; I^2 = 21%; p=0.49) (**Figure 6**). Similarly, we found a similar incidence of infections between the two groups (OR, 0.87; 95% CI, 0.54 to 1.40; I^2 = 54%; p=0.56) (**Figure 7**). And, our results were similar for all studies using immediate reconstruction; only in the study by Abott et al (21) did we find the incidence of infections to be significantly lower in the tumescent group than in the non-tumescent group (OR, 0.23; 95% CI, 0.07 to 0.75; p=0.01) (**Figure 7**). The analysis of studies using immediate alloplastic reconstruction (tissue expander or implant) revealed no statistically significant differences in the incidences of explantation or conversion to autogenous reconstruction between the two groups (OR, 0.78; 95% CI, 0.46 to 1.34; I^2 = 62%; p=0.37) (**Figure 8**).

Multivariable-adjusted ORs on total skin necrosis were available from three studies. Our pooled analysis indicated similarities between the tumescent and non-tumescent groups

TABLE 1 | Details of the studies included.

Author	Year	Study Type	Study location	Surgery type	nTT technique	Number of patients		Number of breasts		Mean age (years)		Smokers (%)		Diabetes mellitus (%)		Pre-mastectomy radiation (%)		Pre-mastectomy radiation (%)		Mean mastectomy weight (g)		Mean follow-up
						TT	nTT	TT	nTT	TT	nTT	TT	nTT	TT	nTT	TT	nTT	TT	nTT	TT	nTT	
Chun et al (23)	2011	RT	USA	Mastectomy with immediate autologous or alloplastic breast reconstruction	NR	275		100	280	46.4 ± 9.5	48± 9.9	30	27.1	1	2.1	7	9.3	7	5.7	625.1 ± 411.7	531.5 ± 292.1	NR
Seth et al (22)	2011	RT	USA	Mastectomy with immediate tissue expander or implant reconstruction	Electrocautery and harmonic scalpel	332	565	457	760	47.4 ± 9.8	48.5 ± 11.4	13.1	11.4	NR	NR	NR	NR	19.3	23.7	NR	NR	36.5 months
Abbott et al (21)	2012	RT	USA	Mastectomy with or without reconstruction	Electrocautery	70	64	113	88	52.5 ± NR	51.3 ± NR	5.7	9.4	NR	NR	NR	NR	NR	NR	712.4 ± NR	675.6 ± NR	NR
Khavanin et al (20)	2013	RT	USA	Mastectomy with immediate tissue expander–implant-based reconstructions	Electrocautery and harmonic scalpel	1030		890	601	47.7 ± 10.5	49.3 ± 11.1	8.88	9.15	NR	NR	2.92*	8.15*	20*	25.29*	NR	NR	21.2 months
Vargas et al (18)	2015	RT	USA	Skin- sparing mastectomy followed by immediate autologous microsurgical breast reconstruction	Electrocautery	504		336	394	49.7 ± 8.5	49.2 ± 8.1	14.6	8.4	2.4	7	21.7	18.2	NR	NR	779.4 ± 419.1	760.3 ± 409.4	NR
Gipponi et al (17)	2017	PT	Italy	Skin- sparing mastectomy or nipple-sparing mastectomy with immediate alloplastic reconstruction	NR	15	15	NR	NR	53.37	48.26	40	33	NR	NR	NR	NR	NR	NR	NR	NR	NR
Ng et al (16)	2019	RT	Canada	Nipple-sparing mastectomy with immediate alloplastic reconstruction	Electrocautery	40	22	77	39	43± 10.7	43.2 ± 8.7	10	9.1	NR	NR	3.9	5.1	NR	NR	326.6 ± 131.4	286.3 ± 103.4	NR
Tasoulis et al (19)	2019	RT	USA	Nipple-sparing mastectomy with immediate alloplastic reconstruction	Electrocautery	23	18	46	36	38 (25-63)^	36.5 (19-52^	0	5.6	0	0	NR	NR	NR	NR	NR	NR	6 months
Lautrup et al (15)	2020	RCT	Denmark	Mastectomy without immediate reconstruction	Electrocautery	105	98	107	102	65.6 ± NR	60.3 ± NR	16	14	8	5	0	0	NR	NR	NR	NR	NR

RT, retrospective; PT, prospective; NR, not reported; RCT, randomised controlled trial; TT, tumescent technique; nTT, non-tumescent technique; RL, Lactated Ringer's solution.

**Statistically significant difference between TT and nTT groups as reported by the study.*

^Median (Range).

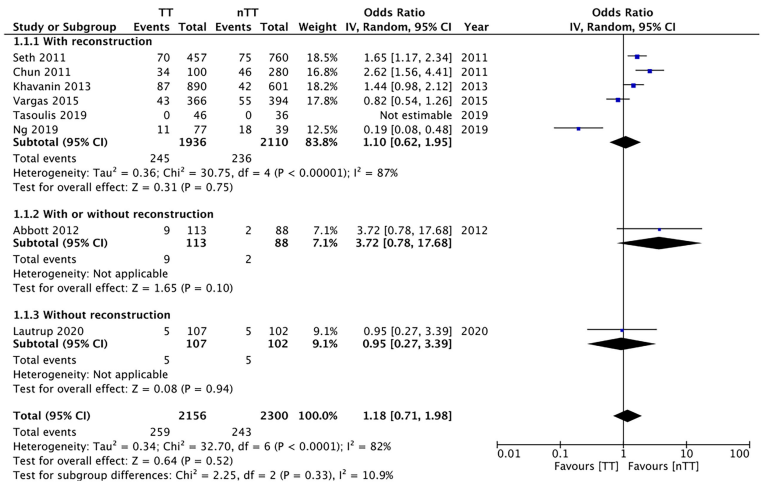

FIGURE 2 | Forest plot for total skin necrosis in sub-group analysis based on immediate reconstruction. TT, tumescent group; nTT, non-tumescent group; IV, inverse variance; OR, odds ratio.

(OR, 1.72; 95% CI, 0.72 to 4.13; I^2 = 87%; p=0.23) (**Figure 9**). Due to lack of data we could not complete this type of analysis for other outcomes.

Quality Assessment

Table 2 presents our quality assessment for the included studies. Blinding was not possible in the RCT due to the nature of the intervention. For all non-RCTs, we found a high risk of bias due to unadjusted confounding factors.

DISCUSSION

The results of our updated systematic review and meta-analysis based mostly on non-RCTs indicate that the complication rates (skin necrosis, hematoma, seroma, and infections) may be similar for both the tumescent and non-tumescent dissection mastectomy techniques. The incidences of explantation or conversion to autogenous reconstruction were similar between the two dissection techniques in patients undergoing alloplastic reconstruction.

The optimal separation of the subcutaneous tissues containing the sub-dermal plexus from the gland parenchyma is essential to maximize flap survival during mastectomies. This dissection is also important from an oncological point of view; thick flaps may result in recurrence of malignancy in the remnant breast tissue, but thin flaps may lead to skin necrosis (18, 24). Electrocautery has been widely used as a conventional dissection technique in institutions worldwide. When compared to scalpel dissection, electrocautery is associated with less blood loss and a lack of cosmetic outcome or patient satisfaction score differences (25). However, the high temperatures needed for the

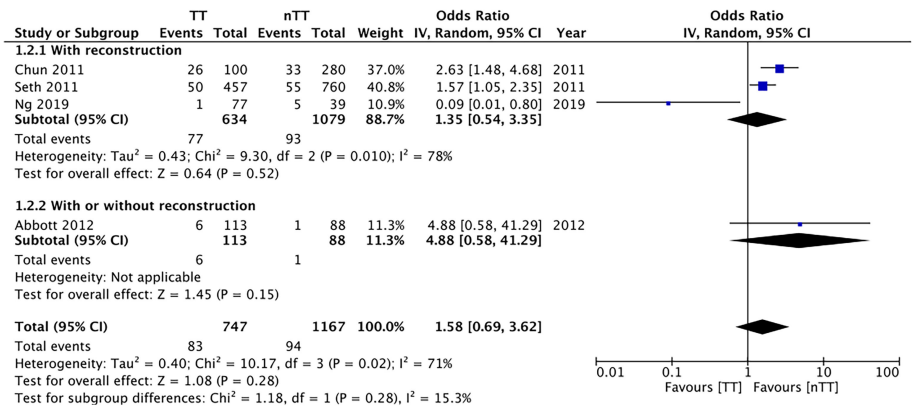

FIGURE 3 | Forest plot for major skin necrosis in sub-group analysis based on immediate reconstruction. TT, tumescent group; nTT, non-tumescent group; IV, inverse variance; OR, odds ratio.

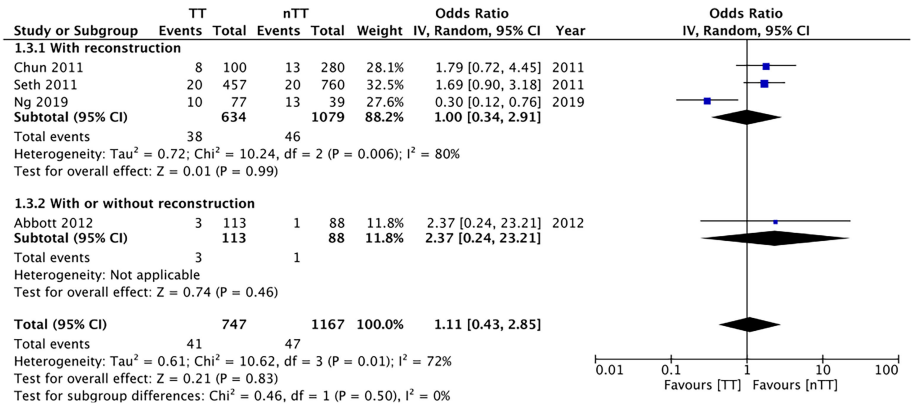

FIGURE 4 | Forest plot for minor skin necrosis in sub-group analysis based on immediate reconstruction. TT, tumescent group; nTT, non-tumescent group; IV, inverse variance; OR, odds ratio.

electrocautery can cause significant ischemic lesions on the skin and subcutaneous tissues leading to wide areas of necrosis (17, 26, 27). The tumescent technique is thought to reduce the thermo-dispersion of the electrocautery thereby improving flap survival. However, concerns about the incidence of skin necrosis with the tumescent technique itself have also been raised. The vasoconstrictor effect of epinephrine and the compressive effect of the solution, which both reduce the blood loss are thought to contribute to reduced skin flap survival (23). In this context, our review presents important findings on the complications of these two techniques for surgeons carrying out mastectomies.

Our analysis revealed similar incidences for minor and major skin necrosis with both techniques. Skin necroses after mastectomies can be influenced by different confounding factors such as age, obesity, smoking, diabetes mellitus, and prior radiation therapy (11, 28, 29) that can be controlled for only in well-conducted RCTs to provide high-quality evidence. Unfortunately, only one RCT was available for inclusion in our review. For the remaining studies, the allocations were not randomized, and known and unknown patient characteristics differed between the study groups. Therefore, our results need to be interpreted with caution as the non-significant difference between the two techniques may not necessarily be due to intervention equivalence, but could have been caused by systematic differences between the groups themselves (30). While all non-RCTs in our analysis reported minimal differences between the two groups, none of them carried out propensity-score matching to adjust for baseline factors. Only three studies reported results of multivariable regression analysis for total skin necrosis. Our pooled analysis of such data indicated a similar incidence of total skin necrosis for both techniques. The use of immediate reconstruction, especially alloplastic

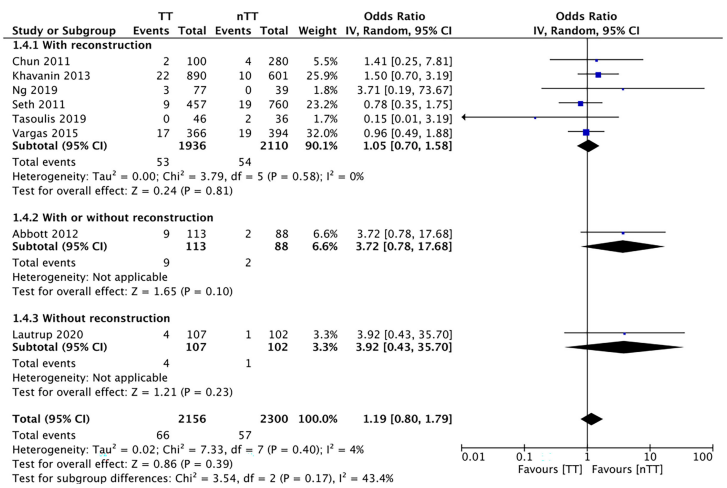

FIGURE 5 | Forest plot for hematoma in sub-group analysis based on immediate reconstruction TT, tumescent group; nTT, non-tumescent group; IV, inverse variance; OR, odds ratio.

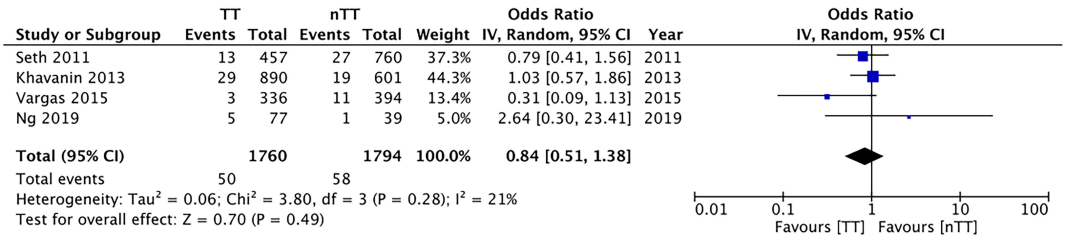

FIGURE 6 | Forest plot for seroma with sub-group analysis based on immediate reconstruction TT, tumescent group; nTT, non-tumescent group; IV, inverse variance; OR, odds ratio.

reconstruction, is an important variable affecting immediate local complications (31). While most of the studies included used reconstruction in all the patients, two studies did not. Hence, we conducted a sub-group analysis including a single study in each group and obtained similar results. We further analyzed the incidence of explantation or conversion to autologous grafts in patients undergoing alloplastic reconstruction and the results of our meta-analysis demonstrated no adverse effect of the tumescent technique on the risk of explantation. However, it needs to be mentioned that the outcomes with tumescent technique can depend on many factors related to breast reconstruction namely the position of implant (pre-pectoral or retro-pectoral) and the use of mesh (synthetic or acellular). Traditionally, there has been a strong correlation between the use of tumescent technique and pre-pectoral implant placement and use of mesh due to advantages like shorter surgical time, reduced bleeding and easier dissection (32). More recently, tumescent technique has been used for retro-pectoral implant placement as well. Shimuzu et al (33) in a retrospective review of 35 patients undergoing awake breast augmentation with intercostal nerve blocks and tumescent technique have reported good outcomes with both pre-pectoral and retro-pectoral implant placement. Depending upon the position of implant, the tumescent solution needs to be injected either between the mammary gland and the pectoralis muscle or beneath the muscle in case of retro-pectoral implant placement. An important difference between the two is the amount of tumescent solution needed. In case of pre-pectoral implant placement, researchers have reported use of 400 to 700 ml of solution per breast while around 740 ml was needed for retro-pectoral implant placement (34). In our review, the included studies used various modalities of autologous and alloplastic reconstruction with differences in the use mesh and position of implant. Since outcomes were not reported separately for each modality of breast reconstruction, we were unable to discern evidence on the efficacy of tumescent technique for different methods of breast reconstruction. Additionally, it also needs to be pointed out that in recent times video-assisted and robot-assisted surgery is slowly gaining attention, especially for nipple-sparing mastectomy (35, 36). These minimally invasive techniques have proven to be safe, with low conversion rate to open surgery and acceptable complication rates. Lai et al (35) in a consensus statement on robotic-nipple sparing mastectomy have recommended the use of tumescent technique for development of the skin flap. Our review was, however, unable to assess the efficacy of tumescent technique for robotic surgeries due to lack of comparative data.

In the case of the tumescent technique, once the effect of the vasoconstrictor disappears, rebound bleeding and hematoma formation can ensue (15). Hematoma requiring re-intervention

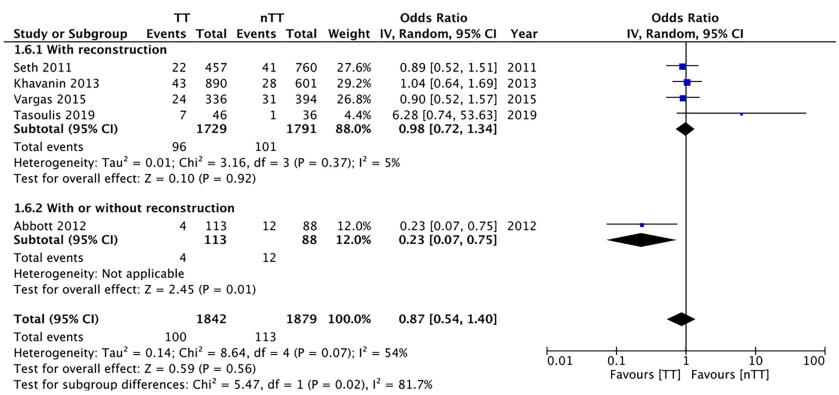

FIGURE 7 | Forest plot for infections in sub-group analysis based on immediate reconstruction TT, tumescent group; nTT, non-tumescent group; IV, inverse variance; OR, odds ratio.

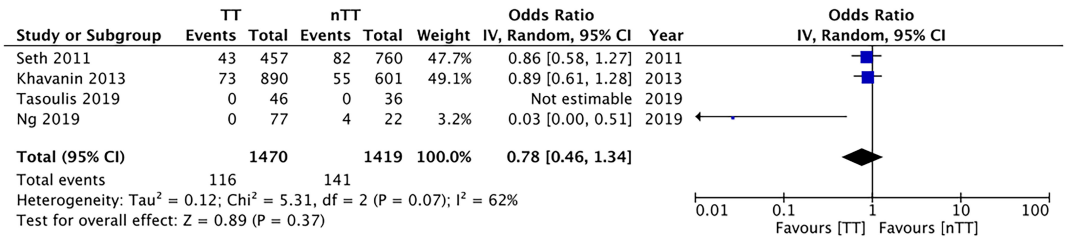

FIGURE 8 | Forest plot for explantation or conversion to autologous reconstruction in patients undergoing immediate alloplastic reconstruction. TT, tumescent group; nTT, non-tumescent group; IV, inverse variance; OR, odds ratio.

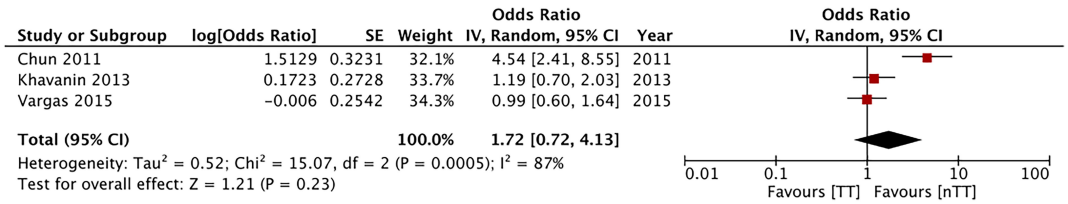

FIGURE 9 | Forest plot of multivariable adjusted odds ratios for total complications and total skin necrosis. TT, tumescent group; nTT, non-tumescent group; IV, inverse variance; OR, odds ratio.

is a serious complication, we assessed its incidence in our review. Our meta-analysis revealed similar hematoma incidences with the use of the tumescent technique. We obtained similar results for seroma and infectious complications. As mentioned earlier, these outcomes could have been caused by several confounding factors like co-morbidities, axillary dissection, surgical technique, use of antibiotics, and local wound care, variables which were not controlled in retrospective studies (37, 38).

Our results differed from those in the previously published meta-analysis. Siotos et al (3) reported a significant increase in

TABLE 2 | Risk of bias in the studies included.

RCT						
Study	**Random sequence generation**	**Allocation concealment**	**Blinding of participants and personnel**	**Blinding of outcome assessment**	**Incomplete outcome data**	**Selective reporting**
Lautrup et al (15)	Low risk	Low risk	High risk	High risk	Low risk	Low risk
Retrospective studies						
Study	Selection of participants	Confounding variables	Intervention measurements	Blinding of outcome assessment	Incomplete outcome data	Selective outcome reporting
Chun et al (23)	Low risk	High risk	Low risk	High risk	Low risk	Low risk
Seth et al (22)	Low risk	High risk	Low risk	High risk	Low risk	Low risk
Abbott et al (21)	Low risk	High risk	Low risk	High risk	Low risk	Low risk
Khavanin et al (20)	Low risk	High risk	Low risk	High risk	Low risk	Low risk
Vargas et al (18)	Low risk	High risk	Low risk	High risk	Low risk	Low risk
Gipponi et al (17)	Low risk	High risk	Low risk	High risk	Low risk	Low risk
Ng et al (16)	Low risk	High risk	Low risk	High risk	Low risk	Low risk
Tasoulis et al (19)	Low risk	High risk	Low risk	High risk	Low risk	Low risk

RCT, randomized control trial.

the risk of total skin necrosis (OR, 1.56; 95% CI, 1.04 to 2.35; I^2 = 71%; p=0.03), major skin necrosis (OR, 2.01; 95% CI, 1.29 to 3.14; I^2 = 29%; p=0.002), and minor skin necrosis (OR, 1.75; 95% CI, 1.06 to 2.90; I^2 = 0%; p=0.03) with the use of the tumescent technique. However, we found no such difference after our analysis and review. This can be attributed to the inclusion of three more studies in our analysis that provided a significant update. Furthermore, our review was strengthened by the additional analyses on the incidences of seroma and explantation, which had not been carried out in the previous study. To account for confounding factors and provide a comprehensive review, we pooled the data on multivariable-adjusted ORs.

The limitations of our review include the large number of retrospective studies in the analysis with their inherent bias and the fact that many studies had small sample sizes, which may have skewed our results. In addition, the studies included presented different types of surgical procedures and of reconstructions during the standard non-tumescent technique, and different follow-up durations creating methodological heterogeneity among them. Moreover, Seth et al (22) and Khavanin et al (20) reported data from the same institution with an overlap of four years. Also, complications with mastectomies can be influenced by the surgical skill and experience of the surgeons, and the impact of this factor on our results is difficult to assess. Lastly, we were unable to analyse oncological outcomes between tumescent and standard surgical techniques due to lack of data from include studies. Future studies should also report oncological outcomes in order to better assess the outcomes associated with the use of tumescent technique.

To conclude, the available evidence was of low-quality and derived mostly from non-randomized studies, but our analysis results suggest that the incidences of skin necrosis, hematoma, seroma, infection, and explantation between the tumescent and non-tumescent mastectomy techniques are similar. High-quality RCTs assessing the role of the tumescent technique with different reconstruction methods are needed to strengthen the evidence.

DATA AVAILABILITY STATEMENT

Publicly available datasets were analyzed in this study. This data can be found here: PubMed, Embase, BioMed Central, Ovid, and CENTRAL databases.

AUTHOR CONTRIBUTIONS

YY designed the project. JZ, XQ, and JF were involved in data collection and data analysis. YY prepared the manuscript. FS edit the manuscript. All authors read and approved the final manuscript.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2021.648955/full#supplementary-material

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Role of Breast-Conserving Surgery on the National Health System Economy From and to SARS-COVID-19 Era

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Day surgery breast-conserving surgery (DS-BCS) is a surgical approach applied in many specialized breast surgery departments. This study demonstrates the benefits of this approach from the perspectives of patients and of the Hospital/National Health System compared to ordinary breast-conserving surgery (ORD-BCS) under general anesthetic. A comparison of costs and diagnosis-related group (DRG) reimbursement demonstrated improved cost-effectiveness in DS-BCS compared to ORD-BCS.

Keywords: SARS-CoV-2, COVID-19, healthcare cost, day-surgery, cost saving, breast conserving surgery, awake surgery

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INTRODUCTION

Day surgery is becoming increasingly utilized in many healthcare systems. It reduces patient waiting time by increasing patient throughput while ensuring high quality care. Day surgery can also significantly reduce the cost of healthcare (1, 2). Traditionally, a minimum of 2 days of inpatient stay is required for breast surgical procedures, such as quadrantectomy, and this has been attributed to general anesthesia.

It has been previously demonstrated that the status of axillary lymph nodes is safely assessed by sentinel node biopsy (SLNB), particularly when approaching early-stage breast cancer (3, 4). Reduced postoperative pain, absence of drainage from the axilla, decreased percentage of neurovascular complication and lymphedema are some of the many advantages of SLNB.

Opioid-based general anesthesia and perioperative analgesia represent the main trigger for postoperative nausea, vomiting, respiratory problems, urinary retention, ileus, and hyperalgesia. Moreover, some studies have shown a higher probability of metastasis related to the choice of anesthetic setting. (5, 6). Previous reports have shown no intraoperative pain during an awake patient quadrantectomy procedure with ropivacaine infiltration (7, 8).

Many protocols have demonstrated that regional anesthesia techniques such as thoracic paravertebral block (TPVB), pectoral nerve block (PECS), erector spinae plane (ESP) block, and serratus anterior plane (SAP) result in a reduction in opioid usage during the postoperative period (9, 10).

We have introduced the concept of awake breast surgery during the COVID-19 pandemic as a means of reducing the incidence of viral infection and maximizing the utility of hospital service during a period of intense pressure (11–13).

TABLE 1 | Discharge criteria.

Discharge criteria
Stable vital signs
Alert and orientated
Absence of respiratory distress
Pain controlled
No bleeding (drainage < 100 cc in 24/h)
Steady gait, no dizziness or meets preoperative level

Based on our report (11), financial analysis of awake breast surgery would be beneficial to help improve the current model of care for patients with breast cancer that require wide local excision.

Based on this, in a health context in which 70% of procedures have been carried out with the awake approach and 30% of them with a conventional approach, it is interesting to make a forecast of income in a 1-year time lapse and compare it to the 30% awake BCS rate before the COVID-19 pandemic.

The objective of this study is to perform a cost analysis of breast surgery undertaken when 70% of cases were performed using regional anesthesia vs. 30% with conventional general anesthesia. This would be compared to the standard of care before the pandemic when the division of regional vs. general anesthesia was reversed.

MATERIALS AND METHODS

Study Design

In this study, we retrospectively enrolled all patients undergoing breast-conserving surgery from January to March 2020. From this cohort, patients undergoing breast conserving surgery and sentinel lymph node biopsy were grouped according to day surgery (DS-BCS) or ordinary surgery (ORD-BCS).

Patients have been assessed pre-operatively by mammography, ultrasound, or MRCP. Lymphoscintigraphy was performed externally the day before surgery. All malignant cases that were suitable for breast-conserving surgery were included. Exclusion criteria were: men, pregnancy, pure breast reconstruction (BR) surgical procedures, and benign disease.

In order to discharge day surgery patients, all discharge criteria (**Table 1**) had to be met; otherwise, they were admitted to an inpatient ward for a one-night stay.

Hospital data concerning the number of patients in the year 2019 were collected in order to do a forecast of income with the adoption of such a greater day surgery surgical approach.

Inclusion and Exclusion Criteria

Patients between 18 and 90 years old whose physical status corresponded to the American Society of Anesthesiologists (ASA) physical status classification system (14) grades I-II were enrolled for awake breast-conserving surgery in a day surgical setting. ASA grade III patients who presented with stable clinical status and well-controlled comorbidities could be enrolled for awake BCS. Older patients who, during the considered period, gave consent to awake breast surgery in the day surgical setting were included.

Patients who did not give their informed consent to the awake procedure, ASA grade IV patients, or patients with preoperative indication to radical mastectomy were excluded.

Hospital Cost and NHS Cost

A cost analysis for both DS-BCS and ORD-BCS was carried out considering both fixed costs, such as surgical instruments, and variable costs (operating theater and ward bed). Bed cost has been modified according to the length of stay in the case of an overnight stay.

Operating time cost was calculated as the actual cost per hour. For DS-BCS, this was calculated as € 240/h and € 600/h for ORD-BCS (the difference in cost is due to the number of nurses, operating staff, devices, and operating room length of usage). All costs are updated for the 2020/2021 health costs (15).

Ward bed cost was € 150 for DS-BCS and € 605/day for ORD-BCS; for patients who required longer stay, the daily cost was multiplied by the number of inpatient days (15).

Total cost is given by the sum of the operating theater time and ward bed multiplied by the number of procedures performed within each setting. Hospital coding and accounts services provided all data on cost.

In order to analyze the financial cost better from a National Health System perspective, a comparison between DS-BCS diagnosis-related group (DRG) and ORD-BCS (DRG) was performed. The refunded cost was € 2831.47 for ORD-BCS and € 1,362 for DS-BCS, and these represent the maximum tariffs paid to hospitals with a flat fee (www.gazzettaufficiale.it) according to the current Legislative Decree of October 18, 2012.

Endpoints

The primary outcome was to evaluate the total cost difference between DS-BCS and ORD-BCS assuming a zero 30-day readmission rate. This assumption represents one limitation of this study. Readmission is defined as hospitalization occurring within 30 days from discharge and lasting at least 24 h.

The secondary outcome was to make a forecast of net income; adopting the awake surgery approach as the main operating setting. This was the standard practice in March 2020 when 70% of cases were carried out as awake surgery in order to reduce hospitalization and increase the number of oncologic patients who could have access to needed surgical procedures.

Statistical Analysis

We calculated means and ranges for continuous variables. Differences between the two groups were assessed by *t*-test. Categorical data were recoded into numbers and percentages. Fisher's exact test was performed to analyze dichotomous variables such as different surgical procedures. A p-value < 0.05 was necessary for a variable to be considered statistically significant. SPSS statistical package version 23.0 (SPSS Inc., Chicago, IL, United States) was used to perform the statistical analysis.

TABLE 2 | Patient characteristics of day surgery breast-conserving surgery (DS-BCS) vs. ordinary breast-conserving surgery (ORD-BCS).

Variables	Day surgery BCS	Ordinary BCS	*p*-value
Number of patients	39	17	-
Age (years)	71, 56 (SD = 7, 8)	67, 82 (SD = 8, 4)	0, 1
Weight (Kg)	62, 15 (SD = 9, 73)	66, 76 (SD = 6, 8)	0, 08
ASA Score			0, 5
ASA grade 1	18 (46%)	6 (36%)	-
ASA grade 2	10 (26%)	7 (41%)	-
ASA grade 3	11 (28%)	4 (23%)	-
Major comorbidities			
Cardiovascular disease	3 (7, 6%)	1 (5, 8%)	0, 78
CKD	2 (5, 1%)	0	0,77
Respiratory disorders	1 (2, 5%)	0	0, 56
Diabetes	2 (5, 1%)	1 (5, 8%)	1

TABLE 3 | Composite cost evaluation.

Variables	Day surgery BCS	Ordinary BCS	*p*-value
Number of patients	39	17	-
Hospital cost per patient	784, 42 (SD = 12, 58)	3158,76 (SD = 53, 76)	0, 001
Operative time cost	449, 53 (SD = 55, 14)	1527, 35 (SD = 198, 76)	0, 001
Ward cost	150 (SD = 20, 07)	605 (SD = 48, 28)	0, 001
DRG reimbursement per patient	1362	2831, 47	0, 001
Total hospital cost	30703, 53	53950, 89	0, 001
Total DRG Reimbursement	53118	48135	0, 001

TABLE 4 | One-year income forecast.

Operative setting percentage	Net income
30% DS 70% ORD	−21.431, 67
70% DS 30% ORD	+99.591, 43

RESULTS

A total of 56 cases were identified during the study period. Thirty-nine (70%) were eligible for day surgery cases [female 100%, mean age = 71.56 years (SD = 7.8), mean weight 62.15 (SD = 9.73) kg]. The remaining patients (17) who did not satisfy the day surgery criteria were included in the ordinary surgical procedure group [female 100%; mean age = 67.82 (SD = 8.4), mean weight = 66.76 kg (SD = 6.8), $p = 0.1$]. Characteristics of both day surgery and ordinary BCS patients, ASA scores, and comorbidities are listed in **Table 2**. No major complications were reported. No statistically significant difference in patient characteristics between the two groups was found ($p > 0.05$).

Day surgery BCS resulted in a total hospital expense of € 30,703.53 [mean tariff paid per patient: € 784.42 (SD = 12.58)], while ordinary BCS resulted in a total hospital expense of € 5,3950.89 [mean tariff paid per patient: € 3,158.76 (SD = 53.76)] ($p = 0.001$) (**Table 3**).

Overall NHS costs for day surgery and ordinary surgery were € 53,118 and 48,135, respectively ($p = 0.001$). Mean DS-BCS DRG was € 1,362 vs. € 2,831.47 for BCS-ORD DRG, resulting in a difference (Δ DRG = € 2,831.47– € 1,362) of € 1,469.47 per inpatient procedure and, thus, representing a total overcharge for the Italian NHS of € 24,981 (€ 1,469.47 × 17 ordinary BCS) when day surgical regimen was not considered; this is limited to 2 months (**Table 3**).

The annual forecast of net income adopting the day surgical awake surgery (70% DS-BCS vs. 30% ORD-BCS) transformed a total annual loss of € 21,431.67 into a net income of € 99,591.43 (**Table 4**).

DISCUSSION

The search for less invasive treatment of breast cancer is still ongoing. Sentinel node biopsy and wide local excision under local anesthesia are important steps toward optimal results. We are witnessing a more conservative surgical approach to breast cancer. Breast-conserving surgery is superseding mastectomy.

Immunosuppression represents the physiological response to stress. This may represent a risk for a patient in the perioperative setting. Therefore, one of the most important objectives for patient care is the reduction of perioperative stress (16, 17). Lifestyle factors account for a small (at most 30%) percentage of cytotoxic activity that might become an additional biomarker to consider in a lifestyle intervention for cancer prevention. In a trial for women who had breast cancer more than 5 years before the intervention, it has been demonstrated that cytotoxic activity can be modified by changing several lifestyle factors (18, 19).

The probability of metastases and tumor progression can be increased by blood lymphocyte cytotoxic activity reduction (20, 21). Moreover, surgical site infection (SSI) is predicated by decreased immune function. Minimally invasive techniques have a reduced impact on immune function. However, the protective role of minimally invasive techniques in early lymphocyte response has not been properly demonstrated (7). As reported by Pompeo et al. (22) and Roselli et al. (23), the choice of a general anesthesia setting could influence the immune system; hence, awake breast surgery, avoiding general anesthesia, can positively interfere with postoperative lymphocyte response. Patients' quality of life is positively affected by day surgical BCS, because of shorter hospitalization and early return to normal activities. Furthermore, the day surgical setting is fundamental for better utilization of limited healthcare resources.

To our knowledge, this is the first cost analysis to evaluate the benefits of BCS in day surgery both on the hospital and

on the NHS in Italy reported in the literature. Hospital costs resulted in € 784.42 per patient in a day surgical setting and € 3,158.76 for an ordinary setting. Prior to the SARS-CoV2 pandemic, the ratio of surgical approaches was 30% for the awake setting and 70% for the general anesthesia setting. In March 2020, the ratio completely reversed with a 70% awake setting, transforming a loss of € 3,572 into a profit of € 16,599 during 2 months. Furthermore, the ordinary BCS constitutes an important financial burden for NHS. In the Lazio region (Italy), the mean reimbursement for day surgery and ordinary BCS reaches € 1,362 and € 2,831.5, respectively, resulting in NHS mean overcharge of € 1,469.47 for each inpatient BCS. Interestingly, making a 1-year forecast of such a change in the operative setting DS-BCS could represent a prospective profit of € 99,591.4 instead of a loss of € 2,1431.7 when considering BCS inpatient (total DRG reimbursement–hospital cost).

Considering the social impact of breast cancer and the growing importance breast-conserving surgery has acquired during the years, it is rational to analyze and consider the financial burden for healthcare services. We performed a cost effectiveness evaluation by a complete cost analysis that took into account surgery-related costs as well as DRG refunded fees, providing a complete financial assessment that takes into account both local tertiary care centers and NHS.

Thus, we can conclude that considering clinical benefits for patients and financial benefits for hospitals, the awake day surgical approach must always be considered and promoted in well-selected centers. Cost savings that can be achieved could be used for investments in research and patient care. This strategy adopted at our breast unit should be performed routinely and not only during the emergency period. Further larger controlled scale trials are needed to establish safety and more robust cost predictions.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary materials, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The manuscript was approved by the local Ethical Committee of the Fondazione Policlinico Tor Vergata (reference 122/20). Due to retrospective analysis and anonymous data analysis, written informed consent to participate in this study was not provided in accordance with the national legislation and institutional requirements.

AUTHOR CONTRIBUTIONS

OB, DV, MP, and GV analyzed the data and wrote the manuscript. GD acquired the economic data. MP performed the statistical analysis. FP analyzed and performed the economic cost evaluation and economic forecast. AS, CB, and MD reviewed the manuscript. All the co-authors gave a contribution to the article and approval to the submitted version.

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Higher Pathological Complete Response Rate of Less than 10 Total Axillary Lymph Nodes After Axillary Lymph Node Dissection Following Neoadjuvant Chemotherapy in Breast Cancer

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Background: The American Joint Committee on Cancer (AJCC) guideline recommends the evaluation of ≥10 axillary lymph nodes (ALN) in patients with breast cancer to assess the N stage. However, the total ALN count in ALN dissection (ALND) often decreases after neoadjuvant chemotherapy in breast cancer. The authors compared clinicopathological factors and oncological outcomes between <10 vs. ≥10 ALNs after ALND following neoadjuvant chemotherapy in breast cancer.

Methods: Data of 159 patients with breast cancer, treated with neoadjuvant chemotherapy and ALND, were reviewed, and the cases were classified into two groups (<10 vs. ≥10 ALN count). The treatment response was determined based on the RECIST 1.1 criteria, and histopathological regression of the tumor was assessed based on the Miller-Payne grading scales.

Results: Most of the clinical and pathological factors did not demonstrate any significant differences between the two groups. However, the pathological complete response (pCR) rate in breast lesion and ALNs were the higher trend in the group with <10 ALNs. During the 88-month follow-up period, there was no significant difference in locoregional recurrence, distant metastasis, or overall survival.

Conclusions: Although there was a limitation due to different sample sizes, additional axillary surgery may not be necessary even in cases with <10 total ALNs after ALND, following neoadjuvant chemotherapy because the lymph nodes are more likely to have been regressed themselves due to neoadjuvant chemotherapy, and the residual lymph nodes may be absent.

Keywords: breast cancer, axillary lymph node, neoadjuvant chemotherapy, pathological complete response, dissection

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BACKGROUND

Recent advanced treatment strategies developed for breast cancer have improved the prognosis of patients with breast cancer. Based on the National Surgical Adjuvant Breast and Bowel Project B-18 and B-27 results, neoadjuvant chemotherapy (NAC) is considered before surgery in locally advanced breast cancer, which has allowed not only better oncological outcomes, but also a high rate of breast conservation in surgery (1, 2). However, it is important to perceive the clinical stage and histological characteristics before initiation of treatment, because those may change, owing to NAC.

The goal of NAC in breast cancer is pathological complete response (pCR) for breast or axillary metastatic lesions. When the pCR is achieved in the breast or axillary lesions, the prognosis of breast cancer becomes better (1, 3–5). However, the normal structures are also damaged along with the breast cancer during NAC. The edematous breast parenchyma or fibrotic change in the axillary area is a common surgical finding in breast cancer managed with NAC. In addition, normal lymph node structures are usually denatured, and, as a result, the total lymph node count may decrease.

Based on the AJCC staging guideline, at least 10 total lymph nodes should be evaluated for accurate determination of the N stage (6–8). However, occasionally, the total lymph node count is reported as <10 after NAC in breast cancer, even if the complete axillary lymph node dissection (ALND) was performed by a well-experienced surgeon.

We compared the oncological outcomes of breast cancer treated with NAC between groups with <10 and 10 or more total lymph nodes after ALND, identifying pathological results and evaluating the associated clinical factors.

METHODS

Between 2010 and 2016, the data of 159 patients, with locally advanced breast cancer who underwent breast surgery and ALND after NAC, were selected from 1,131 patients with breast cancer, who were diagnosed and treated at the Kyungpook National University Hospital. The data included the patients' characteristics, medical history, follow-up oncological results, and histopathological characteristics, including molecular subtypes. Before the initiation of treatment, all the patients had undergone core needle biopsy for the diagnosis of breast cancer and fine-needle aspiration cytology for that of ALN. The patients who had noninvasive breast cancer or *de novo* metastatic breast cancer were excluded (**Figure 1**).

All procedures in this study that involved human participants were performed in accordance with the ethical standards of the Institutional Review Board of the Kyungpook National University Chilgok Hospital (KNUCH 2015-05-205). The experimental protocol was also approved by the Institutional Review Board of the Kyungpook National University Chilgok Hospital, and all the experiments were performed in accordance with relevant guidelines and regulations.

Treatment and Follow-Up Strategy

All the patients had undergone NAC before the surgery. The NAC regimens were anthracylin + cyclophosphamide (AC) (n = 5; 3.1%), AC + taxane (n = 116; 73%), AC + taxane + trastuzumab (n = 26; 16.4%), and others (n = 12; 7.6%). After 3 to 4 cycles of NAC, mammography, breast and neck ultrasound, chest/abdomen computed tomography (CT), and bone scan were rechecked to evaluate the treatment response. Additional cycles were completed if the breast cancer showed partial or complete response. After completion of NAC, breast surgery was performed, including a breast-conserving surgery and mastectomy with ALND (Levels I and II). When the tumor showed stable or progressive disease status during NAC, surgery was considered without completion of NAC. According to the residual tumor burden and molecular subtype in the final pathological report, adjuvant chemotherapy or radiotherapy was offered, and trastuzumab and endocrine therapy were applied, if necessary.

Cancer surveillance was performed in all the patients with blood test monitoring, tumor marker assessment, mammography, breast ultrasound, chest x-rays or CT, abdominal ultrasound or CT, and bone scans biannually for the first 2 years and annually for additional 3 years. The oncological outcomes were assessed based on locoregional recurrence, distant metastasis, or death during the follow-up period.

Evaluation of Treatment Response and Pathological Results

Treatment response was determined based on the RECIST 1.1 criteria (9). The clinical complete response was defined when there was no evidence of tumor in physical examination with radiological complete response. Clinical partial response was defined when the largest tumor diameter was reduced by more than 30% in radiological images. Clinical stable disease was defined when the largest tumor diameter increased <20%. However, when the largest tumor diameter showed an increase of the largest tumor diameter of 20% or more, it was regarded as a clinically progressive disease.

For each case, all the available hematoxylin and eosin-stained specimens, including frozen-diagnosed and subsequent frozen-permanent samples, were retrospectively reviewed by two pathologists (NJP and JYP) with 10 and 18 years of experience in breast pathology, respectively, in a blinded manner without information about the clinicopathological data or outcomes. The histopathological reviews were conducted independently. Cases with a discrepancy were repeatedly reviewed until a consensus was reached.

The histopathological regression of primary tumor was assessed according to the Miller–Payne grading scales based on the overall cellularity in the excision and mastectomy samples compared with the pretreatment biopsy (10). Grade 1 indicated no change or some alteration to individual malignant cells, but no reduction in overall cellularity (pathologic non-response, pNR). Grade 2 indicated a minor loss of tumor cells, but overall high

Abbreviations: NAC, neoadjuvant chemotherapy; pCR, pathological complete response; AJCC, American Joint Committee on Cancer; ALND, axillary lymph node dissection; pNRL, pathologic non-response; pPR, pathologic partial response.

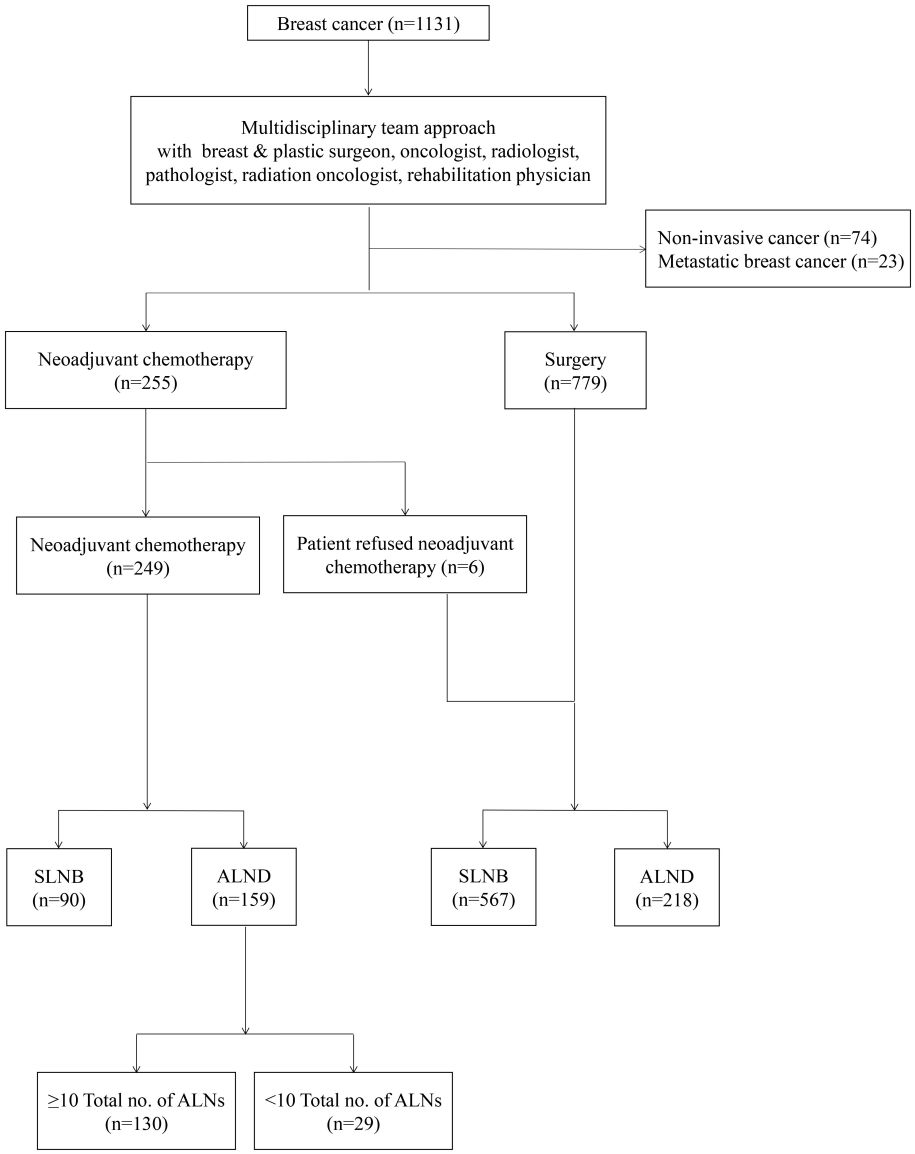

FIGURE 1 | A flow chart showing management of breast cancer with a multidisciplinary team approach. SLNB, Sentinel lymph nodes biopsy; ALND, axillary lymph nodes dissection.

cellularity, with 30% loss (pPR). Grade 3 indicated an estimated reduction in tumor cells (pathologic partial response, pPR) between 30 and 90%. Grade indicated a marked disappearance of tumor cells such that only small clusters or widely dispersed individual cells remain, with more than 90% loss of tumor cells (almost pCR). Grade 5 indicated that no malignant cells were identifiable in sections from the site of the tumor, with only vascular fibroelastotic stroma remaining, often containing macrophages, but ductal carcinoma *in situ* may be present (pCR).

The evaluation of treatment response in ALNs was more complicated because each specimen had a variable number of lymph nodes, and each lymph node had different treatment regression and therapy-related changes. The presence of nodal tissue was assessed for each specimen, and then the residual tumor burden and any therapy-related histopathological findings at the individual lymph node were independently evaluated. The regression parameters in lymph nodes included size and overall cellularity (percent scale) of residual tumor cells, presence of extranodal tumor extension, intranodal lymphovascular invasion, fibrosis, necrosis, foamy histocytic aggregates, microcalcification, and fibroelastic vascular change (11, 12).

Statistical Analysis

All statistical analyses were performed using SPSS (version 25.0; SPSS, Chicago, IL). Categorical variables were analyzed using the chi-squared test in univariate analysis, and oncological outcomes were assessed using Kaplan–Meier

analysis to identify factors affecting locoregional recurrence, distant metastasis, or death. A $P < 0.05$ was considered statistically significant.

RESULTS

The mean age of 159 patients was 48. years (SD, ± 9.6 years), and 67 patients (42.1%) were in a postmenopausal state. The patients underwent ALND with mastectomy ($n = 138$; 86.8%) and breast-conserving surgery ($n = 21$; 13.2%). Immediate or delayed breast reconstruction was performed in 26 patients (16.4%). The mean hospital stay after surgery was 12.8 days (SD, ± 3.4 days). Although the mean clinical tumor size was 5.1 cm (SD, ± 2.6 cm) in mammography, breast ultrasound, and breast magnetic resonance, the pathological tumor size after NAC was 2.9 cm (SD, ± 2.2 cm). After the surgery, the patients received additional adjuvant treatments according to the residual tumor burden and immunohistochemistry results [chemotherapy, $n = 21$ (13.2%); target therapy, $n = 40$ (25.2%); radiotherapy, $n = 130$ (81.8%); and hormone treatment, $n = 119$ (74.8%)].

There were 130 cases that showed at least 10 ALNs after NAC in a dissected specimen and 29 cases that showed <10 ALNs. However, the clinical and pathological characteristics were not different between the 2 groups. There were 33 cases (20.8%) of pCR in the breast and 38 cases (23.9%) of pCR in the axilla after NAC. Although there was no significant difference between the 2 groups in the clinical T stage ($P = 0.590$) and the pathological

TABLE 1 | Clinicopathological characteristics of patients with breast cancer who received axillary lymph node dissection followed by neoadjuvant chemotherapy.

Variables	Total ($n = 159$)	≥59 ALNs* ($n = 130$)	<10 ALNs ($n = 29$)	*p*-value
Mean age (years, ±SD)	48.0 ± 9.6	47.2 ± 9.6	51.7 ± 8.9	0.617
Postmenopausal state (*n*, %)	67 (42.1)	51 (39.2)	16 (55.1)	0.378
Type of breast surgery (*n*, %)				0.104
Breast conserving surgery	21 (13.2)	16 (12.3)	5 (17.2)	
Mastectomy	138 (86.8)	114 (87.7)	24 (82.8)	
Breast reconstruction (*n*, %)	26 (16.4)	23 (17.7)	3 (10.3)	0.501
Mean period of hospital stay (day, ±SD)	12.8 ± 3.4	12.6 ± 3.3	13.3 ± 3.7	0.675
Mean clinical tumor size (cm, ±SD)	5.1 ± 2.6	5.2 ± 2.6	4.7 ± 2.3	0.606
Clinical T stage (*n*, %)				0.590
T1	19 (12.0)	12 (9.2)	7 (24.1)	
T2	90 (56.6)	77 (59.2)	13 (44.8)	
T3	35 (22.0)	28 (21.5)	7 (24.1)	
T4	15 (9.4)	13 (10.0)	2 (6.9)	
Clinical N stage (*n*, %)				0.931
N0	6 (3.8)	5 (3.9)	1 (3.5)	
N1	58 (36.5)	49 (37.7)	9 (31.0)	
N2	59 (37.1)	49 (37.7)	10 (34.5)	
N3	36 (22.6)	27 (20.8)	9 (31.0)	
Clinical stage (*n*, %)				0.084
IIA	9 (5.7)	7 (5.4)	2 (6.9)	
IIB	36 (22.6)	30 (23.1)	6 (20.7)	
IIIA	67 (42.1)	55 (42.3)	12 (41.4)	
IIIB	11 (6.9)	11 (8.5)	-	
IIIC	36 (22.6)	27 (20.8)	9 (31.0)	
Regimen of NAC (*n*, %)				0.612
Anthracycline + Cyclophosphamide (AC)	5 (3.1)	5 (3.9)	-	
AC + Taxane	116 (73.0)	94 (72.3)	22 (75.9)	
AC + Taxane + Trastuzumab	26 (16.4)	23 (17.7)	3 (10.3)	
Others	12 (7.6)	8 (6.2)	4 (13.8)	
Adjuvant chemotherapy (*n*, %)	21 (13.2)	15 (11.5)	6 (20.7)	0.075
Adjuvant target therapy (*n*, %)	40 (25.2)	32 (24.6)	8 (27.6)	0.176
Adjuvant radiotherapy (*n*, %)	130 (81.8)	108 (83.1)	22 (75.9)	0.093
Adjuvant hormone treatment (*n*, %)	119 (74.8)	99 (76.2)	20 (69.0)	0.146

**Axillary lymph nodes.*

† Neoadjuvant chemotherapy. Thirty-three cases of pathological complete response on breast were excluded in this group.

T stage ($P = 0.183$), the pCR in breast lesions showed higher incidence in the group with <10 removed ALNs (18.5 vs. 31%; $P = 0.009$). In addition, the pCR in ALNs showed higher incidence in the group with <10 removed ALNs (21.5 vs. 34.5%; $P = 0.014$), even if there was no significant difference between the two groups in the clinical and pathological N stage ($P = 0.931$ and 0.513). Furthermore, the pCR in both breast and ALNs was higher in the group with <10 removed ALNs ($P = 0.001$) (**Table 1**). However, there were no differences between the two groups in the subtypes of breast cancer, which showed a nodal pCR (**Table 2**).

The various treatment-related histopathological findings of ALNs are shown in **Figure 1**. Metastatic tumor cells in ALNs are often identified at the subcapsular area or show intranodal lymphovascular emboli or floating tumor cell clusters (**Figures 2A–C**). Meanwhile, regressed ALNs usually show fibrosis, fibroelastic vascular change, or histocytic infiltrations (**Figures 2D–I**).

During more than 7 years of mean follow-up, there were 22 cases (13.8%) of locoregional recurrence, 45 cases (28.3%) of distant metastasis, and 30 cases (18.9%) of death. There was no significant difference between the two groups (≥ 10 *vs.* < 10 removed ALNs) in locoregional recurrence, distant metastasis, and death ($P = 0.197$, 0.371, and 0.144) (**Figure 3**, **Table 3**). Comparing each by the N stage, the pCR in ALNs was highest in the cN2 group (12.3%) of 10 or more removed ALNs and lowest in the cN2 group (6.9%) of <10 removed ALNs (**Table 4**).

TABLE 2 | Pathologic results of patients with breast cancer who received axillary lymph nodes dissection followed by neoadjuvant chemotherapy.

Variables	Total ($n = 159$)	≥ = ALNs ($n = 130$)	<10 ALNs ($n = 29$)	*p*-value
Mean pathologic tumor size (cm, ±SD)	2.9 ± 2.2	2.9 ± 1.6	3.0 ± 2.6	0.418
Pathologic T stage (*n*, %)				0.183
pCR (including DCIS only)	33 (20.8)	24 (18.5)	9 (31.0)	0.009
T1	50 (31.5)	43 (33.1)	7 (24.1)	
T2	57 (35.9)	48 (36.9)	9 (31.0)	
T3	49 (30.8)	45 (34.6)	4 (13.8)	
Pathologic N stage* (*n*, %)				0.513
pCR in axilla	38 (24.8)	28 (22.4)	10 (35.7)	0.014
N1	68 (44.4)	58 (46.4)	10 (35.7)	
N2	39 (25.5)	30 (24.0)	9 (32.1)	
N3	14 (9.2)	14 (11.2)	-	
Pathological stage (*n*, %)				0.437
pCR (both breast and axilla)	21 (13.2)	14 (10.8)	7 (24.1)	0.001
IA	13 (8.2)	11 (8.5)	2 (6.9)	
IIA	35 (22.0)	30 (23.1)	5 (17.2)	
IIB	29 (18.2)	25 (19.2)	4 (13.8)	
IIIA	46 (28.9)	35 (26.9)	11 (37.9)	
IIIB	1 (0.6)	1 (0.8)	-	
IIIC	13 (8.2)	13 (10.0)	-	
Estrogen receptor, positive (*n*, %)				
In biopsy before NAC	105 (66.0)	88 (67.7)	17 (58.6)	0.909
In surgical specimen after NAC†	86 (54.1)	61 (46.9)	13 (44.8)	0.719
Progesterone receptor, positive (*n*, %)				
In biopsy before NAC	100 (62.9)	85 (65.4)	15 (51.7)	0.759
In surgical specimen after NAC†	74 (46.5)	64 (49.2)	10 (34.5)	0.954
HER2/neu gene, positive (*n*, %)				
In biopsy before NAC	44 (27.7)	38 (29.2)	10 (34.5)	0.709
In surgical specimen after NAC†	36 (22.6)	25 (19.2)	11 (37.9)	0.420
Subtypes of breast cancer with nodal pCR* (*n*, %)	38 (24.8)	28 (22.4)	10 (35.7)	0.501
Luminal A	8 (5.2)	4 (3.2)	4 (14.3)	
Luminal B	13 (8.5)	12 (9.6)	1 (3.6)	
HER2	8 (5.2)	5 (4.0)	3 (10.7)	
Triple negative	9 (5.9)	7 (5.6)	2 (7.1)	

**Total number of patients with metastatic lymph nodes was 153.*

† Neoadjuvant chemotherapy. Thirty-three cases of pathological complete response on breast were excluded in this group.

DISCUSSION

The metastatic status of ALNs is an important prognostic factor in breast cancer, and complete removal of metastatic ALNs improves oncological outcomes (13). In particular, when the metastatic ALN is identified at Level II or III, NAC is initiated before surgery because of the difficulty of complete resection of metastatic ALNs. The main role of NAC is reducing the tumor burden, which can lead to increasing the rate of breast-conserving surgery through tumor reduction. Furthermore, the physician can evaluate the treatment response of tumors with NAC (14–16). However, because the tumor status or characteristics can be changed by therapeutic effect, it is very important to investigate

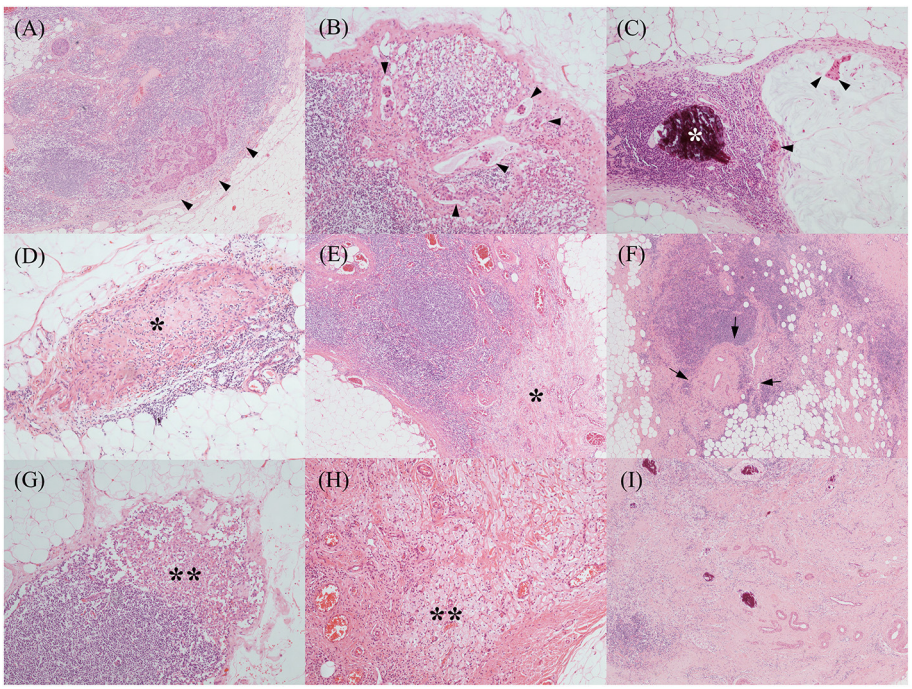

FIGURE 2 | Various treatment-related histopathological findings of axillary lymph nodes. Metastatic tumor cells were often identified at the subcapsular area [**(A)**, black arrowheads], which showed occasional intranodal lymphovascular emboli [**(B)**, black arrowheads]. Another metastatic mucinous carcinoma **(C)** showed floating tumor cell clusters in the mucin pool (black arrowheads) and microcalcification (the white asterisk). Regressed lymph nodes showed a variable degree of fibrosis [**(D,E)**, black asterisks] and fibro-elastic vascular change [**(F)**, black arrows]. Histiocytic infiltrations [**(G,H)**, black double asterisks] were also noted. Above histopathological features, such as fibrosis, vascular change, and microcalcification, were frequently mixed **(I)**. [All, H&E stain; original magnification, **(A,E,F,I)**, x 40; **(B–D,G,H)**, x 100].

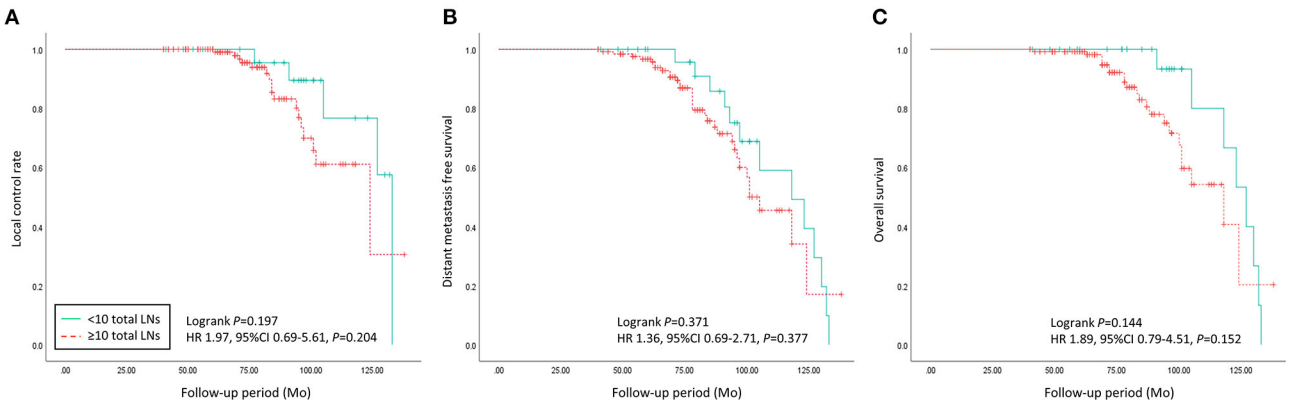

FIGURE 3 | Oncologic outcomes of patients with advanced breast cancer who underwent axillary lymph nodes dissection following neoadjuvant chemotherapy were compared between <10 and ≥ 10 of the total axillary lymph nodes count group. **(A)** Local control rate, **(B)** distant metastasis, and **(C)** overall survival did not show significant differences between the two groups ($p = 0.197$, 0.371, and 0.144).

TABLE 3 | Oncological outcomes of patients with breast cancer who received axillary lymph nodes dissection followed by neoadjuvant chemotherapy.

Variables	Total ($n = 159$)	≥ot ALNs ($n = 130$)	<10 ALNs ($n = 29$)	*p*-value
Mean follow-up period (months, ±SD)	88.8 ± 21.5	86.2 ± 19.6	90.2 ± 26.1	0.054
Locoregional recurrence (*n*, %)	22 (13.8)	17 (13.1)	5 (17.2)	0.197
Ipsilateral breast	8 (5.0)	5 (3.9)	3 (10.3)	
Ipsilateral axillary lymph node	7 (4.4)	5 (3.9)	2 (6.9)	
Ipsilateral supraclavicular lymph node	12 (7.6)	9 (6.9)	3 (10.3)	
Distant metastasis (*n*, %)	45 (28.3)	32 (24.6)	13 (44.8)	0.371
Lung	23 (14.5)	16 (12.3)	7 (24.1)	
Liver	16 (10.1)	11 (8.5)	5 (17.2)	
Bone	17 (10.7)	12 (9.2)	5 (17.2)	
Brain	2 (1.3)	2 (1.5)	-	
Mediastinal lymph nodes	5 (3.1)	3 (2.3)	1 (3.5)	
Others	7 (4.4)	4 (3.1)	4 (13.8)	
Death (*n*, %)	30 (18.9)	22 (16.9)	8 (27.6)	0.144

TABLE 4 | Changes of nodal stages in patients with breast cancer who underwent axillary lymph node dissection followed by neoadjuvant chemotherapy.

Pathological N stage / Clinical N stage	≥10 ALNs ($n = 130$)				<10 ALNs ($n = 29$)			
	pCR	N1	N2	N3	pCR	N1	N2	N3
N0	-	3 (2.3)	1 (0.8)	1 (0.8)	-	1 (3.5)	-	-
N1	2 (1.5)	35 (26.9)	12 (9.2)	-	4 (13.8)	2 (6.9)	3 (10.3)	-
N2	16 (12.3)	17 (13.1)	12 (9.2)	4 (3.1)	2 (6.9)	5 (17.2)	3 (10.3)	-
N3	10 (7.7)	3 (2.3)	5 (3.9)	9 (6.9)	4 (13.8)	2 (6.9)	3 (10.3)	-

pCR, pathological complete response.

the initial tumor stage and characteristics before initiation of treatment.

After the results of the Z0011 trial were published, the feasibility of sentinel lymph node biopsy was established with short- and long-term results (17, 18). However, it may be difficult to confirm the standard additional surgical intervention when the metastasis of the sentinel lymph node is confirmed in pathology because of uncontrolled conditions of the population in the Z0011 trial. The ALN dissection is still a standard treatment in metastatic ALNs of breast cancer, even if the Z0011 trial had been reported. According to the AJCC staging system, at least 10 ALNs should be removed and evaluated to accurately determine the nodal stages (7, 8).

Although the AJCC staging system recommended evaluating more than 10 ALNs when staging nodal status, the total number of ALNs is occasionally <10 in breast cancer treated with NAC, even if complete ALND was performed. Many researchers have reported that the total lymph node count decreases even after NAC in breast cancer (19–22). As subsequent research of those results, the authors investigated the oncological outcomes in breast cancer for which it was reported that the total number of ALNs was <10 after ALND following NAC. The hypothesis of this study was that, if normal lymph nodes were regressed by chemotherapy, the tumor cells in the lymph nodes would have been more affected, which leads to a higher pCR rate in lymph nodes and better oncological outcomes. Although the incidence of pCR in ALNs was higher in breast cancer with metastatic ALNS that showed <10 total ALNs, the oncological outcomes did not show significant differences between the groups with <10 *vs.* 10 or more. This discrepancy may be due to the difference in sample size between the two groups, which is one of the limitations of this study. However, if the sample size increases in further study, we may get more consistent results.

The histopathological findings of ALNs after NAC vary, including various degrees of fibrosis, fibroelastic vascular change, histiocytic infiltrations, or mixture type with microcalcifications. Because the treatment-related histopathological findings have extreme variations, well-experienced pathologists should review and conclude to predict the disease prognosis and to establish the additional treatment strategy.

The extent of ALND may differ according to the surgeon from Levels I and II to Levels I-III. Although there is no specific definition of ALND, thus far, the thoracodorsal vessels and the nerve bundle, the long thoracic nerve should be well exposed after completion of ALND. However, surgeons sometimes think about whether they have performed an incomplete surgery when

the total ALN count is <10, even if the complete ALND was performed. According to this study, if the ALND is completely performed after ALND following NAC in locally advanced breast cancer, the oncological outcomes were not inferior to those of the group with 10 or more ALNs. The pCR rates of both ALNs and breast were significantly higher in the group with <10 ALNs, which are expected to have better oncological outcomes in longer follow-up periods. However, in this study, there was no significant difference in oncologic outcomes between the two groups, and this may be due to the small population.

The limitation of this study is that the population of the group with <10 ALNs was small compared to the group with 10 or more ALNs. However, even if the total number of ALNs was <10, the results of this study indicate that additional surgery is not required, and that the surgeon does not need to feel guilty if extensive surgery was performed conscientiously.

CONCLUSIONS

Our study provided a novel finding that the oncological outcomes of the group with <10 ALNs maybe not be inferior to the group with 10 or more ALNs, including locoregional recurrence, distant metastasis, and overall survival. The pCR rate in breast and ALNs was higher in the group with <10 ALNs compared with that of 10 or more. Although due to the small sample size, the accurate significant findings could not be obtained; the results suppose that the surgeon does not need to consider it as incomplete surgery, even if the total ALN count was <10 after ALND following NAC.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

AUTHOR CONTRIBUTIONS

JL: the guarantor of the integrity of the study and data analysis. JL and NP: study concepts. JL, NP, HP, and J-YP: study design. JL, BK and SL: definition of intellectual content and manuscript preparation. JJ and WK: literature research. J-YP, NP, SL, YC, HK, BK and WK: clinical studies. WK, YC, and SL: data acquisition. JJ: manuscript editing. JJ and HP: manuscript review. All authors have read and approved the manuscript.

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Survival Analysis in Male Breast Cancer With Bone Metastasis Based on the SEER Database

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Purpose: Breast cancer (BC) has been extensively and deeply studied as the number one malignant tumor in women, but its status in male patients, especially in male metastatic patients, is rarely reported. Thus, this study aimed to explore the prognosis and risk factors of male BC with bone metastasis.

Patients and Methods: We searched the Surveillance, Epidemiology, and End Results (SEER) database to identify all patients diagnosed with male BC with bone metastasis from 2010 to 2016. Risk factors of overall survival (OS) and cancer-specific survival (CSS) were analyzed by univariable and multivariable Cox analyses. We also drew Kaplan–Meier plots to show the correlation between independent risk factors and survival.

Results: A total of 207 male BC patients with bone metastasis were included for analysis. Approximately one-third of patients also had lung metastasis. Luminal A subtype comprised 58.5% of the overall patient population. These patients had a poor prognosis, with 3-year OS and CSS rates, 36.7% and 39.5%, respectively. Further analysis revealed that age ≤60 years old, luminal A or B, and surgery were independent predictors of prolonged OS and CSS. On Cox multivariable analysis, brain metastasis was associated with OS and not CSS.

Conclusion: We identified four independent factors associated with prognosis in male BC patients with bone metastasis, namely age, tumor subtype, surgery, and brain metastasis. Knowing these risk factors will help clinicians make more appropriate treatment plans.

Keywords: breast cancer, bone metastasis, clinicopathological characteristics, survival, risk factors

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INTRODUCTION

Male breast cancer (BC) is a rare malignancy representing less than 1% of all BCs and less than 1% of all male cancers (1, 2). With the increasing incidence of male BC in recent years (3, 4), researchers have begun to pay attention to the treatment and prognosis of this special group (5). At present, the treatment of male BC mainly refers to the treatment of female patients (6). Additionally, compared with female patients, male BC patients had a worse prognosis (7, 8). Bone is not only the most common metastatic site for female BC, but it is also the most common metastatic site for male BC (5).

As far as we know, clinical studies on systematic prognosis analysis of male BC patients with bone metastasis are lacking. To date, the standardized treatment of male BC with bone metastasis has not been proven.

Many previous studies have shown that male breast cancer is not the same as female disease (9, 10). Recently, Xie et al. (5) reported that metastatic male BC patients had unique clinicopathological characteristics, which were different from nonmetastatic male BC patients. We cannot help wondering how the prognosis of male BC with bone metastasis and whether its risk factors are the same as those of female patients? Therefore, we applied the Surveillance, Epidemiology and End Results (SEER) database to solve the above questions, which is the largest population database for clinical cancer research. Our findings may provide a better understanding of, male BC with bone metastasis and further improve their prognosis.

MATERIAL AND METHODS

Study Population

Clinical data on BC with bone metastasis were retrieved by using the SEER*Stat version 8.3.8. Since the database only included patients diagnosed with bone metastases after 2010, we only included patients from 2010 to 2016. This population-based database collects information on cancer patients in 18 registries, representing nearly 30% of the US population (www.seer.cancer.gov). In the current study, we included clinicopathological data, sociological data, and treatment data. This study obtained approval from our institutional review board.

When selecting target patients, we define three keywords, namely male, breast cancer, and bone metastasis. Cases without histopathological diagnosis were excluded (n = 3). The patient selection flowchart is shown in **Figure 1**. Surgery or radiotherapy in this study refers to the primary BC (11). Based on previous literature (12, 13), CSS is defined as the time from initial diagnosis to death due to BC itself. All patients were initially diagnosed with breast cancer and bone metastasis (stage IV), and follow-up surgery refers to surgery on the primary site.

Statistical Methods

We first performed the univariable Cox regression analyses to rule out nonsignificant survival predictors. We then included statistically significant factors into multivariate Cox regression analysis to identify independent risk factors. At the same time, we calculated hazard ratios (HRs) and 95% confidence interval (CI). We drew survival curves to show the relationship between independent risk factors and survival and applied the log-rank test method for comparative analysis. Variables with two-tailed $p < 0.05$ were considered statistically significant. All statistical analyses were performed by using IBM SPSS Statistics 21.

RESULTS

Patient Characteristics

Table 1 summarizes the baseline characteristics of 207 male BC patients with bone metastasis identified from the SEER database. Of 207 patients, 74.9% were white. More than half of the patients were aged over 60 years old. High tumor grade was detected in 39.1% of cases. The pathological type of most patients (n = 170, 82.1%) was ductal and lobular neoplasms. In total, 58.5% of cases presented luminal A, 17.9% presented luminal B, and 9.2% presented triple negative. Tumor size distribution was 55.6% and 30.0% for <5 and ≥5 cm, respectively. Distant organ metastasis included the lung (35.7%), liver (13.0%), and brain

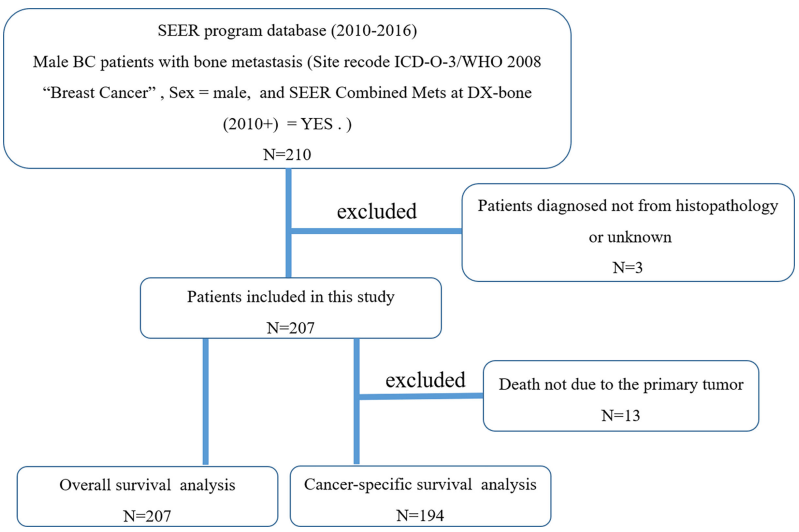

FIGURE 1 | The flowchart for selection of study population. (SEER, Surveillance, Epidemiology, and End Results; ICD-O-3, International Classification of Diseases for Oncology, 3rd edition; BC, breast cancer).

TABLE 1 | Baseline characteristics of 207 male breast cancer with bone metastasis.

Variable	Value
Race	
White	155 (74.9%)
Black	39 (18.8%)
Others	13 (6.3%)
Age (years)	
≤60	82 (39.6%)
>60	125 (60.4%)
Mean	64
Median	65
Tumor grade	
Low grade	84 (40.6%)
High grade	81 (39.1%)
Unknown	42 (20.3%)
Histologic subtype	
Ductal and lobular neoplasms	170 (82.1%)
Others	37 (17.9%)
Tumor subtype	
Luminal A	121 (58.5%)
Luminal B	37 (17.9%)
Triple negative	19 (9.2%)
Unknown	30 (14.5%)
Tumor size (cm)	
<5	115 (55.6%)
≥5	62 (30.0%)
Unknown	30 (14.5%)
Surgery	
Yes	67 (32.4%)
No	140 (67.6%)
Radiotherapy	
Yes	77 (37.2%)
No	130 (62.8%)
Chemotherapy	
Yes	99 (47.8%)
No	108 (52.2%)
Brain metastasis	
No	189 (91.3%)
Yes	18 (8.7%)
Liver metastasis	
No	180 (87.0%)
Yes	27 (13.0%)
Lung metastasis	
No	133 (64.3%)
Yes	74 (35.7%)
Insurance status	
Insured	163 (78.7%)
Others	40 (19.3%)
Unknown	4 (1.9%)
Marital status	
Married	108 (52.2%)
Others	87 (42.0%)
Unknown	12 (5.8%)
Dead	
Yes	116 (56.0%)
No	91 (44.0%)
1-Year OS rate	69.70%
1-Year CSS rate	70.30%
3-Year OS rate	36.70%
3-Year CSS rate	39.50%

Low grade: ICD-O-3 grade 1 (well-differentiated) and grade 2 (moderately differentiated). High grade: ICD-O-3 grade 3 (poorly differentiated) and grade 4 (undifferentiated anaplastic). OS, overall survival; CSS, cancer-specific survival.

(8.7%). More than three-quarters (78.7%) of the patients were insured. Over half of the patients were married. In terms of treatment-related variables, 67 (32.4%) patients received surgery, 77 (37.2%) received radiotherapy, and 99 (47.8%) received chemotherapy. Three-year OS and CSS rates for all cases were 36.7% and 39.5%, respectively.

Survival Analysis

On univariable analysis, variables found to be significantly associated with OS and CSS were age, histologic subtype, tumor subtype, surgery, brain metastasis, and liver metastasis (**Table 2**). There was no significant difference in OS or CSS by race, tumor grade, tumor size, radiotherapy, chemotherapy, lung metastasis, insurance status, and marital status (**Table 2**).

On multivariable analysis, age over 60 years old, other histologic subtypes, triple-negative subtype, no surgery, and brain metastasis were independent predictors of decreased OS (**Table 3**). Multivariable analysis revealed age, histologic subtype, tumor subtype, and surgery were significant predictors for CSS (**Table 3**). The Kaplan–Meier survival curves showed that patients with age ≤60 years old (**Figure 2**), luminal A or B (**Figure 3**), or surgery (**Figure 4**) had better OS and CSS. Moreover, brain metastasis had a negative influence on OS (**Figure 5**) but not CSS.

DISCUSSION

With the popularization of precision medicine, it is necessary to discuss the clinical difficulty of male BC with bone metastasis. This study first explored the factors associated with prognosis in BC patients with bone metastasis based on the public SEER database. This study found that the significant independent predictors affecting BC with bone metastasis were not as many as expected, including age, tumor subtype, surgery, and brain metastasis. The results of this study provide an important reference value for clinicians to guide patients to receive personalized treatment. In addition, this study is also a good start for clinical research on male BC with bone metastasis.

On the whole, the prognosis of male BC with bone metastasis (3-year OS and CSS rates: 36.7% and 39.5%) was worse than that of female patients (3-year OS and CSS rates: 51.7% and 53.6%) (13), suggesting that the prognosis and treatments of such patients need more attention. Previous studies indicated that older BC patients were prone to bone metastasis (14) and age was an important independent predictor of survival (15, 16). Our multivariable results also highlighted this finding in male BC patients with bone metastasis. A significant difference in survival was not revealed among various races, which was congruent with some previous studies (13, 17). However, other studies found race was an independent prognostic factor among BC with bone metastasis (15, 16). Tumor grade is usually recognized as an independent risk factor for the prognosis of BC (16, 18). Wang et al. (13) recently identified higher tumor grade was an independent predictor of worse survival among female BC patients with bone metastasis.

TABLE 2 | Univariate Cox analysis of variables in male breast cancer with bone metastasis.

Variable	OS		CSS	
	HR (95% CI)	*p*	HR (95% CI)	*p*
Race				
White	1		1	
Black	1.066 (0.670–1.696)	0.788	1.003 (0.605–1.662)	0.991
Others	1.376 (0.634–2.988)	0.42	1.429 (0.620–3.293)	0.402
Age (years)				
≤60	1		1	
>60	1.667 (1.121–2.477)	**0.012**	1.762 (1.153–2.691)	**0.009**
Tumor grade				
Low grade	1		1	
High grade	0.918 (0.598–1.409)	0.695	0.991 (0.623–1.577)	0.97
Histologic subtype				
Ductal and lobular neoplasms	1		1	
Others	2.500 (1.614–3.872)	**<0.001**	2.557 (1.629–4.014)	**<0.001**
Tumor subtype				
Luminal A	1		1	
Luminal B	0.866 (0.508–1.474)	0.595	0.862 (0.488–1.521)	0.607
Triple negative	4.857 (2.802–8.419)	**<0.001**	4.777 (2.701–8.448)	**<0.001**
Tumor size (cm)				
<5	1		1	
≥5	1.475 (0.981–2.218)	0.062	1.368 (0.882–2.124)	0.162
Surgery				
Yes	1		1	
No	2.180 (1.437–3.306)	**<0.001**	2.154 (1.382–3.357)	**0.001**
Radiotherapy				
Yes	1		1	
No	1.156 (0.794–1.682)	0.45	1.150 (0.770–1.718)	0.494
Chemotherapy				
Yes	1		1	
No	1.171 (0.810–1.691)	0.401	1.211 (0.820–1.790)	0.336
Brain metastasis				
No	1		1	
Yes	2.614 (1.448–4.719)	**0.001**	2.426 (1.282–4.588)	**0.006**
Liver metastasis				
No	1		1	
Yes	1.906 (1.172–3.099)	**0.009**	1.894 (1.146–3.128)	**0.013**
Lung metastasis				
No	1		1	
Yes	1.203 (0.829–1.747)	0.33	1.207 (0.811–1.795)	0.354
Insurance status				
Insured	1		1	
Others	0.895 (0.562–1.428)	0.642	0.858 (0.520–1.416)	0.549
Marital status				
Married	1		1	
Others	1.192 (0.815–1.745)	0.366	1.094 (0.729–1.641)	0.665

Variables with bold values were statistically significant.

However, this study failed to identify tumor grade as a significant risk factor for survival.

Several researchers have reported an effect of histologic subtype on survival among BC with bone metastasis (13, 19). Although the univariable analysis suggested that the histologic subtype was a significant risk factor affecting survival among our patients, the multivariable analysis did not support this finding. The tumor subtype might be one of the most useful survival predictors in male BC patients with bone metastasis. In line with our traditional knowledge of breast cancer, those with a triple-negative subtype had the worst prognosis. In contrast to a prior study on female BC with bone metastasis (13), we noted that tumor size in the current study was not correlated with survival. Of note, the presence of brain metastasis was an independent risk factor associated with a decreased OS, not CSS. Lung or liver metastases seem to have little effect on prognosis in male BC patients with bone metastasis. Therefore, treatment of brain metastasis may have survival benefits in such patients. Additionally, insurance status and marital status had no association with survival in this study.

At present, standard treatments of BC with bone metastasis have not been established, let alone the treatments of male BC with bone metastasis. In our study, surgery of primary sites was an effective treatment method to prolong the prognosis of male BC with bone metastasis, which was consistent with the situation of female BC patients with bone metastasis (13, 17). Wang et al. (13) found that

TABLE 3 | Multivariate Cox analysis of variables in male breast cancer with bone metastasis.

Variable	OS		CSS	
	HR (95% CI)	*p*	HR (95% CI)	*p*
Age (years)				
≤60	1		1	
>60	1.671 (1.110–2.515)	**0.014**	1.806 (1.159–2.815)	**0.009**
Histologic subtype				
Ductal and lobular neoplasms	1		1	
Others	1.205 (0.674–2.155)	0.53	1.236 (0.678–2.255)	0.489
Tumor subtype				
Luminal A	1		1	
Luminal B	0.881 (0.507–1.530)	0.652	0.955 (0.526–1.734)	0.881
Triple negative	3.029 (1.455–6.303)	**0.003**	3.025 (1.427–6.412)	**0.004**
Surgery				
Yes	1		1	
No	1.764 (1.132–2.749)	**0.012**	1.734 (1.080–2.784)	**0.023**
Brain metastasis				
No	1		1	
Yes	2.045 (1.082–3.865)	**0.028**	1.950 (0.982–3.872)	0.056
Liver metastasis				
No	1		1	
Yes	1.293 (0.744–2.248)	0.362	1.330 (0.755–2.341)	0.324

Variables with bold values were statistically significant.

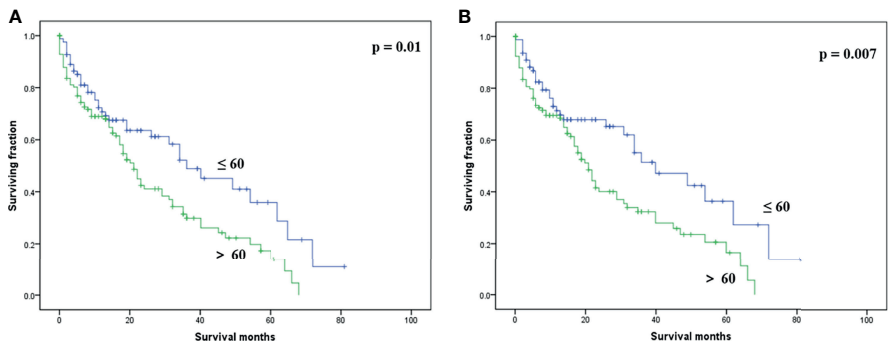

FIGURE 2 | Kaplan–Meier method-estimated OS **(A)** and CSS **(B)** male breast cancer with bone metastasis stratified by age. (OS, overall survival; CSS, cancer-specific survival).

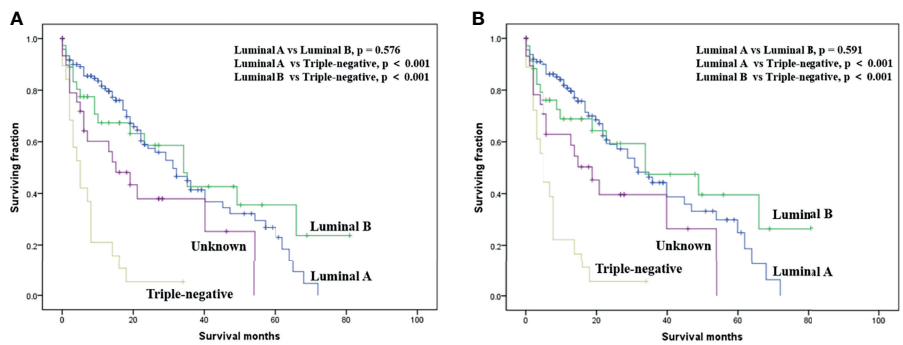

FIGURE 3 | Kaplan–Meier method-estimated OS **(A)** and CSS **(B)** male breast cancer with bone metastasis stratified by tumor subtype. (OS, overall survival; CSS, cancer-specific survival).

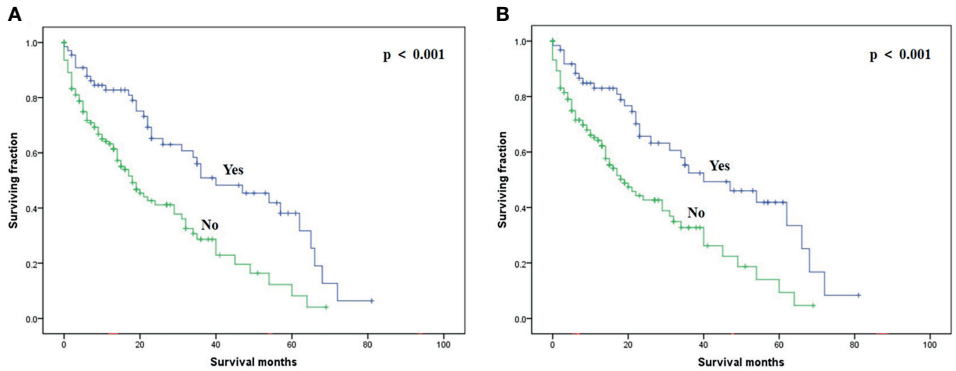

FIGURE 4 | Kaplan–Meier method-estimated OS **(A)** and CSS **(B)** male breast cancer with bone metastasis stratified by surgery. (OS, overall survival; CSS, cancer-specific survival).

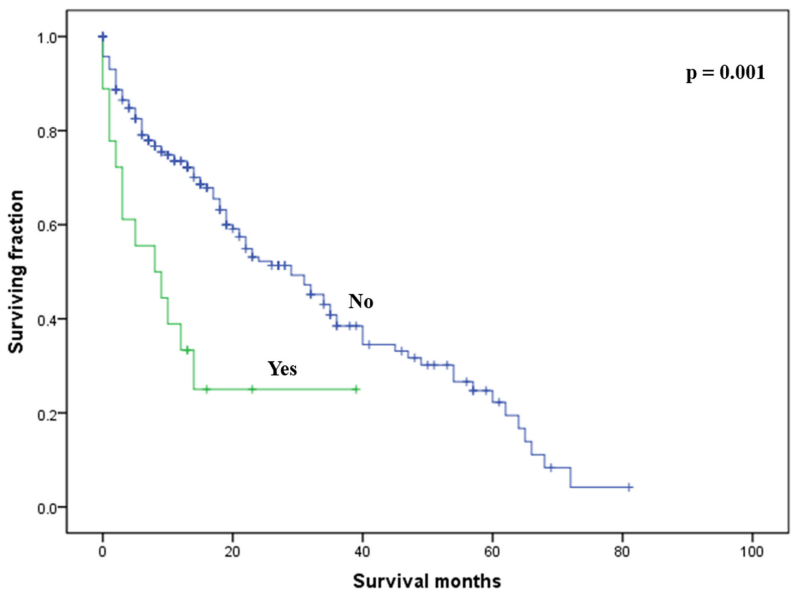

FIGURE 5 | Kaplan–Meier method-estimated OS male breast cancer with bone metastasis stratified by brain metastasis. (OS, overall survival).

chemotherapy can significantly improve the prognosis of female BC with bone metastasis, while radiotherapy has no significant effect on prognosis. Interestingly, chemotherapy and radiotherapy did not improve the prognosis of male BC with bone metastasis. Further validation of the different treatment methods of such patients is clinically required.

We need to point out some limitations presented in this study. First, the retrospective nature of this study can lead to bias. Second, endocrine therapy information is not available in the database. Third, recurrence or metastasis data during follow-up were also not available in the database. Additionally, the sample size of this study was relatively small. Relevant clinical studies with larger sample sizes can be carried out in the future.

CONCLUSIONS

This is the largest study of survival analysis on male BC patients with bone metastasis. Age, tumor subtype, surgery, and brain metastasis were identified as independent risk factors of survival. Surgery of the primary tumors is recommended for such

populations. However, more studies are needed to confirm our results and identify more survival predictors in the future.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Institutional Review Board of Xuzhou Medical University. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

XZ and ZC conceived and designed the study. XZ and JZ collected the data. XZ, JZ and YW performed the statistical analysis. XZ wrote the manuscript and ZC revised it. All authors read and approved the final manuscript.

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