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Best surgical treatment of breast cancer managed primarily with neoadjuvant medical therapy

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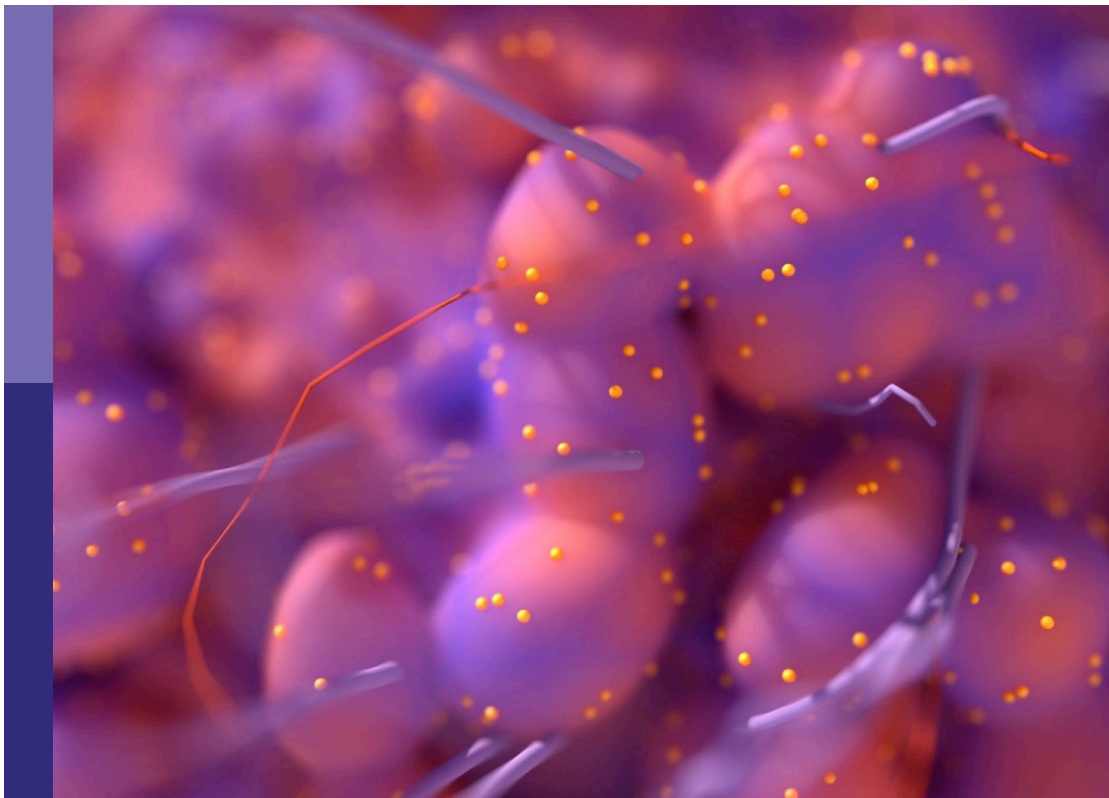

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Best surgical treatment of breast cancer managed primarily with neoadjuvant medical therapy

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Editorial: Best surgical treatment of breast cancer managed primarily with neoadjuvant medical therapy

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KEYWORDS

neoadjuvant chemotherapy, breast surgery, conservative mastectomies, conservative surgery, axillary lymph node dissection (ALND)

Editorial on the Research Topic
Best surgical treatment of breast cancer managed primarily with neoadjuvant medical therapy

The rationale for neoadjuvant chemotherapy

Neoadjuvant chemotherapy (NAC) has currently taken on a predominant role in the treatment of patients with breast cancer.

While in past years this type of treatment was mainly used to make locally advanced breast tumors operable, therefore for reduction of the tumor size, currently, it is the biological profile of the tumor that indicates the use of neoadjuvant therapy thanks to the increase in the constellation of drugs that can be used and the optimal pathological response, in many cases complete, that can be obtained in certain bioprofiles, such as triple negative and HER2 positive (1).

Radiological consideration

For the breast surgeon, it is essential to verify two main points: verifying the extent of the residual tumor during post-treatment radiological diagnostic evaluation, comparing it with the initial state, and establishing the most appropriate surgical intervention in terms of conservative surgery vs. mastectomy procedures with simultaneous plastic reconstruction (2, 3).

In our research topic we have tried to collect scientific works specifically focused on the study of radiological methods that can provide a better definition of residual tumor disease after neoadjuvant therapy, such as ultrasound with elastosonography and nuclear magnetic resonance associated with predictive models also obtained with artificial intelligence procedures.

Surgical approaches (conservation vs. mastectomy)

Regarding the surgical point of view, surgical treatment approach for breast cancer has changed from "maximum tolerable" to "minimum effective". Evaluating the response of

breast cancer patients to NAC before surgery is vital for adapting personalized surgical procedures and treatment approaches.

Crucial points of topic's papers were to establish selection criteria to designate patients for conservative or mastectomy procedures and understand if subcutaneous mastectomies are the most appropriate surgical procedures in those categories of patients compared to conservative surgery, and if so, in which instances.

Patients with isolated residual tumors by unifocal or initially multifocal tumors within the same quadrant, with concentric narrowing pattern of clinical-radiological response, are prone to conservative surgery.

In the instance of multicentric or advanced disease at the outset with patchy or multifocal regression, satellite lesions or uneven reduction of tumor volume, also in relation to the size and shape of the involved breast, are better handled surgically by conservative mastectomies, combined with immediate breast reconstruction, not done immediately only in cases of inflammatory breast cancer or when there is direct skin infiltration by the residual tumor. Several retrospective studies have demonstrated that all this doesn't increase the risk of local relapse or negatively affect long-term survival, while significantly improving the psychophysical recovery from the disease.

Axillary management

The utilization of NAC has also altered the method to axillary lymph node management in breast cancer. Axillary lymph node dissection (ALND) is performed where strictly necessary, reducing the onset of the known possible complications associated with this procedure, emphasizing its prognostic role.

ALND can be omitted for patients whose positive nodes become negative and the appropriate treatment also for these patients is represented by the sentinel lymph node biopsy (SLNB), with the use of dual tracer sampling and removing a minimum of three lymph nodes, or performing SLNB with targeted axillary dissection, to lessen the false negative rate related to this procedure after NAC.

The accurate definition of the residual tumor volume at lymph node level, as a response to NAC, capable of influencing subsequent ALND, is still under study, bearing in mind that the macroscopic involvement of the lymph node detected by intraoperative molecular examination represents one of the most valid opportunities to more stringently select patients deserving of ALND (4).

Author contributions

UM: Writing – original draft, Writing – review & editing.

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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Breast-conserving surgery versus mastectomy for treatment of breast cancer after neoadjuvant chemotherapy

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Background: To compare recurrence and survival outcomes between breast-conserving surgery (BCS) and mastectomy after neoadjuvant chemotherapy (NACT).

Methods: The data of 730 patients who underwent NACT between 2000 and 2014 were retrospectively reviewed. A total of 104 (14.2%) patients received BCS and 626 (85.8%) received mastectomy. Locoregional recurrence (LRR), distant metastases (DM), disease-free survival (DFS), breast cancer–specific survival (BCSS), and overall survival (OS) were analyzed using the Kaplan–Meier method. The impact of BCS versus mastectomy on outcomes was assessed by multivariate Cox models. Inverse probability of treatment weighting (IPTW) was used to balance covariates between the two groups.

Results: The median follow-up of BCS and mastectomy groups were 86.5 and 87.4 months, respectively. There were significant differences in distribution of most baseline characteristics between two groups. Compared with those who underwent mastectomy, the patients with BCS had similar 5-year LRR, DM, and DFS rates, but had significantly higher 5-year BCSS (98.9% vs. 90.4%, P = 0.005) and OS (98.9% vs. 90.1%, P = 0.003) rates. Multivariate analysis also showed that BCS significantly improved BCSS (HR = 0.27, 95% CI: 0.08-0.85, P = 0.025) and OS (HR = 0.25, 95% CI: 0.08-0.79, P = 0.018). After IPTW adjustment, the LRR, DM, DFS, BCSS and OS between two groups had no significant differences.

Conclusions: The recurrence and survival outcomes are comparable with BCS and mastectomy. Thus, BCS is a safe treatment option for selected breast cancer patients after NACT.

KEYWORDS

breast cancer, neoadjuvant chemotherapy, breast-conserving surgery, mastectomy, oncological outcomes

Introduction

Several prospective randomized clinical trials have demonstrated that breast-conserving surgery (BCS) plus radiotherapy can provide long-term survival outcomes comparable to that with mastectomy (1–3) and better cosmetic outcomes and quality of life (4–6) in early-stage breast cancer (BC). Some recent large population-based studies have even shown better survival rates with BCS (7–10).

Traditionally, neoadjuvant chemotherapy (NACT) was a standard treatment of unresectable locally advanced breast cancer (LABC) to convert these patients to candidates for surgery. Two prospective randomized trials, the NSABP B18 and EORTC 10902, compared NACT and adjuvant chemotherapy in operable BC, and reported similar survival outcomes between two groups (11, 12). Moreover, these two trials both also found that NACT increased the rate of BCS by reducing the size of primary tumor. Based on the findings, NACT has been more widely accepted for operable BC and to facilitate BCS for the patients with large tumors who are initially considered for mastectomy (13, 14). In addition, it has potential to reduce resected volumes for the patients who are already candidates for BCS and achieve better cosmetic outcomes (15). Meanwhile, NACT can determine the chemo-sensitivity and reduce micrometastasis.

However, it is a main concern that whether BCS after NACT would increase the rate of ipsilateral breast tumor recurrence. A meta-analysis including ten studies (from 1983 to 2002) by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) found that 69% of patients achieved complete or partial clinical response after NACT and that the frequency of BCS increased from 49% to 65% after NACT. Nevertheless, the 15-year local recurrence rate was higher with NACT than with adjuvant chemotherapy (21.4% vs. 15.9%) (16). Other studies also showed unexpectedly high local recurrence rates for patients who received BCS after NACT (17, 18). One of the most important challenges for surgeons is to determine the original tumor location and excision extent to obtain tumor-free margins and achieve good cosmetic outcomes when performing BCS after NACT, especially for the patients with good response to NACT but whose residual tumor cells are scattered over the residual volume of disease. A consensus has been reached among the experts that "no ink on tumor" guideline was an adequate resection margin for BCS after NACT, because no relationship has been found between the margin width and outcomes (19, 20). Nowadays, the safety of BCS after NACT for the operable LABC remains controversial. Therefore, we conducted this study to compare the oncological outcomes after BCS versus mastectomy in patients receiving NACT.

Materials and methods

Study population

The data of patients treated with NACT between 2000 and 2014 in our institution were retrospectively reviewed. The inclusion criteria were 1) receiving NACT with large primary tumor and/or heavy axillary lymph nodal burden; 2) breast cancer with cT1-3N0-2M0 stage and ypT0-2N0-2M0 stage; 3) information available on estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) status; and 4) information available on whether or not to receive adjuvant treatment, such as chemotherapy, radiotherapy, endocrine therapy, or HER2-targeted therapy. The exclusion criteria were 1) received BCS without adjuvant radiotherapy; 2) mastectomy patients with proven ypN1-2 stage but no postmastectomy radiotherapy (PMRT); 3) relapse within 2 months; or 4) failure to complete at least 6 months of follow-up after surgery. We also excluded the patients with cT4/ypT3-4/ypN3 disease, because none of them had received BCS in our initial cohort. This study was approved and the need for informed consent was waived by Ethics Committee of National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College (approval number: 15-057/984), as this was a retrospective analysis of chart data.

Outcomes

Locoregional recurrence (LRR) was defined as recurrence in the ipsilateral breast or chest wall, ipsilateral axilla, supra- or infra-clavicular lymph nodes, or internal mammary lymph nodes. Distant metastasis (DM) was defined as evidence of metastatic disease beyond the locoregional regions. Disease-free survival (DFS) was calculated from the date of definitive surgery to the date of LRR, DM, death, or the last follow up. Breast cancer–specific survival (BCSS) was calculated from the date of start of NACT to the date of death from

BC or last follow-up. Overall survival (OS) was calculated from the date of start of NACT to the date of death or the last follow up.

Statistical analysis

The chi-square test was used to compare patient characteristics between the BCS and mastectomy groups. Multivariate Cox regression models were used to assess the impact of surgery methods on recurrence and survival after adjusting for confounding factors including treatment era, age, clinical stage, NACT cycles, response to NACT, histological grade, lymphovascular invasion (LVI), molecular subtype/trastuzumab, ypStage (pathologic stage after NACT), hormone receptor (HR) status/endocrine therapy, and adjuvant chemotherapy. To reduce the effect of selection bias and potential confounding factors, the differences in baseline covariates between BCS and mastectomy groups were balanced by the inverse probability of treatment weighting (IPTW) method (21). The IPTW approach attempts to mimic a situation in which treatment is randomly allocated to individuals. The Kaplan–Meier method was used for analysis of recurrence and survival before and after IPTW; the log-rank test was used for comparisons between the groups. Statistical analysis was performed using the SPSS 22.0 (IBM Corp., Armonk, NY, USA) and R 4.1.2 (https://www.r-project.org/). Two-sided P <.05 was considered statistically significant.

Results

Baseline characteristics

A total of 730 patients were enrolled in this analysis (Figure 1). Table 1 summarizes the patients' demographic characteristics and the tumor and treatment characteristics. The median age of the patients was 46 years (range, 20–73 years). Breast magnetic resonance imaging (MRI) was performed for 160 (21.9%) patients. Pretreatment median tumor diameter was 4 cm (range, 1–10 cm) in the BCS group and 5 cm (range, 1.1–13 cm) in the mastectomy group. There were 621 (85.1%), 80 (76.9%), and 541 (86.1%) patients who had tumor size ≥ 3cm in the entire, BCS, and mastectomy group, respectively. After NACT, there were 563 (77.1%), 97 (93.3%), and 466 (74.4%) patients who had pathologic tumor size < 3cm in the entire, BCS, and mastectomy group.

All 730 patients received NACT, with a median of 4 cycles (range, 1–8 cycles); 704 (96.4%) patients received anthracycline- and/or taxane-based regimens. After NACT, 104 (14.2%) patients received BCS and 626 (85.8%) received modified radical mastectomy. Seven (1.0%) patients underwent sentinel lymph node biopsy and 723 (99.0%) underwent axillary lymph node dissection; the median number of axillary lymph nodes removed was 19 (range, 1-44). After resection of the primary tumor, positive margin was found in 5 (0.7%) patients; all were focal and in the BCS

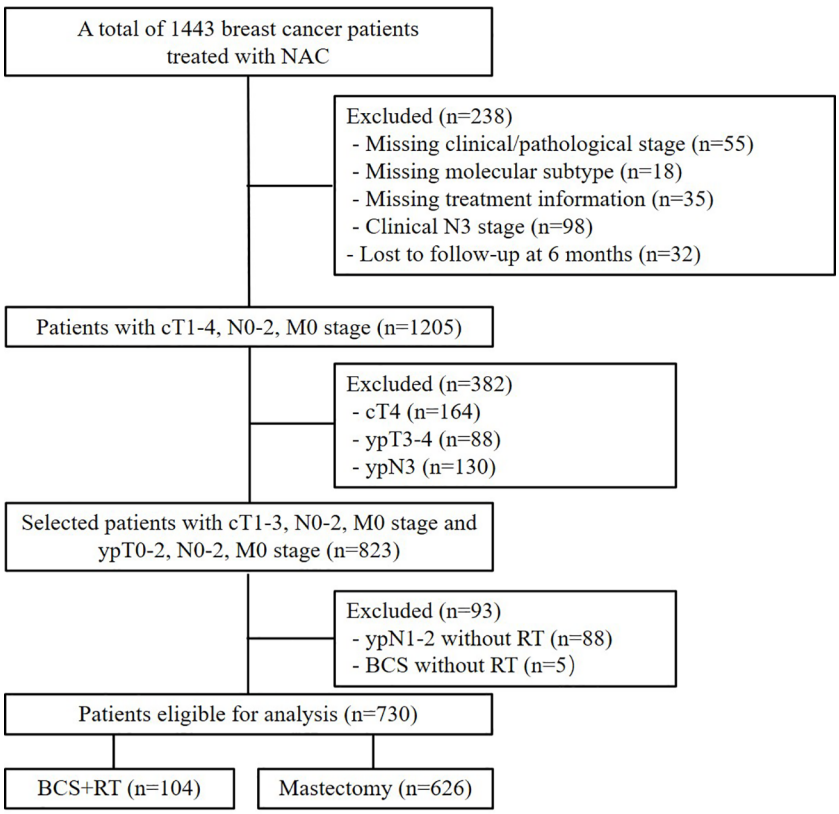

FIGURE 1
CONSORT diagram.

TABLE 1 Baseline characteristics of the study populations before and after IPTW (n = 730).

Variables	Unweighted population N (%)			Weighted population, N (%)		
	BCS 104 (14.2%)	Mastectomy 626 (85.8%)	*P*	BCS 837.5 (53.6%)	Mastectomy 725.1 (46.4%)	*P*
Treatment era						
2000-2008	38 (36.5)	223 (35.6)	.857	224.2 (26.8)	261.0 (36.0)	.240
2009-2014	66 (63.5)	403 (64.4)		613.2 (73.2)	464.0 (64.0)	
Age (y)						
<50	92 (88.5)	391 (62.5)	<.001	669.9 (80.0)	478.3 (66.0)	.091
≥50	12 (11.5)	235 (37.5)		167.6 (20.0)	246.7 (34.0)	
Clinical T stage						
1	6 (5.8)	28 (4.5)	.062	32.7 (3.9)	33.9 (4.7)	.892
2	70 (67.3)	354 (56.5)		511.2 (61.0)	419.9 (57.9)	
3	28 (26.9)	244 (39.0)		293.6 (35.1)	271.3 (37.4)	
Clinical N stage						
0	37 (35.6)	120 (19.2)	<.001	131.4 (15.7)	153.4 (21.2)	.572
1	62 (59.6)	405 (64.7)		534.2 (63.8)	465.4 (64.2)	
2	5 (4.8)	101 (16.1)		171.8 (20.5)	106.3 (14.6)	
Clinical stage						
II	77 (74.0)	360 (57.5)	.001	504.7 (60.3)	432.1 (59.6)	.948
III	27 (26.0)	266 (42.5)		332.7 (39.7)	293.0 (40.4)	
NACT cycles						
≤4	65 (62.5)	484 (77.3)	.002	669.7 (80.0)	548.2 (75.6)	.484
>4	39 (37.5)	142 (22.7)		167.7 (20.0)	176.8 (24.4)	
Response to NACT						
CR	9 (8.7)	79 (12.6)	.495	69.1 (8.3)	88.3 (12.2)	.059
PR	83 (79.8)	472 (75.4)		731.3 (87.3)	552.4 (76.2)	
SD+PD	12 (11.5)	75 (12.0)		37.0 (4.4)	84.4 (11.6)	
Histological grade						
I+II	59 (56.7)	303 (48.4)	.106	447.8 (55.4)	360.2 (49.7)	.446
III	17 (16.3)	161 (25.7)		222.6 (26.6)	178.7 (24.7)	
Unknown	28 (26.9)	162 (25.9)		133.3 (15.9)	186.2 (25.7)	
LVI						
No	96 (92.3)	564 (90.1)	.596	792.3 (94.6)	656.3 (90.5)	.307
Yes	8 (7.7)	62 (9.9)		45.2 (5.4)	68.8 (9.5)	
Molecular subtype/trastuzumab						
Luminal (HER2−)	57 (54.8)	281 (44.9)	.013	400.9 (47.9)	334.3 (46.1)	.564
HER2+Trastu+	15 (14.4)	78 (12.5)		83.7 (10.0)	91.2 (12.6)	
HER2+Trastu−	11 (10.6)	158 (25.2)		256.8 (30.7)	169.8 (23.4)	
Triple negative	21 (20.2)	109 (17.4)		96.1 (11.5)	129.8 (17.9)	
ypT stage						

(Continued)

TABLE 1 Continued

Variables	Unweighted population N (%)			Weighted population, N (%)		
	BCS 104 (14.2%)	Mastectomy 626 (85.8%)	*P*	BCS 837.5 (53.6%)	Mastectomy 725.1 (46.4%)	*P*
0-Tis	22 (21.2)	132 (21.1)	<.001	122.3 (14.6)	153.4 (21.2)	.347
1	67 (64.4)	250 (39.9)		318.1 (38.0)	312.4 (43.1)	
2	15 (14.4)	244 (39.0)		397.0 (47.4)	259.3 (35.8)	
ypN stage						
0	60 (57.7)	312 (49.8)	.071	406.2 (48.5)	371.0 (51.2)	.964
1	30 (28.8)	167 (26.7)		241.6 (28.9)	193.6 (26.7)	
2	14 (13.5)	147 (23.5)		189.6 (22.6)	160.5 (22.1)	
ypStage						
0	20 (19.2)	106 (16.9)	.006	112.6 (13.4)	125.6 (17.3)	.834
I	33 (31.7)	117 (18.7)		150.6 (18.0)	149.4 (20.6)	
II	37 (35.6)	256 (40.9)		384.6 (45.9)	289.5 (39.9)	
III	14 (13.5)	147 (23.5)		189.6 (22.6)	160.5 (22.1)	
HR status/endocrine therapy						
HR+ET+	65 (62.5)	382 (61.0)	.288	626.9 (74.9)	445.1 (61.4)	.104
HR+ET−	8 (7.7)	28 (4.5)		53.0 (6.3)	34.3 (4.7)	
HR−	31 (29.8)	216 (34.5)		157.6 (18.8)	245.7 (33.9)	
Adjuvant chemotherapy						
No	39 (37.5)	132 (21.1)	<.001	152.2 (18.2)	166.5 (23.0)	.401
Yes	65 (62.5)	494 (78.9)		685.2 (81.8)	558.6 (77.0)	

IPTW, inverse probability of treatment weighting; BCS, Breast conserving surgery; NACT, neoadjuvant chemotherapy; PR, partial remission; CR, complete remission; SD, stable disease; PD, progressive disease; LVI, lymphovascular invasion; HER2, human epidermal growth factor receptor 2; Trastu+, with trastuzumab; Trastu-, without trastuzumab; ypT stage, pathologic tumor stage after NACT; ypN, pathologic lymph node stage after NACT; ypStage, pathologic stage after NACT; HR, hormone receptor; ET, endocrine therapy.

group. After surgery, 126 (17.3%) patients achieved pathologic complete response (pCR), defined as breast pCR (ypT0 and ypTis) and axillary pCR (ypN0). Adjuvant chemotherapy was administered to 559 (76.6%) patients, with median of 3 cycles (range, 1–9 cycles). A total of 483 (66.2%) patients had ER/PR-positive disease; among them, 447 (92.5%) received endocrine therapy. Of the 262 (35.9%) HER2-positive patients, 93 (35.5%) received HER2-targeted therapy with trastuzumab, because trastuzumab was approved by the Chinsese Food and Drug Administration in September 2007.

In the BCS group, all 104 patients received whole-breast irradiation, 102 (98.1%) received tumor-bed boost, 42 (40.4%) received supra/infraclavicular nodal irradiation, and 1 (1.0%) received internal mammary nodal irradiation. Information on radiotherapy dose was available for 91 (87.5%) patients. The median dose delivered to the whole breast ± nodal regions was 50 Gy (range, 48–50 Gy) in 25 fractions (range, 24–25) for 86/91 (94.5%) patients or 43.5 Gy in 15 fractions for 5/91 (5.5%) patients. The median tumor-bed boost dose was 10 Gy (range, 10–20 Gy) in 5 fractions (range, 5–10) for 86/91 (94.5%) patients or 8.7 Gy in 3 fractions for 5/91 (5.5%) patients. Information on radiotherapy technique was available for 87 (83.7%) patients; while 29/87 (33.3%) received two-dimensional radiotherapy, 6/87 (6.9%) received three-dimensional conformal radiotherapy (3DCRT), and 52/87 (59.8%) received intensity-modulated radiotherapy (IMRT).

PMRT was recommended for patients with ypN1-2 stage and for ypN0 patients with high-risk factors (i.e., age < 45 years, cT3, cN2, presence of LVI, or ER/PR negative status). In the mastectomy group, 442 (70.6%) patients underwent PMRT. Information on radiotherapy fields was available for 415/442 (93.9%) patients. All 415 patients received chest wall irradiation, 407/415 (98.1%) received supra/infraclavicular nodal irradiation, 18/415 (4.3%) received axillary nodal irradiation, and 14/415 (3.4%) received internal mammary nodal irradiation. Information on radiotherapy dose was available for 379/442 (85.7%) patients; the median dose was 50 Gy (range, 42–60 Gy) in 25 fractions (range, 21–30) for 329/379 (86.8%) patients and 43.5 Gy in 15 fractions for 50/379 (13.2%) patients. Information on radiotherapy technique was available for 396/442 (89.6%) patients; while 381/396 (96.2%) received two-dimensional radiotherapy, 6/396 (1.5%) received 3DCRT, and 9/396 (2.3%) received IMRT.

Compared with mastectomy patients, BCS patients were significantly younger, had earlier clinical and pathological stage, and more likely to receive adjuvant chemotherapy. After IPTW

adjustment, there were 837.5 (53.6%) patients in the BCS group and 725.1 (46.4%) patients in the mastectomy group, and clinical characteristics were comparable between the two groups (Table 1).

Treatment outcomes

The median follow-up of BCS and mastectomy groups were 86.5 months (range, 6.5-169.9 months) and 87.4 months (range, 6.1-201.3 months), respectively. A total of 58 (7.9%) patients had developed LRR, 159 patients (21.8%) had developed DM, and 83 (11.4%) patients had died. Among the 83 patients who died, 78 (94.0%) died of the BC and 5 (6.0%) died of other causes. All five patients that died from other causes were in the mastectomy group; the causes of death included pulmonary fibrosis (n = 1), acute pancreatitis (n = 1), leukemia (n = 1), anemia and thrombocytopenia (n = 1), and unknown cause (n = 1). The patient who died from acute pancreatitis had hypertension, gastric ulcer, and hyperthyroidism; the other four patients had no comorbidity at the time of diagnosis of BC.

The 5-year LRR, DM, DFS, BCSS, and OS rates in the entire cohort were 7.5%, 18.6%, 78.9%, 91.7%, and 91.4%, respectively. As Figure 2 shows, there were no significant differences between the mastectomy group and the BCS group in 5-year LRR (6.9% vs. 7.6%, P = 0.805), DM (10.8% vs. 19.9%, P = 0.145), and DFS (83.4% vs. 78.2%, P = 0.514); however, the BCS group had significantly better BCSS (98.9% vs. 90.4%, P = 0.005) and OS (98.9% vs. 90.1%, P = 0.003).

Multivariate analysis did not reveal significant differences between the BCS and mastectomy groups in LRR (HR = 1.15, 95% CI: 0.52-2.56, P = 0.731), DM (HR = 0.80, 95% CI: 0.48-1.34, P = 0.400), and DFS (HR = 1.06, 95% CI: 0.67-1.68, P = 0.809); however, the BCS group had significantly better BCSS (HR = 0.27, 95% CI: 0.08-0.85, P = 0.025) and OS (HR = 0.25, 95% CI: 0.08-0.79, P = 0.018) (Table 2). Further, multivariate analysis showed clinical stage, ypStage, and HR status to be independent predictors of prognosis.

In the IPTW-adjusted cohort, 5-year LRR, DM, DFS, BCSS and OS were comparable between the BCS and mastectomy groups, which were 5.1% vs. 7.4% (P = 0.725), 16.0% vs. 19.1% (P = 0.726), 79.1% vs. 79.0% (P = 0.927), 99.7% vs. 90.8% (P = 0.148), and 99.7% vs. 90.3% (P = 0.133), respectively (Figure 2).

Discussion

In this single-center cohort study, we retrospectively evaluated the oncologic safety of BCS compared with mastectomy following NACT in patients with BC and found that LRR, DM, DFS, BCSS, and OS are comparable with BCS and mastectomy. Overall, our findings suggest that BCS is a safe and effective treatment option after NACT for patients with BC.

In recent years, NACT has become standard treatment for unresectable or resectable LABC and is being increasingly used in early-stage BC. The NSABP B18 trial examining the sequencing of chemotherapy demonstrated that patients treated with NACT had similar survival outcomes with those treated with adjuvant chemotherapy and NACT could increase BCS rates by tumor down-staging (11). The ipsilateral breast tumor recurrence (IBTR) rates were comparable in the NACT and adjuvant chemotherapy groups (7.9% vs. 5.8%). However, among women being converted from mastectomy to BCS candidates after NACT, the IBTR rate was higher (14.3%). Thus, the effectiveness of BCS after NACT remains unclear. Chen et al. reported acceptably low 5-year IBTR and LRR rates of 5% and 9% for the patients treated with BCS after NACT in a cohort of 340 patients from the MD Anderson Cancer Center; however, women with any one of the high-risk factors (i.e., cN2-3, pathologically residual tumor > 2 cm, multifocal residual disease, and LVI) had higher IBTR and LRR rates (9%–13% and 16%–23%) (18).

In our study, the surgical method was selected based on tumor response to NACT and patients' preference. Given the small breast size for most eastern women and few applications of oncoplastic surgery, the guidelines recommended that BCS should be offered to the patients who had tumor size < 3cm or had appropriate ratio of tumor to breast volume to achieve good cosmesis. In our study, 621 (85.1%) patients had tumor size ≥ 3cm who were not good candidates for BCS initially. After NACT, 563 (77.1%) had pathologic tumor size < 3cm who were presumed to be appropriate for BCS. However, most patients selected to receive mastectomy, which constituted a comparable cohort for the present study. In the present study, the LRR, DM, and DFS were similar in BCS and mastectomy patients; BCSS and OS were better in BCS patients, although the differences were not statistically significant after confounding factors were adjusted by IPTW. A meta-analysis found no significant difference in local and regional recurrence between BCS and mastectomy patients after NACT and that BCS patients had lower incidence of DM and better DFS and OS (22). Previous studies that reported the oncologic safety of BCS after NACT are summarized in Table 3 (13, 23–36). All studies were retrospective and most had small sample size. In a cohort of 561 patients treated with NACT, Simons et al. found significantly better DFS and OS after BCS than after mastectomy, but the statistical significance disappeared after correcting for confounders (36). An analysis of population-based data from the New Jersey State Cancer Registry (NJSCR) demonstrated that BCS patients after NACT had significantly better 10-year BCSS than mastectomy patients, and the difference remained even in propensity-matched comparison. However, the study findings must be interpreted cautiously because all patients did not receive radiotherapy after mastectomy and some important clinical factors such as tumor size, radiotherapy and chemotherapy data were missing in the database (35). Barranger et al. reported a 72.3% "mastectomy to BCS" conversion rate after NACT for resectable LABC. For whom mastectomy was the only conceivable surgical option initially, the 5-year DFS and OS of BCS and mastectomy patients were comparable (74% vs. 59% and 77% vs. 77%, respectively). But baseline tumor characteristics were not balanced between the two groups, the BCS patients having smaller tumor size and higher pCR rate, which were not adjusted during survival analysis and would have affected the outcomes (13). Most of the aforementioned studies reported results that were consistent with ours, i.e., that BCS after NACT is a safe alternative to mastectomy in patients with BC; however, these

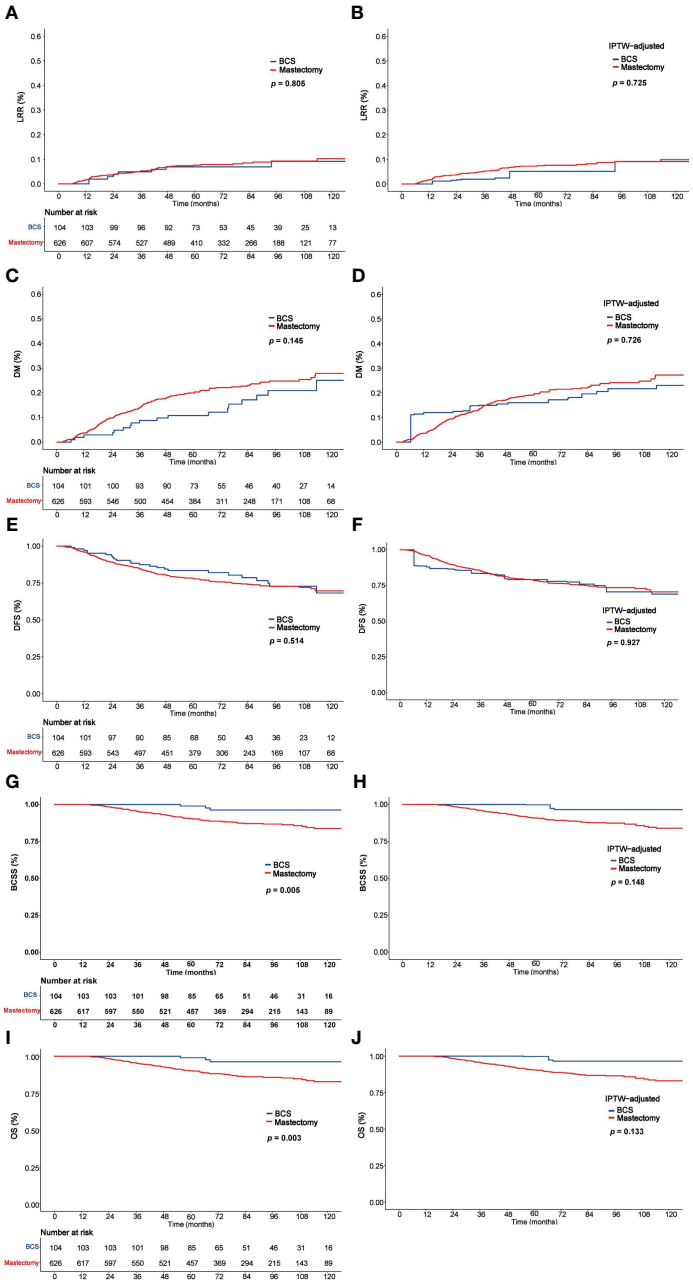

FIGURE 2
Comparison of LRR, DM, DFS, BCSS, and OS between the BCS and mastectomy groups before and after IPTW analysis. LRR **(A)**, DM **(C)**, DFS **(E)**, BCSS **(G)**, and OS **(I)** before IPTW analysis. LRR **(B)**, DM **(D)**, DFS **(F)**, BCSS **(H)**, and OS **(J)** after IPTW analysis. LRR, Locoregional recurrence; DM, distant metastasis; DFS, disease-free survival; BCSS, Breast cancer–specific survival; OS, overall survival; IPTW, inverse probability of treatment weighting.

TABLE 2 Multivariate analysis of the entire cohort.

Characteristics	LRR			DM			DFS			BCSS			OS		
	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*
Treatment era (2009-2014 vs. 2000-2008)	0.603	0.356-1.020	.059	0.840	0.592-1.190	.326	0.746	0.548-1.016	.063	0.922	0.558-1.523	.752	0.901	0.557-1.459	.673
Age (≥50 vs. <50)	0.934	0.534-1.635	.812	1.006	0.721-1.402	.973	1.069	0.782-1.461	.676	1.107	0.700-1.751	.665	1.102	0.707-1.719	.668

(Continued)

TABLE 2 Continued

Characteristics	LRR			DM			DFS			BCSS			OS		
	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*
Clinical stage (III vs. II)	1.559	0.925-2.625	.095	1.350	0.969-1.880	.076	1.434	1.066-1.928	.017	1.216	0.758-1.950	.417	1.280	0.809-2.027	.292
NACT cycles (>4 vs. ≤4)	0.927	0.333-2.583	.885	1.261	0.698-2.276	.443	1.054	0.601-1.848	.855	1.219	0.514-2.891	.653	1.171	0.500-2.742	.715
Response to NACT			.663			.525			.708			.863			.910
PR vs. CR	1.886	0.472-7.534	.369	0.920	0.418-2.026	.837	1.311	.603-2.849	.495	1.032	.327-3.252	.958	1.131	0.364-3.511	.832
SD+PD vs. CR	1.764	0.372-8.363	.475	1.187	0.492-2.862	.703	1.441	0.607-3.424	.408	1.228	.342-4.406	.753	1.272	0.360-4.499	.709
Histological grade			.760			.288			.476			.430			.438
III vs. I+II	0.879	0.451-1.715	.705	0.737	0.483-1.124	.156	0.789	0.532-1.169	.237	0.829	0.469-1.463	.517	0.923	0.537-1.584	.770
Unknown vs. I+II	0.777	0.393-1.534	.467	0.798	0.531-1.199	.277	0.881	0.605-1.282	.507	0.672	0.364-1.240	.204	0.678	0.374-1.230	.201
LVI (Yes vs. No)	1.515	0.745-3.082	.252	0.861	0.520-1.423	.559	1.012	0.640-1.601	.960	0.822	0.389-1.740	.609	0.776	0.368-1.636	.505
Molecular subtype/ trastuzumab			.405			.863			.890			.717			.806
HER2+/Trastu+ vs. Luminal (HER2-)	2.057	0.846-5.002	.112	1.083	0.604-1.944	.788	1.237	0.721-2.123	.440	0.969	0.401-2.342	.944	0.952	0.398-2.277	.912
HER2+/Trastu- vs. Luminal (HER2-)	1.083	0.489-2.397	.844	0.863	0.535-1.393	.546	1.082	0.697-1.682	.724	0.710	0.340-1.485	.363	0.831	0.411-1.680	.606
Triple negative vs. Luminal (HER2-)	1.611	0.522-4.978	.407	1.013	0.496-2.069	.971	1.083	0.563-2.080	.812	0.649	0.242-1.746	.392	0.655	0.253-1.691	.382
ypStage			<.001			<.001			<.001			<.001			<.001
I vs. 0	0.850	0.245-2.943	.797	1.640	0.731-3.680	.230	1.379	0.669-2.846	.384	5.905	1.280-27.239	.023	6.762	1.484-30.805	.013
II vs. 0	1.931	0.733-5.082	.183	3.661	1.820-7.366	<.001	3.041	1.650-5.606	<.001	8.067	1.922-33.854	.004	9.051	2.166-37.820	.003
III vs. 0	3.963	1.514-10.378	.005	7.701	3.795-15.627	<.001	5.851	3.135-10.918	<.001	19.112	4.543-80.400	<.001	20.433	4.867-85.780	<.001
Surgery (BCS vs. Mastectomy)	1.150	0.517-2.558	.731	0.801	0.477-1.344	.400	1.058	0.668-1.676	.809	0.265	0.083-0.845	.025	0.249	0.078-0.791	.018
HR status/endocrine therapy			.908			.654			.653			.008			<.001
HR+/ET- vs. HR+/ET+	0.773	0.182-3.281	.727	1.243	0.594-2.598	.564	1.061	0.510-2.208	.873	1.551	0.555-4.338	.403	1.526	0.546-4.262	.420
HR- vs. HR+/ET+	1.111	0.466-2.651	.813	1.251	0.714-2.191	.434	1.266	0.767-2.090	.357	2.093	1.313-3.334	.002	2.288	1.460-3.584	<.001
Adjuvant chemotherapy (No vs. Yes)	1.148	0.398-3.313	.798	1.412	0.958-2.082	.082	1.394	0.955-2.036	.086	1.018	0.412-2.513	.969	0.972	0.398-2.372	.951

LRR, Locoregional recurrence; DM, distant metastasis; DFS, disease-free survival; BCSS, Breast cancer–specific survival; OS, overall survival; HR, hazard ratio; CI, confidence interval; NACT, neoadjuvant chemotherapy; PR, partial remission; CR, complete remission; SD, stable disease; PD, progressive disease; LVI, lymphovascular invasion; HER2, human epidermal growth factor receptor 2; Trastu+, with trastuzumab; Trastu−, without trastuzumab; ypStage, pathologic stage after NACT; BCS, Breast conserving surgery; HR, hormone receptor; ET, endocrine therapy.

TABLE 3 Summary of previous studies comparing BCS and mastectomy after NACT in patients with breast cancer.

Author, Year	Enrollment Period	Median follow-up, mo	Eligibility (No.)	Surgical method	Response to NACT			Median tumor size (cm)		LRR (%)	DM (%)	5-year DFS (%)	5-year OS (%)
					CR (%)	PR (%)	SD+PD (%)	Pre-NACT	Post-NACT				
Schwartz, 1994 (23)	1983-1991	46	T2N2, T3-4N0-2 (n=158)	BCS	100		–	NA	NA	NA	NA	77	80
				Mastectomy				NA	NA	NA	NA	56	67
Cance, 2002 (24)	1992-1998	70	T3-4, N2 (n=59)	BCS	22	76	2	NA	NA	10	NA	NA	96*
				Mastectomy				NA	NA	16	NA	NA	51*
McIntosh, 2003 (25)	1992-1997	62	T2 > 4cm, T3-4N0-1 (n=166)	BCS	21	54	25	NA	1.3	2.3	NA	NA	MST: 75m
				Mastectomy				NA	3.4	5.2	NA	NA	MST: 22m
Rouzier, 2004 (26)	1987-2001	67	T2-3N0-2 (n=594)	BCS	14.6	59.6	25.8	4.9	3.1	NA	25*	NA	NA
				Mastectomy	2.9	35.2	61.9			NA	37*	NA	NA
Sadetzki, 2005 (27)	1995-2001	>27	Stage II > 3cm, III (n=119)	BCS	NA	NA	NA	4.67	1.68	NA	NA	NA	NA
				Mastectomy	NA	NA	NA	4.74	3.29	NA	NA	NA	NA
Parmar, 2006 (28)	1998-2002	30	LABC (n=664)	BCS	92.7		7.3	6	1.5	NA	11.1*	62*	NA
				Mastectomy	67.1		32.9	8.3	4.1	NA	25.6*	37*	NA
Sweeting, 2011 (29)	1991-2007	76.8	Stage II, III (n=122)	BCS	43	44	13	5.6	1.3	13	NA	82*	88*
				Mastectomy				6.7	3.2	18	NA	58*	61*
Cho, 2013 (30)	1998-2010	45.9	pathologic tumor size ≤3 cm (n=431)	BCS	30.6	NA	NA	NA	NA	5.5	11.0	80.7	89.1
				Mastectomy	11.1	NA	NA	NA	NA	6.2	16.0	74.6	84.2
Shin, 2013 (31)	2004-2007	62.4	Stage III (n=129)	Preplanned BCS	NA	NA	NA	NA	< 4	5.3 (LR)	NA	NA	NA
				Downstaged BCS	NA	NA	NA	NA		9.1 (LR)	NA	NA	NA
				Mastectomy	NA	NA	NA	NA		3.7 (LR)	NA	NA	NA
Levy, 2014 (32)	2002-2012	75.6	Stage I-III (n=284)	BCS	27	NA	NA	4	NA	9.2 (10y)	27 (10y)	NA	63 (10y)
				Mastectomy	5	NA	NA	5	NA	10.7 (10y)	41 (10y)	NA	60 (10y)

(Continued)

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TABLE 3 Continued

Author, Year	Enrollment Period	Median follow-up, mo	Eligibility (No.)	Surgical method	Response to NACT			Median tumor size (cm)		LRR (%)	DM (%)	5-year DFS (%)	5-year OS (%)
					CR (%)	PR (%)	SD+PD (%)	Pre-NACT	Post-NACT				
Cureton, 2014 (33)	2002-2006	46.8	Clinical tumor size ≤3 cm (n=206)	BCS	NA	NA	NA	6	NA	NA	16.9	NA	NA
				Mastectomy	NA	NA	NA		NA	NA	23.9	NA	NA
Barranger, 2015 (13)	2007-2012	41.1	Candidates for Mastectomy initially (n=119)	BCS	NA	NA	NA	3.4	1.7	3.5	NA	74	77
				Mastectomy	NA	NA	NA	5.5	3.3	3.0	NA	59	77
Debled, 2015 (34)	2005-2012	38	cT2-4, HER2+ (n=152)	BCS	NA	NA	NA	4.5	NA	5.6 (LR)	15.7	NA	NA
				Mastectomy	NA	NA	NA	7.0	NA	0	25	NA	NA
Arlow, 2018 (35)	1998-2003	110.5	BCS with RT, Mastectomy without RT (n=718)	BCS	NA	NA	NA	NA	NA	NA	NA	NA	BCS had better BCSS
		106.0		Mastectomy	NA	NA	NA	NA	NA	NA	NA	NA	
Simons, 2020 (36)	2008-2017	81.6	cT1-4N0-N+M0 (n=561)	BCS	25.7	NA	NA	NA	NA	NA	NA	90.9*	95.3*
				Mastectomy	19.1	NA	NA	NA	NA	NA	NA	82.9*	85.9*
Our study	2000-2014	87.4	cT1-3N0-2M0 and ypT0-2N0-2M0 (n=730)	BCS	8.7	79.8	11.5	4.0	1.0	6.9 (5y)	10.8 (5y)	83.4	98.9*
				Mastectomy	12.6	75.4	12.0	5.0	2.0	7.6 (5y)	19.9 (5y)	78.2	90.1*

* Statistically significant.

BCS, Breast conserving surgery; NACT, neoadjuvant chemotherapy; CR, complete remission; PR, partial remission; SD, stable disease; PD, progressive disease; LRR, Locoregional recurrence; DM, distant metastasis; DFS, disease-free survival; OS, overall survival; NA, not available; MST, median survival time; LABC, locally-advanced breast cancer; LR, Local recurrence; HER2, human epidermal growth factor receptor 2; RT, radiotherapy; BCSS, breast cancer–specific survival.

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earlier studies had obvious limitations such as unbalanced baseline characteristics and missing important data. In our study, we included patients who had received adjuvant radiotherapy per the current guideline (e.g., radiotherapy after BCS, PMRT if ypN1-2 or ypN0 with high-risk factors). Confounding due to differences in baseline covariates between the two surgical groups was minimized by using the IPTW method. These measures make our results more convincing. All five patients who died from non-breast-cancer causes were in the mastectomy group, but most had no comorbidities at diagnosis of BC; therefore, the poorer OS in the mastectomy group might not be related to presence of comorbidities.

In multivariate analysis, ypStage was independent prognostic factors for most oncologic outcomes, and hormone receptor–negative status was a significant predictor of poor OS. As other authors have also demonstrated that advanced post-NACT stage and triple-negative status were significant predictors of poor outcome; this is not surprising since these factors indicate aggressive disease (30, 37).

Though this study suggests that BCS is a safe treatment option for patients after NACT, some concerns remain. In clinical practice, the primary tumor site is usually difficult to locate after tumor regression. One study that assessed pathological response of BC to NACT found increased incidence of multifocality and *in situ* lesions localized within the original tumor-bearing area after tumor shrinkage (38); this can lead to difficulty in defining the extent of resection necessary to achieve safe margin during BCS. However, over the past few years, there have been major advances to improve the probability of safe BCS after NACT. These advances include increased application of breast MRI, use of metal markers to improve definition of tumor location, and improved detection of multifocal or multicentric tumor, greater attention to achieving pathologically negative BCS margins and use of modern radiotherapy techniques that provide more precise dose coverage and thus improve local control and decrease toxicity. A policy review endorsed by several European societies and clinical trial groups has provided a practical working toolbox for the surgical treatment of early-stage BC after NACT (39). There is now consensus that all patients receiving NACT must undergo comprehensive evaluation in multidisciplinary team meetings, undergo imaging by multiple modalities (e.g., MRI and ultrasound) at diagnosis, and have clips placed at the primary site before NACT. In addition, response assessment at different time points must be done by the same imaging modality used at initial diagnosis; careful preoperative evaluation for localization, volume excision, and retrieval of breast markers is essential before BCS. Precise margin assessment and appropriate radiotherapy are also important for successful BCS. Through the close cooperation of multidisciplinary team, not only do the patients with resectable LABC have an opportunity to be converted from mastectomy to BCS candidates after NACT, but the women with early-stage triple-negative or HER2 - positive BC who are currently candidates for NACT are safe to receive BCS.

Some limitation of this study should be acknowledged. First, the retrospective design might have introduced a selection bias. Although IPTW was used to balance known variables in the two groups, it is possible that other confounders were unevenly distributed. Second, the 15-year span of patient inclusion was very long; but the patients in different treatment era between the two groups were comparable, and the influences of the changes in the diagnosis and treatment of BC over this period between the two groups were similar, e.g. the proportion of the patients who had HER2 - positive disease but did not received trastuzumab-targeted therapy was comparable after IPTW between the two groups. Third, the findings of this study can only be applied to specific populations, i.e. patients with cT1-3N0-2M0 and ypT0-2N0-2M0 BC, and the effect of BCS in patients with more advanced stage remains to be accessed. To our knowledge, this is the largest study to compare the outcomes between BCS and mastectomy after NACT, thus, we believe that our study makes a meaningful contribution to clinical practice.

Conclusions

Breast-conserving surgery appears to be a safe treatment option for selected BC patients after neoadjuvant chemotherapy. It does not compromise locoregional, distant control, DFS, BCSS and OS compared with mastectomy.

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 Ethics Committee of National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College (approval number: 15-057/984). Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

Y-CS: Formal analysis, investigation, data collection, methodology, and writing of the first draft. ZH: statistical analysis, investigation, data collection, methodology. HF, YuT, HJ, Y-WS, JJ, Y-PL, BC, YuanT, S-NQ, N-NL, and NL: Patient care and review, and editing of the manuscript. Y-XL and S-LW: Study design, formal analysis, validation, statistical analysis guidance, patient care, and editing of the manuscript. All authors contributed to the article and approved the submitted version.

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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.

Publisher's note

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Machine learning for predicting breast-conserving surgery candidates after neoadjuvant chemotherapy based on DCE-MRI

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Purpose: This study aimed to investigate a machine learning method for predicting breast-conserving surgery (BCS) candidates, from patients who received neoadjuvant chemotherapy (NAC) by using dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) obtained before and after NAC.

Materials and methods: This retrospective study included 75 patients who underwent NAC and breast surgery. First, 3,390 features were comprehensively extracted from pre- and post-NAC DCE-MRIs. Then patients were then divided into two groups: type 1, patients with pathologic complete response (pCR) and single lesion shrinkage; type 2, major residual lesion with satellite foci, multifocal residual, stable disease (SD), and progressive disease (PD). The logistic regression (LR) was used to build prediction models to identify the two groups. Prediction performance was assessed using the area under the curve (AUC), accuracy, sensitivity, and specificity.

Results: Radiomics features were significantly related to breast cancer shrinkage after NAC. The combination model achieved an AUC of 0.82, and the pre-NAC model was 0.64, the post-NAC model was 0.70, and the pre-post-NAC model was 0.80. In the combination model, 15 features, including nine wavelet-based features, four Laplacian-of-Gauss (LoG) features, and two original features, were filtered. Among these selected were four features from pre-NAC DCE-MRI, six were from post-NAC DCE-MRI, and five were from pre-post-NAC features.

Conclusion: The model combined with pre- and post-NAC DCE-MRI can effectively predict candidates to undergo BCS and provide AI-based decision support for clinicians with ensured safety. High-order (LoG- and wavelet-based) features play an important role in our machine learning model. The features from pre-post-NAC DCE-MRI had better predictive performance.

KEYWORDS

machine learning, breast cancer, neoadjuvant chemotherapy, magnetic resonance imaging, breast-conserving surgery

1 Introduction

Breast cancer is the most prevalent cancer among women and its incidence is increasing yearly worldwide (1). Neoadjuvant chemotherapy (NAC) is the standard treatment for early breast cancer (2). For patients with heavy tumor load, it is designed to reduce tumor stage and surgical interventions, provide more patients with opportunities for breast-conserving surgery (BCS), and avoid axillary lymph node dissection (3–5). For human epidermal growth factor receptor 2 (HER2) + or triple-negative (TN) breast cancer, NAC can provide doctors with more *in vivo* information regarding drug sensitivity, a so-called individual drug-sensitive platform (6). With the development of new targeted drugs for early breast cancer, both the population receiving NAC and the rate of achieving pathological complete response (pCR) are increasing (7, 8). Meanwhile, patients without pCR still have the opportunity to downstage to BCS through NAC, which can cause less damage to the breast (9, 10). Thus, safe selection of candidates for BCS after NAC is a critical issue.

The pCR rate varies among breast cancer subtypes, and HER2+ status is more likely to result in pCR (11). However, evaluation of pCR is not sufficient to identify candidates for BCS. The efficacy response of breast cancer patients after NAC can be classified into three categories: pCR, partial remission, and non-remission. Partial remission can be further divided into single-lesion shrinkage, major residual lesions with satellite foci, and multifocal residuals based on microscopic morphology (12–14). Fukada et al. (15) classified tumors into concentric shrinkage (CS) and non-CS patterns. The CS pattern was associated with better disease-free and overall survival rates. However, in their study, the CS was composed of single lesion shrinkage and major residual lesions with satellite foci. Wang et al. (16) further specified this by defining single lesion shrinkage as type 1, multifocal and patchlike lesions as type 2, and major residual lesions with satellite foci as type 3. They proposed that types 2 and 3 in partial remission had relatively high recurrence rates after undergoing BCS. This is because types 2 and 3 have the risk of missing tiny lesions, and negative surgical margins are not guaranteed. Therefore, a detailed differentiation of tumor shrinkage patterns is necessary for clinical work. The European Society of Breast Imaging (EUSOBI) recommends magnetic resonance imaging (MRI) to evaluate the efficacy of NAC in breast cancer (17). Dynamic contrast-enhanced MRI (DCE-MRI) is a technique for contrast imaging that uses differences in the distribution of contrast agents within the tissues. It serves as the most sensitive MRI sequence for breast cancer, allowing simultaneous assessment of tissue perfusion and morphological changes to reflect the response of breast tumors to NAC (18). Machine learning (ML) can be used to extract information that cannot be recognized by clinicians in medical images (19). Thus, ML can greatly improve the ability to evaluate NAC with MRI, and most studies have focused on building an ML model to distinguish pCR from non-pCR (20). Previous studies have reported that multiparametric MRI performed better than single sequences for prediction (21, 22). Nevertheless, in multiparametric MRI radiomics, the outlining of the region of interest (ROI) is usually performed in DCE-MRI and applied to other sequences using image registration algorithms (23). The Speeded Up Robust Features algorithm, an accelerated version of the scale-invariant feature transform algorithm, still suffers from problems, such as insufficient feature points and accuracy (24). Another way to outline the ROI is to complete the ROI on all sequences separately (25), but the shortcoming is that the differences in the ROI of each sequence are difficult to avoid. In addition, general radiomics features, such as texture features, and first-order features, have been adequately analyzed, while the use of high-order features is relatively inadequate.

The image before the first phase of NAC is called the baseline image. The image obtained after the last phase of NAC and before surgery is referred to as the preoperative image. We used pre-NAC DCE-MRI as the baseline image and post-NAC DCE-MRI as the preoperative image. In this study, we constructed a model that has the potential to provide clinicians with appropriate candidates for BCS based on pre- and post-NAC DCE-MRIs.

2 Materials and methods

2.1 Patients

This study was approved by the Institutional Review Board, and the requirement for informed consent was waived. This study included 75 patients with breast cancer at the Second Hospital of Dalian Medical University between June 2014 and May 2021. Pre- and post-NAC images of the patients were used for the analysis, and the total number was 150. The inclusion criteria were as follows (1): invasive breast cancer confirmed by biopsy (2), accepted MRI examinations before and after NAC (3), underwent definitive surgery after standard NAC in our hospital, and (4) available pathologic results. The exclusion criteria were as follows (1): receiving other treatments during NAC. The ratio of the training set to validation sets was 4:1.

The chemotherapy regimen for all enrolled patients was based on the standard regimen recommended by the National Comprehensive Cancer Network (NCCN) Breast Cancer Guidelines. The preoperative chemotherapy regimens were taxane-based, anthracycline-based, or a combination of both. For HER2+ patients, the addition of anti-HER2 therapy (e.g., trastuzumab or a combination of trastuzumab and pertuzumab) is required.

2.2 MRI technique and immunohistochemistry

All patients were examined with 1.5T or 3.0T breast MRI (GE Signa HDxt 1.5T, GE Discovery MR 750 W 3.0T, Siemens Verio 3.0T) before and after NAC (Table 1). Axial DCE-MRI: A T1-weighted pre-contrast scan was first performed, followed by injection of a contrast agent (Gd-DTPA). After injection, 20 ml of saline was used to flush the tube, which was then continuously scanned for nine phases.

TABLE 1 DCE-MRI protocol for each scanner.

DCE-MRI	GE Signa HDxt 1.5T	GE Discovery MR 750W 3.0T	Siemens Verio 3.0T
TR (ms)	5.1	6.9	4.54
TE (ms)	2.5–12	minimum	1.61
Matrix (pixels)	320 × 384	288 × 320	346 × 384
FOV (mm)	320 × 320	360 × 360	340 × 340
Slice thickness (mm)	2.8	1.4	1.6
Flip angel	15	10	10

TR, repetition time; TE, echo time; FOV, field of view.

2.3 ROI masking

Two radiologists assessed the tumor borders. A radiologist with 5 years of experience completed ROI masking and was then reviewed by another radiologist with over 23 years of experience. The two radiologists reached a consensus on tumor bounderies. The tumor contours on each slice of the third post-enhanced image were manually outlined, and a 3D volume of interest (VOI). This step was performed on pre-NAC images and post-NAC images separately by using 3D Slicer 4.10.2 (www.slicer.org, including the following steps unless noted).

2.4 Pathological assessment

Biopsies and surgical specimens were handled by a pathologist with more than 8 years of experience. Surgical specimens were fixed in standard formalin solution and processed in a standard breast tissue processor, according to which the longest diameter of the tumor was recorded.

Immunohistochemistry was used to determine the expression of Ki-67, progesterone receptor (PR), estrogen receptor (ER), and HER2. HER2 expression was graded as 0, 1+ was negative, and 3+ was positive. If HER2 expression was graded as 2+, additional fluorescence *in situ* hybridization was required.

The maximum diameter of the tumor was measured using a 3D slicer in pre-NAC DCE-MRI as the baseline. Shrinkage patterns were assessed by comparing the surgical specimens with the baseline values. The definition of shrinkage patterns was based on the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, Chalian et al., Schwartz et al. (26–28). Type 1 shrinkage pattern included pCR and single-lesion shrinkage. pCR was defined as no residual invasive carcinoma in the primary lesion or axillary lymph node after NAC, and single lesion shrinkage was defined as a lesion that had shrunk by more than 30% of its longest diameter. Type 2 shrinkage patterns include major residual lesions with satellite foci, multifocal residuals, stable disease (SD), and progressive disease (PD). Major residual lesions with satellite foci were defined as the main residual lesions accompanied by at least one minor lesion on the continuous slides. Multifocal residuals were defined as the presence of at least two separate lesions. SD was defined as a lesion shrinking by less than 30% of its longest diameter, and PD was defined as a lesion exceeding the baseline in its longest diameter. Two experienced pathologists independently examined the specimens and agreed to the regression patterns.

2.5 Image processing and features extraction

Non-uniform intensity normalization (N4) bias correction was applied to extract the bias field in MR imaging and correct it to eliminate the effect of artifacts. The voxel sizes of the images were resampled to (1, 1, 1).

The features of the pre-NAC model (pre-NAC features) were extracted from pre-NAC DCE-MRI, and those of the features of post-NAC model (post-NAC features) were extracted from post-NAC DCE-MRI. The features of the pre-post-NAC model (pre-post-NAC features) were obtained by subtracting the value of the post-NAC features from the pre-NAC features. The features of the combination model (combination features) consisted of pre-NAC, post-NAC, and pre-post-NAC features.

2.6 Statistical analyses

All features were imported into the Darwin Scientific Research Platform (Medical AI Technology (Beijing) Co., Ltd.) for subsequent operations. The feature values were normalized between −1 and 1 by maximum absolute value normalization. Minimum redundancy maximum relevance (mRMR) feature selection was utilized to select highly relevant features from pre-NAC, post-NAC, pre-post-NAC, and combination features. The filtered features were used to construct logistic regression (LR) models. LR is a model for solving binary classification problems. The importance of each independent variable is quantified in LR, and a set of independent variables with optimal classification performance is utilized to form a linear combination (29). As an optimization problem, the binary class L2 penalized LR minimizes the following cost function:

$$y = \min_{w,c} \frac{1}{2} \boldsymbol{w}^{\top} \boldsymbol{w} + C \sum_{i=1}^{n} \log(\exp(-y_i(\boldsymbol{x}_i^{\top} \boldsymbol{w} + c)) + 1)$$

x_i is the radiomics features for sample i, y_i is the sample i label, w is the coefficient vector of the LR model, and c the inverse of the regularization intensity.

The performance of the LR model was demonstrated by the receiver operating characteristic curve. Then the area under the curve (AUC), accuracy, sensitivity, and specificity were calculated. Type 1 was defined as negative and type 2 was defined as positive.

The patient characteristics were calculated by SPSS software (version 26, IBM). The normally distributed continuous data were expressed as mean ± standard deviation and examined by independent t-tests. Continuous variables between two groups were examined by Fisher's exact test or chi-square test. 0.05 was used as the significant level.

3 Result

3.1 Patient characteristics

The radiomics framework is shown in Figure 1. A total of 75 patients were enrolled in the study, in which type 1 accounted for 67.2% (53.2 ± 9.1 years), and type 2 for 32.8% (53.3 ± 8.8 years). Premenopausal patients accounted for 48.1% and 47.8% of patients with type 1 and type 2 diseases, respectively. ER >1% accounted for 61.5% of type 1 cases and 60.9% of type 2 cases. A PR >1% accounted for 57.7% of type 1 cases and 52.2% of type 2 cases. HER2 positive accounted for 57.7% of the type 1 cases and 65.2% of the type 2 cases. Clinical T-stages 1–2 accounted for 78.8% and 65.2% of patients with type 1 and type 2 tumors, respectively. Luminal A, luminal B, HER2, and TN accounted for 13.5%, 59.6%, 17.3%, and 9.6% in type 1 while 21.7%, 39.1%, 34.8%, and 4.3% in type 2. Age (P = 0.947), menopausal status (P = 0.984), ER status (P = 0.956), PR status (P = 0.657), clinical T-stage (P = 0.211), and molecular subtype (P = 0.215) were not significantly different between types 1 and 2. The expression level of Ki-67 was significally different (P = 0.047) between type 1 and type 2, of which the proportion of Ki-67 >20% in type 1 was higher (78.8% in type 1, 56.5% in type 2). The characteristics of the type 1 and type 2 patients are shown in Table 2. There were no significant differences in the patient characteristics between the training and validation sets (Table 3).

3.2 Model effectiveness

The AUC of combination model was 0.84 (95% CI: 0.74–0.94) for the training set and 0.82 (95% CI: 0.60–1.00) for the validation set, pre-NAC model was 0.81 (95% CI: 0.70–0.92) and 0.64 (95% CI: 0.34–0.94), post-NAC model was 0.83 (95% CI: 0.72–0.95) and 0.70 (95% CI: 0.43–0.97), pre-post-NAC model was 0.81 (95% CI: 0.69–0.93), and 0.80 (95% CI: 0.56–1.00) (Figure 2). The model performance details are listed in Table 4.

3.3 VOI features and linear combination

A total of 1,130 features were extracted from each VOI on pre- and post-NAC DCE-MRIs. The categories of features consisted of first-order features, shape features (2D and 3D), textural features, wavelet-based features, and 3D textural features from image data filtered by Laplacian-of-Gauss (LoG) with kernel sizes of 2, 4, and 6. After the feature selection, 15 features were filtered out. The selected features, in combination, are as follows:

pre-wavelet-HLH-gldm-Dependence Variance

pre-wavelet-HLL-glrlm-Short Run Low Gray Level Emphasis

post-original-shape-Elongation

pre-post-log-sigma-4-0-mm-3D-glcm-Informational Measure of Correlation

pre-post-log-sigma-4-0-mm-3D-glcm-Maximum Probability

pre-post-wavelet-HLL-glrlm-Run Entropy

post-original-shape-Maximum 3D Diameter

post-wavelet-HHL-glrlm-Short Run High Gray Level Emphasis

pre-post-log-sigma-6-0-mm-3D-gldm-Small Dependence Low Gray Level Emphasis

pre-wavelet-HLL-first order-Skewness

post-log-sigma-6-0-mm-3D-glcm-Maximal Correlation Coefficient

post-wavelet-HHH-gldm-Dependence Variance

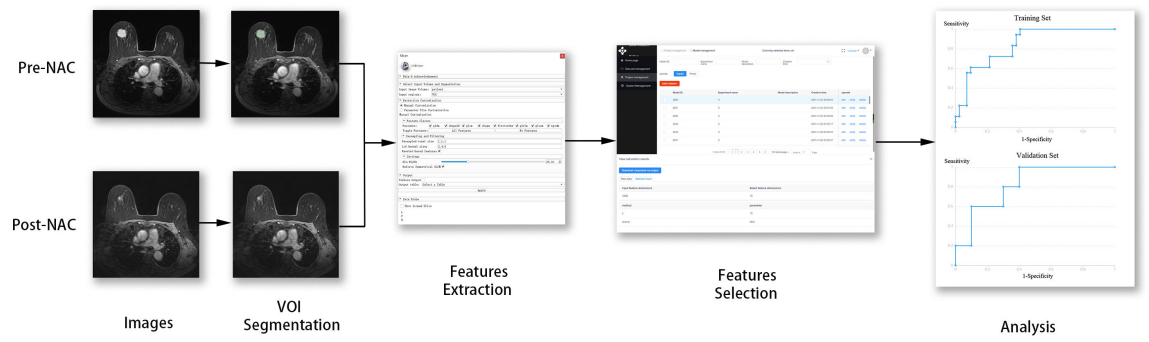

FIGURE 1
Radiomics workflow.

TABLE 2 Characteristics of patients and breast cancers in our study.

Characteristics	Type 1	Type 2	*P*-value
No. of patients	52	23	
Age, years	53.2 (± 9.1)	53.3 (± 8.9)	0.947
Menopausal Status			0.984
Premenopausal	25 (48.1%)	11 (47.8%)	
Postmenopausal	27 (51.9%)	12 (52.2%)	
ER Status			0.956
≤1%	20 (38.5%)	9 (39.1%)	
>1%	32 (61.5%)	14 (60.9%)	
PR Status			0.657
≤1%	22 (42.3%)	11 (47.8%)	
>1%	30 (57.7%)	12 (52.2%)	
HER2 Status			0.540
Positive	30 (57.7%)	15 (65.2%)	
Negative	22 (42.3%)	8 (34.8%)	
Ki-67 Status			0.047
≤20%	11 (21.2%)	10 (43.5%)	
>20%	41 (78.8%)	13 (56.5%)	
Clinical T-stage			0.211
1–2	41 (78.8%)	15 (65.2%)	
3–4	11 (21.2%)	8 (34.8%)	
Molecular Subtype			0.215
Luminal A	7 (13.5%)	5 (21.7%)	
Luminal B	31 (59.6%)	9 (39.1%)	
HER2	9 (17.3%)	8 (34.8%)	
TN	5 (9.6%)	1 (4.3%)	

ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2; TN, triple-negative.

TABLE 3 Characteristics of patients in training set and validation set.

Characteristics	Training set	Validation set	*P*-value
No. of patients	60	15	
Age, years	53.1 (± 9.3)	53.7 (± 7.6)	0.824
Regression pattern			1.000
Type 1	42 (70.0%)	10 (66.7%)	
Type 2	18 (30.0%)	5 (33.3%)	
Menopausal Status			0.131
Premenopausal	29 (48.3%)	4 (26.7%)	
Postmenopausal	31 (51.7%)	11 (73.3%)	
ER Status			0.101
≤1%	22 (36.7%)	9 (60.0%)	
>1%	38 (63.3%)	6 (40.0%)	
PR Status			0.816
≤1%	26 (43.3%)	7 (46.7%)	
>1%	34 (56.7%)	8 (53.3%)	
HER2 Status			0.556
Positive	37 (61.7%)	8 (53.3%)	
Negative	23 (38.3%)	7 (46.7%)	
Ki-67 Status			0.486
≤20%	16 (21.2%)	6 (43.5%)	
>20%	44 (78.8%)	9 (56.5%)	
Clinical T-stage			0.842
1-2	44 (73.3%)	12 (80.0%)	
3-4	16 (26.7%)	3 (20.0%)	
Molecular Subtype			0.425
Luminal A	8 (13.3%)	4 (26.7%)	
Luminal B	33 (55.0%)	7 (46.7%)	
HER2	13 (21.7%)	4 (26.7%)	
TN	6 (10.0%)	0 (0%)	

ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2; TN, triple-negative.

pre-wavelet-LHH-gldm-Dependence Variance

pre-post-wavelet-HHH-glszm-Size Zone Non Uniformity Normalized

post-wavelet-LHL-gldm-Gray Level Non Uniformity

The features of the combination model and their correlation coefficients are presented in Table 5 and Figure 3. Among the 15 features of the combination model, 9/15 (60.0%) were wavelet-based features, 4/15 (26.7%) were LoG features, and 2/15 (13.3%) were shape features from the original images. Wavelet-based features generally have higher correlation coefficients than LoG features do. The four wavelet-based features with the highest correlation coefficients had higher correlation coefficients than the four LoG features with the highest correlation coefficients. Pre-NAC features accounted for 4/15 (26.7%) patients, post-NAC features accounted for 6/15 (40.0%), and pre-post-NAC features accounted for 5/15 (33.3%). Two of the four pre-NAC features had correlation coefficients greater than 2, accounting for 2/4 (50.0%); three of the six post-NAC features had correlation coefficients greater than 2, accounting for 3/6 (50.0%); and four of the five pre-post-NAC features had correlation coefficients greater than 2, accounting for 4/5 (80.0%). Pre-post-NAC features play a more important role in the combination model than pre-NAC and post-NAC features.

The linear combinations of combination features were as follows: RadScore = −2.757

+pre-wavelet-HLH-gldm-Dependence Variance × 4.812

+pre-wavelet-HLL-glrlm-Short Run Low Gray Level Emphasis × 4.436

-post-original-shape-Elongation × 4.101

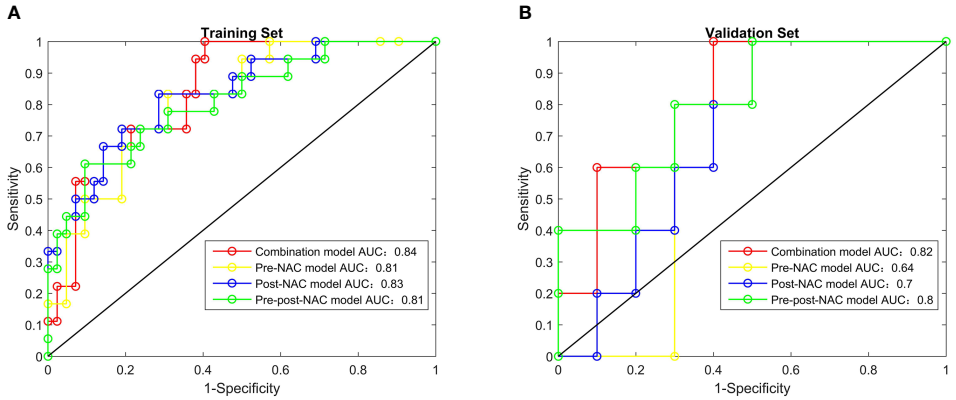

FIGURE 2
The receiver operating characteristic curves of radiomics features, combination model, pre-NAC model, post-NAC model and pre-post-NAC model in both the training set and the validation set, **(A)** is Training Set, **(B)** is Validation Set.

+pre-post-log-sigma-4-0-mm-3D-glcm-Informational Measure of Correlation × 2.874

+pre-post-log-sigma-4-0-mm-3D-glcm-Maximum Probability × 2.87

+pre-post-wavelet-HLL-glrlm-Run Entropy × 2.607

+post-original-shape-Maximum 3D Diameter × 2.331

+post-wavelet-HHL-glrlm-Short Run High Gray Level Emphasis × 2.321

-pre-post-log-sigma-6-0-mm-3D-gldm-Small Dependence Low Gray Level Emphasis × 2.113

-pre-wavelet-HLL-firstorder-Skewness × 0.636

+post-log-sigma-6-0-mm-3D-glcm-Maximal Correlation Coefficient × 0.593

+post-wavelet-HHH-gldm-Dependence Variance × 0.531

-pre-wavelet-LHH-gldm-Dependence Variance × 0.253

-pre-post-wavelet-HHH-glszm-Size Zone Non Uniformity Normalized × 0.242

+post-wavelet-LHL-gldm-Gray Level Non Uniformity × 0.122.

4 Discussion

The pattern of tumor shrinkage is critical for determining which patients should be treated with BCS. We developed a combination model based on pre- and post-NAC DCE-MRI to predict the pattern of tumor shrinkage in our cohort of patients. This model can help clinicians to select suitable candidates for BCS. The performance of the combination model was superior to those of the pre-NAC, post-NAC, and pre-post-NAC models. High-order features contribute significantly to the radiomics model.

Previous studies have demonstrated that first-order features, shape features, and texture features can be used to predict tumor response to NAC (30, 31). Our proposed method extracts general radiomics features containing first-order, shape, and texture features (2D and 3D). Meanwhile, this method computes high-order features from filtered images with different filters. Sutton et al. (32) added Gabor features to the general radiomics features to predict pCR. However, Braman et al. (33) showed that only 2 of the 10 features used in the prediction models of hormone receptor+, HER2−, and TN/HER2+ were Gabor features with a lower correlation. In comparison, Gabor features were not highly correlated with the top 10 features in the all-comers prediction model (all subtypes were included). This discrepancy can be attributed to the inadequate processing capability of the Gabor filter for mutant and non-smooth signals.

The wavelet transform can compensate for the deficiency of the Gabor transform, which is a localized analysis of spatial frequencies. This fact can be applied to effectively extract high- and low-frequency signals from images and to analyze image texture changes more carefully and comprehensively. Zhou et al. (34)

TABLE 4 Performance of different radiomics models in training and validation set.

	Training set				Validation set			
	AUC	ACC	SEN	SPE	AUC	ACC	SEN	SPE
combination model	0.84	0.75	0.72	0.76	0.82	0.73	0.80	0.70
pre-NAC model	0.81	0.72	0.83	0.67	0.64	0.60	0.80	0.50
post-NAC model	0.83	0.75	0.83	0.71	0.70	0.60	0.80	0.50
pre-post-NAC model	0.81	0.73	0.72	0.74	0.80	0.73	0.80	0.70

AUC, area under the curve; ACC, accuracy; SEN, sensitivity; SPE, specificity; NAC, neoadjuvant chemotherapy.

TABLE 5 Description of the selected radiomics features in combination model.

Radiomics feature	Radiomics group	Feature class filter	Image
Dependence Variance	gldm	wavelet-HLH	pre
Short Run Low Gray Level Emphasis	glrlm	wavelet-HLL	pre
Elongation	shape	original	post
Informational Measure of Correlation	glcm	log-sigma-4-0-mm-3D	pre-post
Maximum Probability	glcm	log-sigma-4-0-mm-3D	pre-post
Run Entropy	glrlm	wavelet-HLL	pre-post
Maximum 3D Diameter	shape	original	post
Short Run High Gray Level Emphasis	glrlm	wavelet-HHL	post
Small Dependence Low Gray Level Emphasis	gldm	log-sigma-6-0-mm-3D	pre-post
Skewness	first-order	wavelet-HLL	pre
Maximal Correlation Coefficient	glcm	log-sigma-6-0-mm-3D	post
Dependence Variance	gldm	wavelet-HHH	post
Dependence Variance	gldm	wavelet-LHH	pre
Size Zone Non Uniformity Normalized	glszm	wavelet-HHH	pre-post
Gray Level Non Uniformity	gldm	wavelet-LHL	post

Gldm, gray level dependence matrix; glrlm, gray level run length matrix; glcm, gray level co-occurrence matrix; glszm, gray level size zone matrix.

confirmed that wavelet-transformed textures can be used to predict pCR based on DCE-MRI. Thus, wavelet-based features were added to the models. Nine wavelet-based features were selected using the combination model.

Some scholars have suggested that LoG, which is designed to highlight the regions in an image where the intensity is changing rapidly, is compelling. Choudhery et al. (35) extracted 3D shape and texture features of TN breast cancer for analysis. They found that LoG features, including mean signal intensity, median signal intensity, maximum signal intensity, minimum signal intensity, and standard deviation of intensity, could be used to predict pCR. This study also included LoG features for analysis, namely the Informational Measure of Correlation, Maximum Probability, Small Dependence Low Gray Level Emphasis, and Maximal Correlation Coefficient. Our method uses both wavelet-based and LoG features to achieve better performance. These results suggest that high-order features have more potential for application in the prediction of BCS candidates.

In addition, among the features with correlation importance >2, the number of features from pre-post-NAC DCE-MRI surpassed pre- and post-NAC DCE-MRI. This showed that pre-post-NAC images can provide more effective information about the regression pattern of the tumor response to NAC. This is confirmed by the fact that the pre-post-NAC model is second only to the combination model in terms of predictive performance.

Most of the studies above were dedicated to predicting pCR and lacked further discussion of non-pCR tumors. The accurate identification of tumor remission patterns is critical for deciding the surgical approach. To accurately identify patients suitable for BCS, our study classified all tumor shrinkage patterns into types 1 and 2. Multifocal and major residual lesions with satellite foci are at risk of missing lesions during surgery, resulting in false-negative

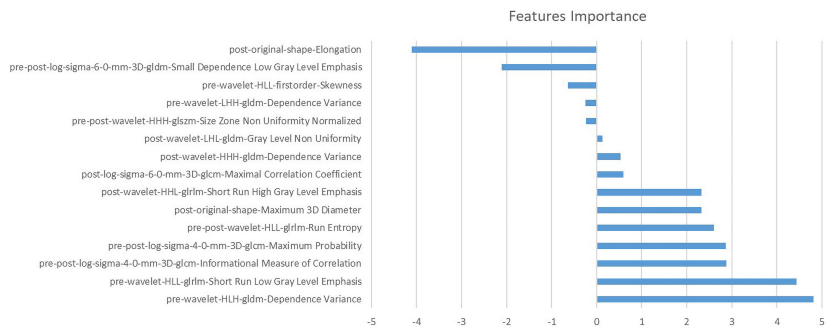

FIGURE 3
The importance of selected features by combination model.

margins. Thus, they were combined with SD and PD, which do not respond well to NAC, to form type 2. The remaining pCR and single-lesion shrinkage were classified as type 1. The combination model used four LoG features, nine wavelet-based features, and two original shape features to classify shrinkage patterns with an AUC of 0.82.

Several studies that used pre-NAC MRI and MRI before and after NAC had predictive effectiveness similar to ours. Cain et al. (36) predicted the pCR of TN/HER2 patients based on pre-NAC DCE-MRI, with an AUC of up to 0.71. Sutton et al. (32) combined pre- and post-NAC DCE-MRI to establish a recursive feature elimination random forest model with AUC of 0.80 and 0.78 for training set and test set. However, these studies only discriminated between pCR and non-pCR patients. In our study, a further distinction was made between non-pCR and types 1 and 2. This approach was also presented in studies by Zhuang et al. (23) and Huang et al. (37). However, there was no comparison between the pre- and post-treatment images in their study. To this end, in addition to the combination model, we built the pre-NAC, post-NAC, and pre-post-NAC models separately for comparison. Our study showed that the performance of pre-post-NAC images was better than that of pre-NAC and post-NAC images. This suggests that changes in tumors before and after NAC treatment have significant predictive power in revealing the patterns of tumor regression. The above mentioned in our research is a further extension of previous research.

Ki-67 is a tumor proliferation marker with the gene located on the long arm of chromosome 10 (10q25) (38). Previous studies have concluded that higher Ki-67 levels in breast cancer are correlated with a better response to NAC (39, 40). Our findings showed that the regression pattern of Ki-67 >20% was more inclined towards type 1. However, the use of Ki-67 as an independent predictor requires further investigation.

Our study had several limitations. First, we did not include tumor subtypes as clinical features in the prediction model. This was because the tumor subtypes were not statistically significant in this study. The reason for this the distribution imbalance caused by the different incidence of each tumor subtype. Second, our proposed method can only be a component of the decision-making of the surgical approach for patients who have received neoadjuvant therapy, but other factors such as age, clinical nodal status, and tumor grade must be taken into consideration. Third, this was a pilot study, conducted with a sample size of 75 patients, and for validation, it required a larger population. Finally, this retrospective study must be evaluated for reproducibility and efficacy in a prospective validation set before its clinical application.

5 Conclusion

We constructed a combination model based on pre- and post-NAC DCE-MRI, utilizing general radiomics features, wavelet-based features, and LoG features to precisely predict tumor shrinkage patterns before surgery in our cohort of patients. High-order features, particularly texture features based on the wavelet transform filter, are significant for the prediction model. Pre-post-NAC features offer a better predictive efficacy than pre- and post-NAC features. The model can help clinicians select suitable candidates for BCS to reduce the likelihood of residual tumors at surgical margins. Further expansion of the sample size and separate discussion by tumor subtype would help improve this model.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors with the consent of the author's organization. Requests to access the datasets should be directed to ZC, chenzhigeng7@163.com.

Ethics statement

The studies involving human participants were reviewed and approved by the Review Board of the Second Hospital of Dalian 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

ZC performed the experiments and finalized the manuscript. MH, JL, and XQ analyzed the data. FH assisted the study. ZC and XL conceived and designed the experiments. All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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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.

Publisher's note

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The potential role of combined shear wave elastography and superb microvascular imaging for early prediction the pathological response to neoadjuvant chemotherapy in breast cancer

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Objectives: The potential role of shear wave elastography (SWE) and superb microvascular imaging (SMI) for early assessment of treatment response to neoadjuvant chemotherapy (NAC) in breast cancer remains unexplored. This study aimed to identify potential factors associated with the pathological response to NAC using these advanced ultrasound techniques.

Methods: Between August 2021 and October 2022, 68 patients with breast cancer undergoing NAC were recruited. Patients underwent conventional ultrasonography, SMI, and SWE examinations at baseline and post-2nd cycle of NAC. Maximum tumor diameter (Dmax), maximum elastic value (Emax), peak systolic velocity (PSV), and resistance index (RI) at baseline and the rate of change of these parameters post-2nd cycle were recorded. After chemotherapy, all patients underwent surgery. Using the Miller-Payne's grade, patients were categorized into response (grades 3, 4, or 5) and non-response (grades 1 or 2) group. Parameters were compared using t-tests at baseline and post-2nd cycle. Binary logistic regression analysis was used to identify variables and their odds ratios (ORs) related to responses and a prediction model was established. ROC curves were drawn to analyze the efficacy of each parameter and their combined model for early NAC response prediction.

Results: Among the 68 patients, 15(22.06%) were categorized into the non-response group, whereas 53(77.94%) were categorized into the response group. At baseline, no significant differences were observed between the two groups (p>0.05). Post-2nd cycle of NAC, rates of change of Emax, PSV and RI (ΔEmax, ΔPSV and ΔRI) were higher in responders than non-responders (p<0.05). Binary logistic regression analysis revealed that ΔEmax (OR 0.797 95% CI, 0.683–0.929), ΔPSV (OR 0.926, 95%CI, 0.860–0.998), and ΔRI (OR 0.841, 95%CI, 0.736–0.960)

were independently associated with the pathological response of breast cancer after NAC. The combined prediction model exhibited higher accuracy in the early evaluation of the response to NAC (AUC 0.945, 95%CI, 0.873–1.000).

Conclusion: SWE and SMI techniques enable early identification of tumor characteristics associated with the pathological response to NAC and may be potentially indicative of an effective response. These factors may eventually be used for the early assessment of NAC treatment for clinical management.

KEYWORDS

breast cancer, neoadjuvant chemotherapy (NAC), superb microvascular imaging (SMI), shear wave elastography (SWE), pathological response

1 Introduction

Breast cancer is one of the leading causes of cancer-related morbidity and mortality in women worldwide (1). Neoadjuvant chemotherapy(NAC) was introduced by Frei in 1982 as a systemic cytotoxic drug treatment for localized tumors prior to radical surgery or radiotherapy (2). According to the current guidelines of the National Comprehensive Cancer Network (NCCN), NAC treatment can not only address locally advanced breast cancer but has also been extended to early operable breast cancer patients (3). However, nearly 20% of patients with NAC may gradually develop drug resistance (4). In instances where the initial phase of NAC treatment is unresponsive or unsatisfactory, the subsequent treatment should be modified accordingly (5). Therefore, early evaluation of the effect of NAC in patients with breast cancer is beneficial for clinical treatment and prognostic evaluation. Pathological assessment is the gold standard for evaluating the efficacy of NAC in patients with breast cancer (6). However, this method is invasive and can lead to a delayed diagnosis. Therefore, imaging techniques play an important role in monitoring the efficacy of NAC in breast cancer.

Currently, several imaging techniques can predict the tumor response to NAC by detecting changes in blood flow and metabolism-related functional indices in the tumor. These techniques include dynamic contrast-enhanced magnetic resonance imaging(MRI), diffusion-weighted imaging, and 18F-FDG PET/CT, which can be used to accurately predict the pathological response of breast cancer to NAC after two cycles of chemotherapy (7, 8). However, MRI and PET examinations are relatively expensive and burdensome for patients undergoing chemotherapy, therefore, their general acceptance among patients is low (9). In contrast, ultrasound is well received by both clinicians and patients because it is safe, noninvasive, and inexpensive. The future development direction lies in integrating multiple ultrasound techniques to assess and predict patient's responsiveness to NAC therapy in a multidimensional manner, thereby optimizing treatment regimens and avoiding unnecessary toxicity (10).

Angiogenesis promotes tumor growth, and alterations in tumor neovascularization are associated with an impaired chemotherapy response (11). Superb microvascular imaging (SMI) is a new type of ultrasound imaging technology, which can display lower blood flow velocities and smaller blood vessels without using contrast agents (12). Tissue stiffness is another important feature that determines the efficacy of NAC. Shear wave elastography (SWE) tissue elasticity to evaluate the stiffness of the breast lesion, it has the advantages of repeatability and objectivity (13). Existing animal model experimental results have shown that tumor hardness is associated with tumor progression and chemotherapy resistance (14).

Tumor development and infiltration is determined by the tumor microenvironment (15).The SMI technique can indirectly reflect changes in tumor neovascularization, and the SWE technique can indirectly provide insights into the mesenchymal composition of collagen (16).Therefore, the combination of the two advanced techniques is expected to provide a comprehensive prediction of alterations in the tumor microenvironment in patients with breast cancer during NAC treatment, and it holds the potential in sensitively identify patients who are unresponsive to the treatment at an early stage.

SMI combined with SWE can improve the ability to determine the benign/malignant nature of breast cancer (17). However, to the best of our knowledge, few reports have been documented on the use of conventional ultrasound, SWE, and SMI to determine the efficacy of NAC in breast cancer. Therefore, this study explored the potential value of combined SMI and SWE for the early evaluation of the pathological response to NAC, thereby providing a supplementary imaging basis for early clinical assessment.

2 Materials and methods

2.1 Patients

This retrospective study was conducted from August 2021 to October 2022, during which 68 patients were enrolled. The inclusion criteria were as follows: (i) core needle biopsy confirming the diagnosis of breast cancer; and (ii) clinical decision to treat using NAC. The exclusion criteria were as

follows: (i) patients whose lesions were not measurable on imaging; (ii) those who could not tolerate chemotherapy and did not complete the entire cycle of chemotherapy; (iii) those who did not complete the surgery at our hospital; and (iv) those who had incomplete data. This study was approved by the Ethics Committee of the General Hospital of Ningxia Medical University (Ethics No.: KYLL-2022-1090) and written informed consent was obtained from all patients.

2.2 US examination

We used an Aplio800 color Doppler ultrasound machine (Canon Medical Systems Corporation, Japan) and an L14-5 high-frequency linear array probe (frequency 5-14 MHz) for examination. All patients underwent conventional ultrasonography, SWE, and SMI before (baseline) and post-2nd cycle of NAC. All ultrasound examinations were performed by a senior ultrasound sonographer with more than 10 years of experience. The Maximum tumor diameter (Dmax) of the tumor was determined from the three grayscale ultrasonography images, and the location of the lesion was marked.

The SMI mode was selected, and the probe was lightly placed on the skin surface, and color gain was adjusted to obtain the maximum blood flow signal. The arterial blood flow pulse was obtained to measure peak systolic velocity (PSV) and resistance index (RI), and the average value was obtained from three measurements. The angle between the ultrasonic sampling line and blood flow direction was maintained below 60°.

SWE was performed in a rectangular field of view, covering the entire lesion and adjacent normal tissues. When the lesion exceeded the detection range, a part of the lesion was selected for measurement. The selected part should exhibit high-quality stiffness that matches the stiffness on the mass map. The quantitative elasticity values in each regions of interest (ROI) (automatically calculated and visualized by the SWE system) were expressed as Young's modulus (kPa). Three non-overlapping ROI (2 × 2 mm) were placed at the location of lesions with high stiffness, including the stroma around the tumor. The measurements were repeated thrice for each lesion and then averaged (Figure 1).

2.3 Chemotherapy regimens

Patients (n=68) who participated in this study received 6–8 cycles of preoperative chemotherapy, at an interval of 21 days, and surgery was performed within 2 weeks after the completion of NAC. Chemotherapy regimens strictly followed the NCCN guidelines (3). The detailed treatment protocol was as follows: paclitaxel, epirubicin, and cyclophosphamide in 25 cases; paclitaxel and epirubicin in 15 cases; paclitaxel and carboplatin in 10 cases; and dual-target therapy with docetaxel combined with carboplatin, trastuzumab, and patulizumab in 18 cases.

2.4 Pathologic assessments

All pathological sections were scored independently by two pathology teachers under a microscope. All data were obtained after mutual agreement between both parties, each possessing a minimum of 5 years of experience in breast pathological diagnosis. We compared the histopathological findings of tumor lesions isolated during surgery with those of specimens obtained from pre-treatment core needle biopsies to determine the grade of pathological response to NAC in patients with breast cancer. According to the MP classification system (18), we categorized the pathological response to NAC into the following five grades: Grade 1: no significant change in the overall tumor cell density compared to before treatment; Grade 2: continued high overall tumor cell density with a decrease of <30%; Grade 3: tumor cell density decreased by 30%–90%; Grade 4: tumor cell density decreased by >90%; Grade 5: complete disappearance of the tumor, no residual invasive carcinoma detectable under a microscope, though this can include ductal carcinoma in situ. In this study, we designated grades 3–5 as the response group and grades 1–2 as the no-response group based on the difference in pathological response.

2.5 Data analysis

At baseline, Dmax, maximum elastic value (Emax), PSV, and RI were expressed as Dmax0, Emax0, PSV0, and RI0, respectively.

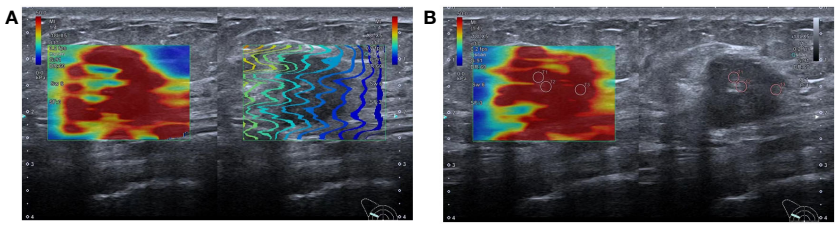

FIGURE 1
Shear wave elastography schematic diagram: **(A)** SWE imaging quality map, the lines in a rectangular field of view are arranged neatly, indicating that the image quality is good; **(B)** SWE imaging and two-dimensional ultrasound were displayed in split-screen mode. Three ROIs of 2mm were placed at the high-stiffness lesion and the value of mean Emax was 110.0kpa.

Post-2nd cycle of NAC, these parameters were expressed as Dmax2, Emax2, PSV2, and RI2, respectively. The differences in the values post-2nd cycle of NAC versus baseline (Δ) were calculated as follows: ΔDmax=100% × (Dmax2-Dmax0)/Dmax0, ΔEmax=100% × (Emax2-Emax0)/Emax0, ΔPSV=100% × (PSV2-PSV0)/PSV0, and ΔRI=100% × (RI2-RI0)/RI0.

2.6 Statistical analysis

Statistical analysis was performed using SPSS 26.0 and MedCalc 20.2. Categorical data were expressed as numbers and percentages (%). Measurement data were expressed as mean ± standard deviation. Differences between the response and the non-response groups were assessed using the Student's t-test, chi-square test, or Fisher's exact test. For parameters showing statistical significance in the univariate analysis (p<0.05), we used binary logistic regression to calculate the odds ratio (OR) and derived a predictive model. Calibration of the model was assessed using the Hosmer–Lemeshow test. The rate of change of each parameter and the value of the model in assessing the pathological response after NAC were also analyzed using receiver characteristic curves (ROC). Areas under the ROC curves (AUC) were compared using the DeLong method to estimate the diagnostic performance of parameters and identify the optimal cut-off value of parameter values for predicting NAC. The optimal cut-off value was calculated by maximizing the Youden index. The performance of the optimal cut-off value for the total points was assessed by sensitivity, specificity, and diagnostic accuracy. AUC >0.9 indicated a good diagnostic value; 0.9 > AUC > 0.7 indicated a moderate diagnostic value; AUC <0.7 indicated a poor diagnostic value (19). A p value of <0.05 was considered statistically significant.

3 Results

3.1 Patient features

The basic clinical and pathological features of the 68 patients included in this study are summarized in Table 1. The results of pathological assessment of the postoperative specimens indicated that 53 patients (77.94%, 53/68) were responders to NAC, whereas 15 of them (22.06%, 15/68) were non-responders. We observed 23, 12, 18, 8, and 7 cases of grades V, IV, III, II, and I, respectively. No significant differences were observed in terms of age, menopause, pathological type, histological grade, ER status, PR status, HER2 status, Ki67 index, and lymphatic metastasis at baseline (p>0.05).

3.2 Comparison of quantitative parameters between responders and non-responders at baseline and post-2nd cycle of NAC

At baseline, no significant differences in Dmax, Emax, PSV, or RI were observed between the two groups (p>0.05, Table 2). Post-2nd cycle of NAC, although no significant difference in the rate of change of Dmax was observed between the two groups (p>0.05), the

TABLE 1 Clinical and pathological characteristics of the patients.

Characteristic	Response group(n=53)	Non-response group(n=15)	p
Age, y	45.83 ± 11.35	48.20 ± 10.30	0.469
Menopause history			0.857
Pre–menopause	34(64.7%)	10(66.7%)	
Post–menopause	19(35.8%)	5(33.3%)	
Pathological type			0.755
Non-specific invasive carcinoma	38(71.7%)	12(80%)	
With others	15(28.3%)	3(20%)	
Histologic grades			0.856
≤2	49(92.4%)	13(86.7%)	
>2	4(7.6%)	2(13.3)	
Estrogen receptor			1.00
Positive (≥1% IHC)	39(73.6%)	11(73.3%)	
Negative (<1% IHC)	14(26.4%)	4(26.7%)	
Progesterone receptor			0.964
Positive (≥1% IHC)	35(66.0%)	10(66.7%)	
Negative (<1% IHC)	18(34.0%)	5(33.3%)	
HER2			0.916
Positive (+3 IHC and/or amplified FISH)	22(41.5%)	6(40.0%)	
Negative (0, + 1 IHC or not amplified FISH)	31(58.5%)	9(60.0%)	
Ki67 index, n (%)	41.23 ± 37.00	37.00 ± 22.02	0.518
Lymphatic metastasis			1.000
Positive	43(81.1%)	12(80.0%)	
Negative	10(18.9%)	3(20.0%)	

Data are presented as mean ± SD and number (percent) where applicable. FISH indicates fluorescence in situ hybridization; and IHC, immunohistochemistry.

TABLE 2 Comparison of quantitative parameters between response and non-response groups before NAC.

parameters	Response group(n=53)	Non-response group(n=15)	t	*p*
Dmax (cm)	3.10 ± 1.11	3.63 ± 1.19	1.580	0.119
Emax (KPa)	107.69 ± 16.09	106.99 ± 16.88	-0.146	0.884
PSV(cm/s)	21.80 ± 12.28	25.63 ± 14.89	1.107	0.313
RI	0.766 ± 0.045	0.773 ± 0.054	0.498	0.620

Data are presented as mean ± SD where applicable.

relative rates of change of Emax, PSV, and RI in the response group were significantly higher than those in of the non-response group (p<0.05, Figures 2, 3, Table 3).

3.3 Factors independently associated with the pathological response of NAC

Among the variables with univariate p<0.05, ΔEmax, ΔPSV, and ΔRI were included in the binary logistic regression model. ΔEmax (OR 0.797, 95% CI, 0.683–0.929, p=0.004), ΔPSV (OR 0.926, 95% CI, 0.860–0.998, p=0.045), and ΔRI (OR 0.841, 95% CI, 0.736–0.960, p=0.010) were independently associated with the pathological response of to NAC for in breast cancer (Table 3).

3.4 The value of independent correlation parameters and combined multiparameter early prediction of pathological response after NAC in patients with breast cancer

The ROC curves for ΔEmax, ΔPSV, and ΔRI to distinguish responders, yielded AUCs of 0.878 (CI = 0.769–0.987), 0.716 (CI=0.581–0.850) and 0.801 (CI = 0.654–0.948) with optimal cut-off value were -18.56%, -38.99% and -15.16%, respectively. The Delong test indicated that the combined model encompassing these three parameters for evaluating the efficacy of NAC in patients with breast cancer significantly outperformed the individual factors (p<0.05). The AUC value of the combination model was 0.945 (CI = 0.873–1.000), the sensitivity was 94.3%, and the specificity was 86.7%. (Table 4, Figures 4, 5).

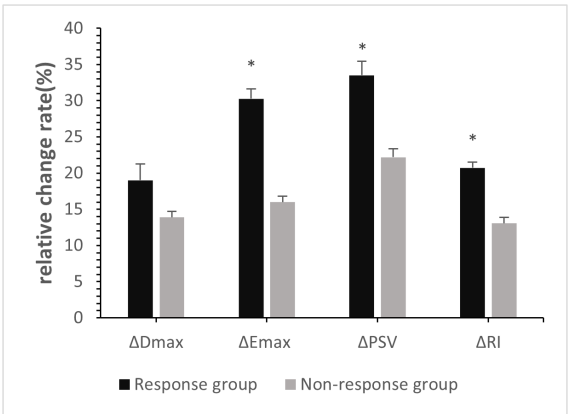

FIGURE 2
Relative Change rates of quantitative parameters in breast cancer patients post-2nd cycle of NAC. ∗p <0:05, compared with non-response group.

We also developed a new prediction model for the pathological response to NAC in patients with breast cancer by combining the SWE and SMI parameter models. The model was obtained by combining ΔEmax, ΔPSV, and ΔRI through binary logistic regression, and the specific equation was as follows: model= –(ΔEmax × 0.228 + ΔPSV × 0.076 + ΔRI × 0.173 + 8.757). The results of the Hosmer–Lemeshow test revealed that the model has p>0.10 (0.587), indicating a good fit between the predicted results of the developed model and the actual results.

4 Discussion

In clinical practice, ultrasonography plays an important role in evaluating the outcomes of NAC treatment in patients with breast cancer; however, conventional ultrasound alone does not provide sufficient evidence for early assessment. Therefore, acquisition of additional imaging features for evaluating tumor response is becoming an important factor (10), as only a comprehensive assessment of tumor features can precisely evaluate the efficacy of NAC. Moreover, no study has combined SWE and SMI to evaluate the pathological responses to NAC in breast cancer.

In the present study, we used conventional ultrasound, SWE, and SMI techniques to measure the changes in tumor morphology and functionality-related indices after early NAC treatment (2nd cycle), observed that ΔEmax, ΔPSV, and ΔRI were independently correlated with the pathological response of tumors to NAC, and the combined use of these three parameters could more effectively predict the pathological response after NAC than the use of the three parameters alone. This suggested that SWE and SMI hold a great clinical value for the early assessment and prediction of pathological response to NAC in breast cancer. The combined application of these two noninvasive and repeatable ultrasound techniques allows for a comprehensive and timely evaluation of the NAC treatment outcomes.

Currently, Chinese experts strongly recommend that patients with breast cancer receiving NAC should undergo conventional ultrasound at 2-cycle intervals, primarily to monitor changes in the size of breast masses (20). In our study, no significant differences in the maximum diameter of the tumor at baseline and rate of change post-2nd cycle were observed between the two groups. Similarly, Gu's concluded that a change in tumor diameter after the 1st and 2nd

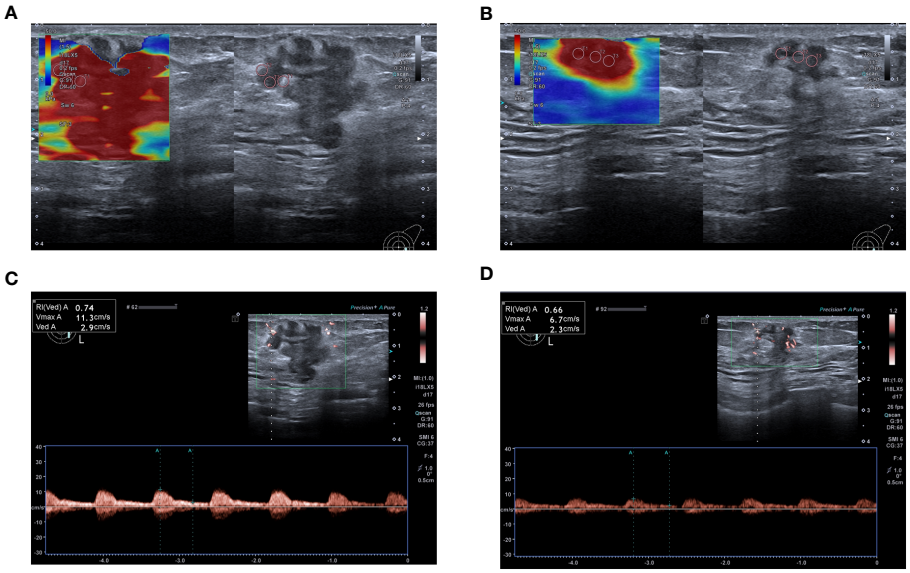

FIGURE 3
A 59-year-old woman achieved complete response after NAC (Grade 5), and model predictions are greater than the optimal cut-off value. **(A)** Emax measured by SWE before NAC was 108.8 kPa. **(B)** Post- 2nd cycle of NAC, the Emax was 76.9 kPa and the relative change rate of the Emax was 29.32%. **(C)** PSV and RI measured by SMI before chemotherapy were 11.3 cm/s and 0.74 respectively. **(D)** Post-2nd cycle of NAC, the PSV and RI were 4.6cm/s and 0.55 respectively, and the relative change rates of PSV and RI were 59.29% and 25.68% respectively.

TABLE 3 Comparison of quantitative parameters between response group and non-response groups post-2nd cycle of NAC.

Change rate of parameters (%)	Response group(n=53)	Non-response group (n=15)	t	Univariate analysis *p*	logistic regression analysis		
					OR	95%CI	*p*
ΔDmax	-19.02 ± 18.45	-13.90 ± 6.84	1.657	0.103			
ΔEmax	-30.27 ± 10.92	-15.98 ± 6.72	-6.232	0.000*	0.797	0.683-0.929	0.004*
ΔPSV	-33.51 ± 16.10	-22.20 ± 9.69	-3.385	0.002*	0.926	0.860-0.998	0.045*
ΔRI	-20.73 ± 6.34	-13.05 ± 6.64	-4.103	0.001*	0.841	0.736-0.960	0.010*

Data are presented as mean ± SD where applicable. OR, odds ratio; CI, confidence. *p <0:05.

cycles of NAC was not valuable in distinguishing the efficacy of chemotherapy (5). This may be because tumor regression is a slow and gradual process induced by chemotherapy drugs (21). In addition, regression of tumor cells after NAC mainly manifests as necrosis and fibrosis of the lesion (22), and conventional ultrasound cannot accurately differentiate between necrosis, fibroplasia, and residual cancer (23). Therefore, it is impossible to accurately assess tumor regression using conventional ultrasonography.

SWE offers repeatable and quantitative measurement of tumor tissue hardness, not only for early identification of benign and malignant breast lesions but also for monitoring treatment response of the disease (24). Tumor stiffness is closely related to the

TABLE 4 SWE and SMI parameters and their combination ROC curve analysis results.

Characters	Cut-off	Sensitivity (%)	Specificity (%)	Accuracy (%)	AUC	95%CI
ΔEmax(%)	-18.56	88.7	86.7	88.2	0.878	0.769-0.987
ΔPSV(%)	-38.99	37.7	100.0	51.5	0.716	0.581-0.850
ΔRI(%)	-15.16	79.2	80.0	79.4	0.801	0.654-0.948
Combination	0.63	94.3	86.7	92.6	0.945	0.873-1.000

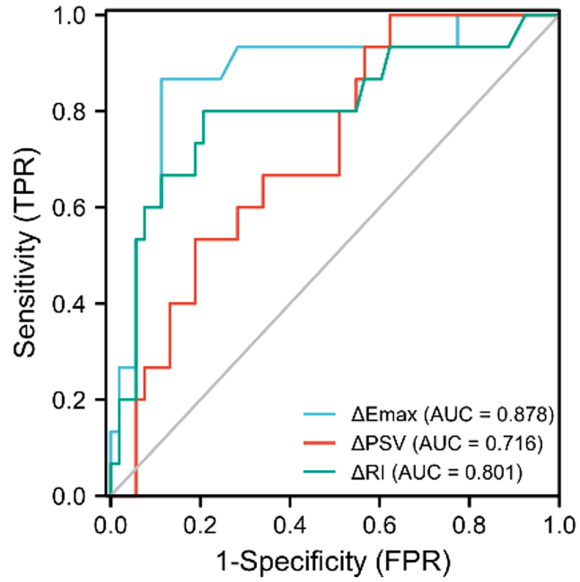

FIGURE 4
ROC curves of ΔPSV(%), ΔRI(%), and ΔEmax(%) in predicting the efficacy of neoadjuvant chemotherapy for patients with breast cancer.

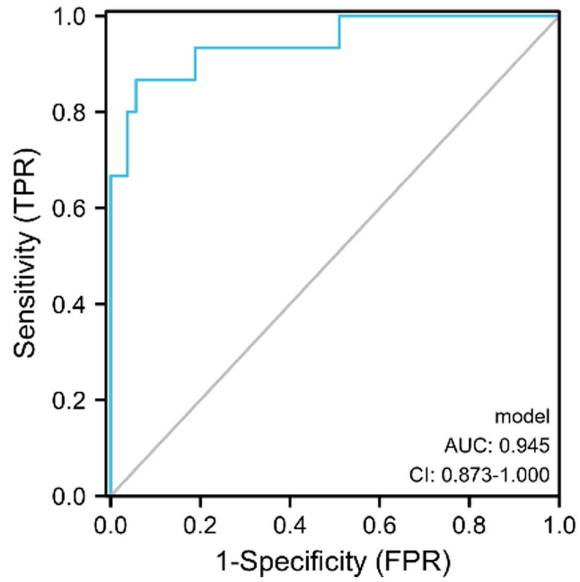

FIGURE 5
The ROC curve of SMI combined with SWE in predicting the efficacy of NAC for patients with breast cancer.

chemotherapy response in breast cancer. Several studies have confirmed that changes in tumor stiffness serve as early response markers during treatment (24–27). In this study, post-2nd cycle of NAC, the relative rate of change of Emax of tumors in the response group was significantly higher than that in the non-response group (−30.27% vs. −15.98%). Jing et al. reported that the Δ stiffness of responders (−42.19%) was significantly higher than that of non-responders (−23.59%) (27), which is comparable to our results. Both studies acknowledged that responsiveness of patients with breast cancer to NAC is an adaptive process, so the corresponding rate of change in tumor stiffness is more meaningful for predicting efficacy than tumor characteristics acquired at a certain time point. Quantitative SWE parameters were measured in a 3 mm diameter area around the region of interest; however, the region of interest they selected had only one circle, which has the possibility of bias. In our study, we manually placed three circles with a diameter of 2 mm to avoid selection bias.

Contrast-enhanced ultrasonography (CEUS) is superior to conventional imaging methods for measuring angiogenic changes as an indicator of response. Several studies have shown that CEUS can predict the efficacy of NAC for breast cancer after two cycles (28–30); however, the contrast agent used is expensive and has certain restrictions for trauma inspection. SMI is a new and rapidly developing imaging method for evaluating tissue micro-vessels. It has similar ability as CEUS in displaying microvessels and low-speed blood flow within breast lesions (31). Therefore, SMI is expected to serve as a simple, noninvasive, and cost-effective alternative to contrast-based inspection. Li et al. demonstrated the consistency of SMI with histopathology in evaluating the efficacy of NAC in 89 patients with locally advanced breast cancer (107 lesions) (32). Yuan et al. confirmed that the decrease in the post-treatment quantitative parameters, PSV and RI, is related to the pathological response to NAC (33). However, these studies were semi-quantitative, primarily using the Adler flow classification (34), which is susceptible to the operator subjectivity. Therefore, the present study used the rates of change of PSV and RI after two cycles as a quantitative evaluation index. We observed no significant differences in PSV and RI before NAC; however, tumors with higher ΔPSV and ΔRI post-2nd cycle of NAC were more effectively detected. This suggested the potential of ΔPSV and ΔRI in the early assessment and prediction of chemotherapeutic efficacy. Patients with greater rates of change in PSV and RI post-2nd cycle of NAC treatment exhibited a better pathological response to NAC, indicating the efficacy of chemotherapeutic agents to some extent. This could be attributed to the direct action of chemotherapeutic agents in the early stages of NAC, wherein cancer tissue cells and blood vessels that sensitive to chemotherapeutic agents are damaged, resulting in reduced blood flow, a slower blood flow rate, and reduced resistance values (35). This study provides further evidence for early prediction of NAC's efficacy in patients with breast cancer. Both ΔPSV and ΔRI, especially ΔRI, exhibited high AUC values and could serve as new effective indicators for the early prediction of pathological responses to NACr patients with breast cancer.

The clinical evaluation potential of the advanced ultrasound techniques used in this study suggested that the relative rates of change of Emax, PSV, and RI were effective imaging indicators for early differentiation of pathological responses after NAC, of which ΔEmax was the best, and the combination of the three can could significantly improve the efficacy of NAC (AUC = 0.947). Therefore, combination of SWE and SMI in imaging is advantageous for the early prediction of the pathological response to NAC in BC with breast cancer. Furthermore, our proposed combined prediction model will offer valuable insights for clinical treatment strategies. The amalgamation of the two advanced techniques can comprehensively reflect the changes in the tumor microenvironment of patients with breast cancer during NAC, enabling a sensitive detection of early-

stage unresponsiveness. In addition, the ultrasound characterization parameters used in our assessment method are easily measurable and do not require additional intervention. Therefore, SWE combined with SMI is advantageous as a convenient, real-time, cost-effective, and non-invasive imaging approach for the early assessment of NAC efficacy in patients with breast cancer.

This study had some limitations. First, the sample size was relatively small; therefore, tumor heterogeneity and chemotherapeutic regimen were not taken into account. Second, SMI was limited to a specific ultrasound system Canon Aplio. Further studies are required to validate these preliminary findings.

In conclusion, the combination of SWE and SMI may be useful for the early identification of breast cancer response to NAC treatment, with good reproducibility and high sensitivity. In addition, the newly developed predictive model has clinical value for the early prediction of pathological responses after NAC.

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 authors.

Ethics statement

This study was approved by the Ethics Committee of the General Hospital of Ningxia Medical University (Ethics No.: KYLL-2022-1090) and written informed consent was obtained from all patients. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin. Written informed consent was obtained from the individual(s), and minor(s)' legal guardian/next of kin, for the publication of any potentially identifiable images or data included in this article.

Author contributions

JQ, CM, and CW were responsible for the collection and screening of cases. JQ, YM, JW, GY, and YW performed the statistical analysis and analyzed the data. JQ, YM, and WH wrote and revised the manuscript. WH provided financial support. The final version of the manuscript has been read and approved by all authors, and each author believes that the manuscript represents honest work. All authors contributed to the article.

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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.

Publisher's note

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Locally advanced breast cancer: breast-conserving surgery and other factors linked to overall survival after neoadjuvant treatment

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Background: Recent data suggest that breast-conserving surgery (BCS) may positively impact overall survival (OS) in early breast cancer. However, the role of BCS in locally advanced breast cancer (LABC) following neoadjuvant therapy (NAT) remains uncertain.

Methods: We conducted a retrospective cohort study involving 530 LABC patients who underwent surgery after NAT between 2010 and 2015. Outcomes examined included OS, distant recurrence rates (DRR), and loco-regional recurrence rates (LRRs).

Results: Among the 927 breast cancer patients who received NAT, 530 were eligible for our study. Of these, 24.6% underwent BCS, while 75.4% underwent mastectomy (MS). The median follow-up duration was 79 months. BCS patients exhibited a higher pathological complete response (PCR) rate compared to those who underwent MS (22.3% vs. 10%, $p < 0.001$). The 6-year OS rates for BCS and MS were 81.5% and 62%, respectively ($p < 0.000$). In multivariate OS analysis, MS was associated with worse outcomes (OR 1.678; 95% CI 1.069–2.635; $p = 0.024$), as was body mass index (BMI) (OR 1.031; 95% CI 1.006–1.058; $p = 0.017$), and stage IIIB or IIIC (OR 2.450; 95% CI 1.561–3.846; $p < 0.000$). Conversely, PCR (OR 0.42; 95% CI 0.220–0.801; $p = 0.008$) was associated with improved survival. DRR was significantly lower in BCS (15.4%) compared to MS (36.8%) (OR 0.298; 95% CI 0.177–0.504). LRRs were comparable between BCS (9.2%) and MS (9.5%) (OR 0.693; 95% CI 0.347–1.383).

Conclusion: Our findings suggest that BCS is oncologically safe, even for patients with large lesions, and is associated with superior OS rates compared to MS. Additionally, lower BMI, lower pretreatment stage, and achieving PCR were associated with improved survival outcomes.

KEYWORDS

breast neoplasms, neoadjuvant therapy, local disease, segmental mastectomy, breast-conserving surgery, survival rate, locally advanced breast cancer

1 Introduction

Locally advanced breast cancer (LABC), categorized as stage IIB or III (1), poses a significant health challenge, accounting for 14.23 deaths per 100,000 Brazilian women in 2019 (2). Approximately 25% of these cases are diagnosed at stage III breast cancer. Contemporary treatment strategies for LABC involve a multimodal approach that combines systemic and local treatments (3). However, one critical aspect of this treatment regimen that remains uncertain is the choice of surgical intervention following neoadjuvant therapy (NAT), especially in cases that initially had a mastectomy (MS) indication. Despite the apparent necessity of complete initial tumor bed removal, there is a growing inclination toward adopting more conservative surgical approaches, introducing a notable gap in the literature regarding the oncological safety of such a shift.

Over the past decade, the scientific community has witnessed a discourse surrounding the comparison of breast-conserving surgery (BCS) versus MS. A meta-analysis, conducted in 2022 and encompassing over 1,500,000 patients, albeit excluding those who underwent NAT, suggested that BCS yielded superior overall survival (OS) outcomes compared to MS (4). Conversely, another meta-analysis, focusing on studies with both neoadjuvant and adjuvant treatments, as conducted by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) (5), revealed that while BCS was associated with higher loco-regional recurrence rates (LRRs), it did not significantly impact OS. In a separate study, Simons et al. reported that BCS contributed to increased OS compared to MS in an unadjusted model (6). Gwark et al. corroborated this observation demonstrating the same outcome in both unadjusted and adjusted analyses (7). Nonetheless, most of these trials included early-stage tumors, with a dearth of data pertaining to LABC.

Considering the uncertainties and the contrasting findings in the existing literature, we have undertaken this study to ascertain whether BCS has a discernible impact on OS and LRR in patients with LABC who have undergone NAT. This investigation aims to contribute valuable insights into the optimal surgical management of LABC, particularly in cases where BCS may present a viable alternative to more radical procedures like MS.

2 Materials and methods

2.1 Patients

This study conducted a retrospective cohort analysis in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines (8). It encompassed all consecutive patients diagnosed with LABC who underwent NAT at Instituto do Câncer de São Paulo (ICESP) between January 2010 and December 2015. Inclusion criteria encompassed women with LABC considered suitable candidates for MS for breast cancer treatment before NAT. The sequence of treatment commenced with NAT, involving chemotherapy or endocrine therapy, followed by surgical intervention. Patients were excluded if they exhibited contraindications to radiotherapy (RT), presented with distant metastasis at the time of diagnosis, or had a history of multiple malignancies.

Patient data extracted from medical records included age at diagnosis, body mass index (BMI), type of surgery, type of NAT, tumor size, pathological stage, clinical stage, RT, histological subtype, histological grade, nuclear grade, and molecular subtype tumor, determined based on the expression of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor-2 (HER2). Immunohistochemical methods were employed to evaluate ER, PR, and HER2 status. ER and PR positivity was established when more than 1% of cells displayed positive staining. HER2 overexpression analysis categorized cases graded 0 or 1+ as negative and 3+ as positive. For cases graded 2+, fluorescence *in situ* hybridization was conducted. Tumor staging followed the TNM classification, 7th edition (9), with LABC defined as encompassing stages IIB and III. NAT and RT adhered to the National Comprehensive Cancer Network (NCCN) guidelines (10).

Pathological complete response (PCR) was defined as ypT0 ypN0. Patients underwent regular follow-up every 3–6 months for the initial 5 years and annually thereafter. Disease relapse and metastasis were detected based on clinical examinations conducted during follow-up visits, along with yearly mammography. Additional assessments, including chest computed tomography, bone scans, and liver ultrasonography, were performed in response to abnormal clinical findings. Loss of follow-up was

defined as an interval exceeding 2 years until the last medical appointment. This study obtained approval from the institutional ethics committee (NP 856/2015).

2.2 Outcomes

The primary outcome was OS, defined as the time from surgery to death attributed to any cause. Secondary outcomes included the assessment of distant recurrence rates (DRRs) and LRRs in relation to the two surgical groups, namely, BCS and MS. LRR was specifically defined as the initial recurrence manifestation in the breast, ipsilateral axilla, and ipsilateral supraclavicular region, while DRR pertained to the first occurrence of distant metastasis.

2.3 Statistical analysis

Measures of central tendency, such as mean and median, along with measures of dispersion, were employed to evaluate continuous variables. The data's distribution characteristics were assessed using the Kolmogorov–Smirnov and Shapiro–Wilk tests. To compare the distribution of quantitative variables across two or more groups, we employed the chi-square and Mann–Whitney tests. Continuous variables were assessed using the unpaired Student's ***t***-test. The odds ratios were estimated utilizing Poisson regression.

Time-to-event outcomes were analyzed through the Kaplan–Meier survival function, and differences between groups were assessed with the Log-Rank test. To assess the independent prognostic effect of the surgical method on OS and disease-free survival (DFS), while accounting for various prognostic factors, we employed the Cox proportional-hazards model.

Statistical analyses were conducted using the SPSS software version 20.0. A significance level of $p = 0.05$ was utilized for all statistical tests, indicating a 5% threshold for statistical significance.

3 Results

3.1 Patient characteristics

Initially, a total of 927 women with breast cancer who underwent NAT were evaluated. A total of 530 eligible patients with LABC who underwent NAT and subsequent surgery, adhering to the eligibility criteria, were included in this study. Among these patients, 506 (95.4%) received neoadjuvant chemotherapy, and 24 (4.5%) received neoadjuvant endocrine therapy. The average age of the patient population was 52.7 ± 1.2 years, with an age range spanning from 23 to 95 years.

Out of the 530 patients, 138 (26.1%) had stage IIB, while 391 (73.9%) had stage III breast cancer. The histological subtypes were distributed as follows: 201 (37.9%) luminal HER2 negative, 189 (35.6%) triple-negative, 71 (13.5%) luminal HER2 positive, and 69 (13.1%) HER2 positive. PCR was observed in 13.0% (69 patients) of cases. Regarding the choice of surgery, 130 patients (24.6%) underwent BCS, while 400 patients (75.4%) underwent MS.

Comparing the BCS and MS groups, statistically significant differences were noted. The BCS group consisted of older patients ($p < 0.001$), individuals with earlier-stage disease ($p < 0.001$), and higher BMI ($p < 0.001$). Additionally, the BCS group had a higher proportion of post-menopausal patients, multiparous individuals, and those who underwent sentinel lymph node (SLN) biopsy ($p < 0.001$). Notably, the PCR rate was significantly higher in the BCS group, with 22.3% (29 patients), compared to 10% (40 patients) in the MS group ($p < 0.001$). Details are provided in Table 1.

TABLE 1 Clinical and pathological characteristics in univariate analysis of patients undergoing conservative surgery when compared to mastectomy.

	Breast-conserving surgery *N* = 130 (24.60%)		Mastectomy *N* = 400 (75.40%)		OR	95% CI	*p*
Age (years) (median ± SD)	55.0 (± 11.7)		50.6 (± 11.9)				0.000
BMI (kg/m²) (median ± SD)	30.3 (± 5.9)		28.3 (± 5.5)				0.001
Menopause							
No	52	40.0%	202	50.5%	1	–	0.043
Yes	78	60.0%	198	49.5%	1.530	1.024–2.287	
Nulliparity							
No	113	87.6%	335	84.2%	1	–	0.396
Yes	16	12.4%	63	15.8%	0.753	0.418–1.356	
Stage							
IIB	55	42.3%	83	20.8%	1	–	0.000
IIIA	56	43.1%	166	41.50%	0.509	0.323–0.803	
IIIB or IIIC	19	14.6%	151	37.80%	0.190	0.106–0.341	

(Continued)

TABLE 1 Continued

	Breast-conserving surgery *N* = 130 (24.60%)		Mastectomy *N* = 400 (75.40%)		OR	95% CI	*p*
Biological subtype							
ER (–) PR (–) HER2 (–)	53	40.8%	136	34.0%	1	–	0.320
ER (-) PR (-) HER2 (+)	12	9.2%	57	14.3%	0.540	0.269–1.086	
ER (+) PR (+) HER2 (+)	15	11.5%	56	14.0%	0.687	0.358–1.320	
ER (+) PR (+) HER2 (-)	50	38.5%	151	37.8%	0.850	0.541–1.333	
Neoadjuvant treatment							
Chemotherapy	122	93.8%	384	96.0%	1	–	0.332
Endocrine therapy	8	6.2%	16	4.0%	1.574	0.657–3.767	
Pathological complete response							
No	101	77.7%	360	90.0%	1	–	0.001
Yes	29	22.3%	40	10.0%	2.584	1.526–4.375	
Axillary surgery							
Sentinel lymph node	18	13.8%	19	4.8%	1	–	0.001
Axillary dissection	112	86.2%	381	95.3%	0.310	0157–0.611	
Radiotherapy							
No	4	3.1%	19	4.8%	1	–	0.62
Yes	126	96.9%	381	95.3%	1.571	0.525–4.704	
Recurrence							
No	98	75.4%	215	53.8%	1	–	0.000
Yes	32	24.6%	185	46.3%	0.379	0.243–0.592	
Systemic recurrence	20	15.4%	147	36.8%	0.298	0.177–0.504	
Local recurrence	12	9.2%	38	9.5%	0.693	0.347–1.383	
Ki-67 (%)							
≤30	54	41.5%	179	45.4%	1	–	0.477
>30	76	58.5%	215	54.6%	1.172	0.784–1.750	
Death							
No	106	81.5%	248	62.0%	1	–	0.000
Yes	24	18.5%	152	38.0%	0.394	0.242–0.641	

BMI, body mass index; ER, estrogen receptor; PR, progesterone receptor; HER2, tissue human epidermal growth factor receptor-2.

Type of NAT, RT, histological subtype, molecular profile, and Ki-67 values were similar between the two surgical groups. A total of 65 patients (12.2%) were lost to follow-up.

3.2 Breast surgical management

Univariate analysis revealed clinical factors favoring BCS, including older age, higher BMI, menopause, lower staging, PCR, and a more conservative axillary approach, such as SLN biopsy (Table 1).

In the multivariate analysis assessing the factors influencing the choice of BCS over MS, it was observed that lower stage (IIB: OR 1.00; 3A: OR 0.49; 95% CI 0.302–0.794; $p = 0.004$; IIIB/IIIC: OR 0.15; 95% CI 0.083–0.286; $p < 0.001$), PCR (OR 2.49; 95% CI 1.403–4.426; $p = 0.002$), age (55.0 ± 11.7 versus 50.6 ± 11.9; OR 1.034; 95% CI 1.015–1.053; $p < 0.001$), and BMI (30.3 ± 5.9 versus 28.3 ± 5.5; OR 1.069; 95% CI 1.029–1.110; $p = 0.001$) were independent factors associated with the choice of BCS (Table 2).

3.3 Local and distant recurrence

The median follow-up period for both the BCS and MS groups was similar, at 80 and 78 months, respectively ($p = 0.89$). Over the course of the follow-up, 217 patients (41%) experienced systemic and/or loco-regional recurrence. A statistically significant difference

TABLE 2 Multivariate analysis of patients undergoing breast-conserving surgery compared to mastectomy.

	OR	95% CI	*p*
Stage			
IIB	1	–	
IIIA	0.490	0.302–0.794	0.004
IIIB or IIIC	0.154	0.083–0.286	0.000
Pathological complete response			
Yes	2.492	1.403–4.426	0.002
No	1	–	
Age	1.034	1.015–1.053	0.000
Body mass index	1.069	1.029–1.110	0.001

in DRR was observed between the BCS and MS groups. Specifically, DRR was 15.4% (20/130) for BCS and 36.8% (147/400) for MS (OR: 0.298; 95% CI: 0.177–0.504). However, LRR did not exhibit a statistically significant difference between the two groups, with LRR rates of 9.2% (12/130) for BCS and 9.5% (38/400) for MS (OR: 0.693; 95% CI: 0.347–1.383) (Table 3).

3.4 Overall survival

The 6-year OS rates for patients who underwent BCS and MS were 81.5% and 62%, respectively (log-rank, p < 0.001) (Figure 1). Univariate analysis revealed that MS was significantly associated with worse OS compared to BCS. Additionally, menopausal status, BMI, PCR, staging, and breast and axillary surgery were factors associated with lower OS. Following multivariate analysis, as presented in Table 4, MS remained a significant predictor of worse OS (OR 1.678; 95% CI 1.069–2.635; p = 0.024), along with BMI (OR 1.031; 95% CI 1.006–1.058; $p = 0.017$) and staging IIIB or IIIC (OR 2.450; 95% CI 1.561–3.846; $p < 0.001$). Conversely, PCR was associated with improved OS (OR 0.42; 95% CI 0.220–0.801; $p = 0.008$).

4 Discussion

Our study demonstrates that BCS following NAT is oncologically safe and an independent factor for improving long-term OS in patients initially considered candidates for MS due to locally advanced tumors.

In early breast cancer, the Veronesi trial (11) established the efficacy of BCS combined with RT as a viable option with comparable OS to MS. A recent meta-analysis, comprising 30 studies and over 1.5 million patients who underwent upfront surgery, reported that BCS plus RT yielded superior OS rates compared to MS, with a 36% improvement (confidence interval ranging from 26% to 45%). Notably, this difference became more pronounced when focusing solely on cohort studies, reaching a 46% improvement in OS. However, after 10 years, these differences tended to disappear. When considering only six clinical trials with 3,933 participants, there was no significant difference in terms of local recurrence in the meta-analysis (4).

Following the introduction of NAT, BCS also emerged as a feasible option for LABC. When comparing BCS to MS in patients who received neoadjuvant chemotherapy, studies consistently demonstrated no significant differences in OS or LRR (12–14). A meta-analysis conducted by Sun et al. (14), incorporating five studies (12, 15–18) with a total of 1,114 patients, indicated that BCS was a safe surgical approach after NAT for LABC and was associated with improved OS (OR 2.12; 95% CI 1.51–2.98, $p < 0.01$) compared to the MS group (14). However, it is important to note that, upon closer examination, only approximately 8.5% ($N = 95/1,114$) of patients had T3 tumors, and approximately 26.8% ($\boldsymbol{N} = 299/1,114$) were classified as stage III (12, 15–17). One study included 119 patients (11.5%) and reported a median tumor size of approximately 41 mm (18). Although these data suggest similar survival rates, the inclusion criteria in these studies were heterogeneous (14).

Gwark et al. published a retrospective cohort study involving 1,641 patients who received NAT before surgery and reported significantly better OS in the BCS plus RT group. Initially, most patients had T2 stage tumors (61.9%, $N = 1,017$). However, after propensity score matching, the study focused on 378 patients, including 198 with T2 tumors, 138 with T3 tumors, and 23 with T4 tumors (7). Our dataset differs in that it includes a higher proportion of patients diagnosed with LABC, comprising 74% ($N = 392$) of stage III and 26% ($N = 138$) of patients diagnosed with stage IIB breast cancer.

The criteria for selecting BCS following NAT for LABC mirror those applied in upfront surgery, including the importance of maintaining a favorable tumor–breast relationship (19). However, a degree of uncertainty exists regarding the extent of primary tumor area removal after NAT. According to recent literature, the post-treatment tumor size serves as the reference point when determining the appropriate surgical approach (14).

In our cohort study, several factors were associated with an increased likelihood of choosing BCS after NAT. These factors included an earlier clinical stage, a higher rate of pathological

TABLE 3 Recurrence rates.

	Breast-conserving surgery $N = 130$ (%)	Mastectomy $N = 400$ (%)	Total patients $N = 530$ (%)	OR	95% CI	*p*
Any recurrence	32 (24.6)	185 (46.3)	217 (40.9)	0.379	0.243–0.592	0.001
Systemic recurrence	20 (15.4)	147 (36.8)	167 (31.5)	0.298	0.177–0.504	
Local recurrence	12 (9.2)	38 (9.5)	50 (9.4)	0.693	0.347–1.383	

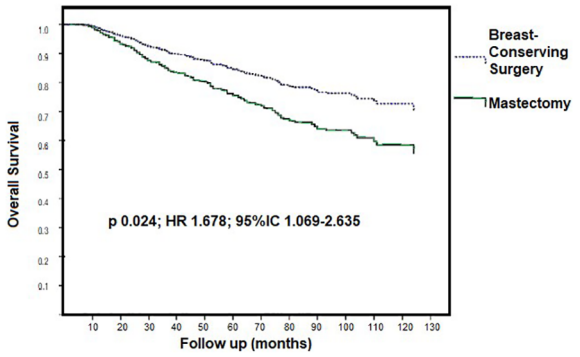

FIGURE 1
Kaplan-Meier curves for survival according to surgery after multidimesional analysis.

clinical responses (PCRs), older age, and a higher BMI. Specifically, BCS was 50% more likely to be chosen in stage IIB cases. When PCR was achieved, the chances of opting for BCS increased 2.5 times. Additionally, women older than 55 and those with a BMI greater than 30 had 3% and 6% higher chances of choosing BCS, respectively. This can be attributed to the fact that individuals with smaller tumors both before and after NAT, and a higher BMI, often have a more favorable tumor–breast relationship.

Regarding OS after NAT, BCS, lower BMI, lower pre-NAT staging, and PCR were all associated with better OS rates. A 2017 meta-analysis involving 3,531 participants (1,465 in the BCS arm and 2,066 in the MS arm) found that BCS was a safe option for LABC patients who showed an excellent response to NAT. This analysis reported a nearly 50% lower risk of distant recurrence, with a real effect protection ranging from 42% to 63%, and a twofold higher rate of OS and DFS in the BCS group (14). These findings align with our own, indicating that the BCS group exhibited improved OS and fewer systemic recurrences.

TABLE 4 Multivariate analysis of factors that significantly differs in overall survival.

	p	HR	95% CI
Body mass index	0.017	1.031	1.006–1.058
Surgery			
Breast-conserving surgery		1	–
Mastectomy	0.024	1.678	1.069–2.635
Stage			
IIB	0.000	1	–
IIIA		1.534	0.978–2.407
IIIB or IIIC		2.450	1.561–3.846
Pathological complete response			
Yes	0.008	0.420	0.220–0.801
No		1	–

In contrast, the EBCTCG meta-analysis described a higher LRR rate for BCS without an increase in breast cancer-specific mortality. It is essential to note the heterogeneity between studies in the EBCTCG analysis, as it included neoadjuvant and adjuvant treatments, and some patients received only RT as local treatment (5). Our results are more in line with recently published studies (6, 7). Gwark et al. demonstrated a 14% absolute improvement in OS in the BCS plus RT group compared to MS in patients who underwent NAT and surgery (7). Since RT can significantly impact OS, it is noteworthy that in our dataset, there were no significant differences in RT rates between the BCS and MS groups. This is because all patients in our dataset had prior indications for RT, given their LABC diagnosis.

It is well-established that a higher BMI increases the risk of breast cancer in women, and it is estimated that approximately 1.4 billion people will be obese by 2035 (20). Patel et al. (21) established a significant causal link between BMI and OS in obese breast cancer patients, particularly those with hormone receptor-positive tumors, which were associated with shorter survival rates. A systematic study in 2014 showed that obesity increased breast cancer mortality, with relative risks (RRs) of 1.41 (95% CI: 1.29–1.53) for obese individuals (BMI >30.0) and 1.07 (95% CI: 1.02–1.12) for overweight individuals (BMI 25.0–30.0). The risk of death rose proportionally with BMI. For every 5 kg/m^2 increase in BMI before diagnosis, the risk of overall death and breast cancer-specific mortality increased by 17% and 18% before and after menopause, respectively (22). These findings further support our study's conclusion that higher BMI is associated with an increased risk of mortality.

We observed that initial staging IIIB or IIIC breast cancer was a significant risk factor for death, increasing the risk by more than 2.4 times compared to staging IIB. This finding aligns with a 1988 article by Hortobagyi et al. (23), which evaluated only stage III patients, including those who had and had not received neoadjuvant chemotherapy. Large tumor sizes may not achieve a PCR, which has been shown to be associated with higher mortality. Interestingly, Meyers et al. (24) did not associate pretreatment stage with a worse prognosis for LRR. They suggest that the post-treatment stage is more related to LRR than the pretreatment stage. It is important to note that they did not analyze OS.

In our dataset, the rate of PCR had the most significant influence on OS. We defined PCR as ypT0 ypN0, which may have impacted our results. According to Cortazar et al.'s 2014 meta-analysis (25), the frequency of PCR varied depending on the definition: 22% of patients achieved ypT0/is, 18% achieved ypT0/is ypN0, and 13% achieved ypT0 ypN0. However, all definitions consistently resulted in an increase in both OS and DFS. Patients who had a favorable response to NAT, such as achieving PCR or a decreased tumor size after NAT, were better candidates for BCS, as confirmed by another meta-analysis conducted in 2017 (14).

While this result should be interpreted cautiously for patients with LABC, as it is from a tertiary single-center investigation with a 5-year follow-up, it underscores the treatment uniformity and provides compelling evidence that BCS after NAT is a favorable option for women with LABC, leading to improved OS. Furthermore, considering the global obesity pandemic, our research highlights the significance of effective weight management in influencing

oncological prognosis. It is worth noting that only approximately 12% of the patients were lost to follow-up.

Nonetheless, there are limitations associated with our study. As a retrospective cohort design, potential biases such as selection bias, an imbalance of prognostic factors, and reporting bias may exist, potentially affecting internal validity. To address these limitations, we performed a multivariable analysis. Despite these drawbacks, our cohort study has robust external validity, and its findings may be generalized to this breast cancer population. Moreover, our study can serve as a basis for other breast cancer study groups to plan clinical trials to further investigate this question.

In conclusion, our study suggests that BCS following NAT is oncologically safe and improves long-term survival for women with LABC. Additionally, it underscores the importance of maintaining a normal BMI, which significantly enhances a patient's likelihood of survival. Based on these findings, patients receiving NAT should consider advocating for BCS when feasible and implementing weight-maintenance strategies that can enhance their quality of life and survival.

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 humans were approved by Comitê de Ética do departamento de Obstetrícia e Ginecologia da Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil. The studies were conducted in accordance with the local legislation and institutional requirements. The ethics committee/institutional review board waived the requirement of written informed consent for participation from the participants or the participants' legal guardians/next of kin because It is a retrospective study with analysis of data from medical records.

Author contributions

GN: Conceptualization, Data curation, Investigation, Methodology, Project administration, Writing – original draft, Writing – review & editing. BM: Data curation, Investigation, Methodology, Project administration, Software, Supervision, Writing – original draft, Writing – review & editing. GF: Data curation, Investigation, Supervision, Writing – review & editing. JM: Data curation, Investigation, Supervision, Writing – review & editing. RM: Formal Analysis, Software, Writing – review & editing. RG: Methodology, Supervision, Writing – review & editing. AT: Supervision, Visualization, Writing – review & editing. MR: Supervision, Visualization, Writing – review & editing. JP: Methodology, Supervision, Validation, Writing – review & editing. JJ: Supervision, Validation, Writing – review & editing. EB: Supervision, Visualization, Writing – review & editing. JF: Investigation, Project administration, Supervision, Validation, Visualization, Writing – review & editing.

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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.

Publisher's note

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Curative effect of immediate reconstruction after neoadjuvant chemotherapy for breast cancer: a systematic review and meta-analysis

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Background: The safety of mastectomy (MT) with immediate reconstruction (IR) in breast cancer patients who have completed neoadjuvant chemotherapy (NAC) is not apparent. This meta-analysis aims to systematically evaluate the differences in surgical complications and postoperative survival rates between MT with IR (MT+IR) and MT alone in post-NAC breast cancer patients.

Methods: The PubMed, Embase, Cochrane Library, WanFang Data, and CNKI databases were systematically searched, and cohort studies of post-NAC breast cancer patients with MT+IR or MT surgery were collected from databases inception to May 25, 2023. Two researchers independently executed literature screening, data extraction, and bias risk assessment, and meta-analysis was performed using Revman 5.3 software.

Results: A total of 12 studies involving 7378 cases who have accepted NAC were collected for this study. The results showed that compared with the MT group, the relative risk of surgical complications in the MT+IR group was increased by 44%, with no statistical significant [RR=1.44, 95% CI (0.99, 2.09), P=0.06]. While among study subgroups with a median follow-up of less than one year, more surgical complications occurred in the MT+IR group by 23% [RR=1.23, 95% CI (1.00, 1.52), P=0.05]. There was no significant differences in overall survival, disease-free survival, local relapse-free survival, and distant metastasis-free survival between the two groups.

Conclusions: Compared with the MT, MT+IR does not affect the postoperative survival rate in post-NAC breast cancer patients, accompanied by a mild increase in short-term surgical complications, but no significant difference in long-term complications.

Systematic review registration: https://www.crd.york.ac.uk/prospero, identifier CRD42023421150.

KEYWORDS

breast cancer, immediate reconstruction, mastectomy, neoadjuvant chemotherapy, meta-analysis

1 Introduction

Breast cancer (BC) is the most popular carcinoma among females worldwide (1). Most of these patients need a mastectomy (MT). Whereas patients who experienced MT, which often requires the removal of the entire breast, may experience long-term negative impacts on their physical and mental health, and their treatment compliance may be reduced (2, 3). MT with immediate reconstruction (MT+IR) has been shown to significantly improve a patient's quality of life by recent researches (4–6). Therefore, MT +IR has become a popular alternative to maintain the breast's appearance and improve patients' quality of life (7).

Neoadjuvant chemotherapy (NAC) is a critical element of systematic breast cancer treatment and is associated with improved survival compared to adjuvant chemotherapy in some breast cancer patients (8, 9). In early breast cancer, NAC can make breast-conserving surgery (BCS) more feasible than the same chemotherapy given after surgery (10, 11). The increasing use of NAC has led to a rapid worldwide increase in the rate of BCS over the past few decades (12–15). However, there is a certain proportion of patients still not suitable for BCS (12, 13, 16, 17). Some patients eligible for BCS post-NAC still chose MT and MT plus reconstructive surgery (18–21). In such cases, MT+IR presents an attractive alternative to BCS as it can help avoid psychosocial morbidity and suboptimal cosmetic outcomes (5, 22). In recent years, the proportion of reconstruction has increased yearly, accompanied by the incidence of complications decreasing (23–25). Due to the lack of high-quality evidence, the safety of IR in post-NAC is still controversial. In Japan, there is a considerable disparity in doctors' opinion of the safety of IR, with nearly one-quarter of doctors believing that IR could adversely impact patient prognosis (26).

Currently, there are no available RCT researches on the effect of MT+IR following NAC. Previous studies have primarily focused on comparing the outcomes of MT+IR after NAC and adjuvant therapy after MT+IR (27–29). However, these studies do not provide sufficient information for breast cancer patients who have completed NAC and are preparing for operation.

It is necessary to conduct a meta-analysis of the differences in surgical complications and postoperative survival between MT+IR and MT alone after NAC. We aimed to provide more reference data for breast cancer patients who are not candidates for BCS after NAC.

Abbreviations: BC, Breast cancer; MT, mastectomy; MT+IR, MT with immediate reconstruction; NAC, Neoadjuvant chemotherapy; BCS, breast-conserving surgery; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analyses; OS, overall survival; DFS, disease-free survival; LRFS, local recurrence-free survival; DMFS, distant metastasis-free survival; NOS, Newcastle Ottawa Scale; RR, relative risk; HR, hazard ratio; DR, delayed reconstruction; SSM, skin-sparing mastectomy; NSM, nipple-sparing mastectomy; TNM, Tumor Node Metastasis.

2 Methods

This meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) standards (30), and the protocol was registered in the PROSPERO database (CRD42023421150).

2.1 Literature search

Two independent researchers searched PubMed, Embase, the Cochrane Library, the Wanfang database, and the CNKI database for studies on breast cancer patients who underwent MT combined with or without IR surgery after NAC. The retrieval time limit was from the establishment of the database to May 25, 2023. The index words used were as follows: "Mammaplasty", "Breast Implantation" and "Neoadjuvant Therapy". An approach involving the combination of subject words and free words was adopted in the retrieval (Supplementary Table 1).

2.2 Inclusion and exclusion criteria

The inclusion criteria were as follows: (1) cohort studies or randomized control studies; (2) patients with breast cancer who underwent breast surgery after NAC; (3) comparison of the MT+IR with the MT; and (4) report of relevant outcomes, including overall survival (OS), disease-free survival (DFS), local recurrence-free survival (LRFS), distant metastasis-free survival (DMFS), and surgical complications.

Studies were excluded if they met the following criteria: (1) literature in languages other than Chinese and English; (2) no outcome indicators mentioned above; (3) repeat studies; (4) uncontrol studies; (5) study without valid data or data that could not be extracted; and (6) abstracts, lectures, conference abstracts, and incomplete data.

2.3 Risk of bias assessment

The included studies used the Newcastle Ottawa Scale (NOS) to assess the risk of bias (31). Two independent researchers conducted the cross-check. If the NOS score was ≥6, the study's quality was considered high.

2.4 Data extraction

Two independent researchers extracted the data, such as the general information, specific intervention measures, number of cases in the MT+IR and MT groups, total number, publication time, research time, first author, and number of complications. The comparison of survival data (OS, DFS, LRFS, and DMFS) between the two groups used the hazard ratio (HR). If the HR value and 95% CI were directly reported in the literature or the survival rates of the two groups at multiple time points were reported, the ln(HR) and

SE[ln(HR)] of the OS, DFS, LRFS, and DMFS between the two groups could be calculated by using the Excel attachment calculations spreadsheet provided by Tierney et al. (32) If the survival curves of OS, DFS, LRFS, and DMFS of the two groups were reported in the literature, the survival data were extracted using Engauge Digitizer version 4.1 software and then calculated using the Excel attachment calculations spreadsheet provided by Tierney et al. (32) We finally used the ln(HR) and SE[ln(HR)] from each study for meta-analysis.

2.5 Statistical analysis

Data were analyzed by RevMan5.3 software. The relative risk (RR) was used as the effective index for count data, and HR was used as the effective index for survival data. The heterogeneity between the results of the studies was assessed using $\chi 2$ inspection analysis, with the inspection level set at α=0.10, combined with I2 to determine the heterogeneity size. The fixed effect model was used when the homogeneity of the results was not significant (I^2<50%, P≥0.05). The random effect model was used when the heterogeneity test showed that the heterogeneity of the results was statistically significant (I^2≥50%, P<0.05), and the source of heterogeneity was further analyzed. Sensitivity analysis was used to evaluate the stability of the results using the one-by-one exclusion method.

3 Results

3.1 Literature screening

Initially, we identified a total of 2040 articles from various databases, including 132 articles from the CNKI database, 425 articles from the Wanfang database, 411 articles from the PubMed database, 13 articles from the Cochrane Library, and 1059 articles from the Embase database. After screening and reviewing the title, abstract and full text, we included 12 cohort studies involving 7378 patients (33–44). The literature screening process is shown in Figure 1.

3.2 Study characteristics and risk of bias

The 12 included studies comprised 2019 patients with MT+IR and 5359 patients with MT. Bias risk assessment showed that the NOS scores of all 12 studies were ≥6, and the studies were regarded as high-quality research (Table 1).

3.3 Surgical complications

3.3.1 Meta-analysis results

A total of five studies reported surgical complications between the two groups (34–37, 39), including 989 patients in the MT+IR group and 3150 patients in the MT group. Meta-analysis using the random effect model showed no significant difference in the incidence of complications between the two groups [RR=1.44, 95% CI (0.99, 2.09), P=0.06] (Figure 2A).

3.3.2 Subgroup analysis of surgical complications

According to different median follow-up times, subgroup analysis was conducted on surgical complications. Among study subgroups with a median follow-up of less than one year, more surgical complications occurred in the MT+IR group [RR=1.23, 95% CI (1.00, 1.52), P=0.05]. However, in the study subgroup with a longer median follow-up, there was no significant difference in the incidence of surgical complications between the two groups [RR=1.98, 95% CI (0.80, 4.94), P=0.14] (Figure 3).

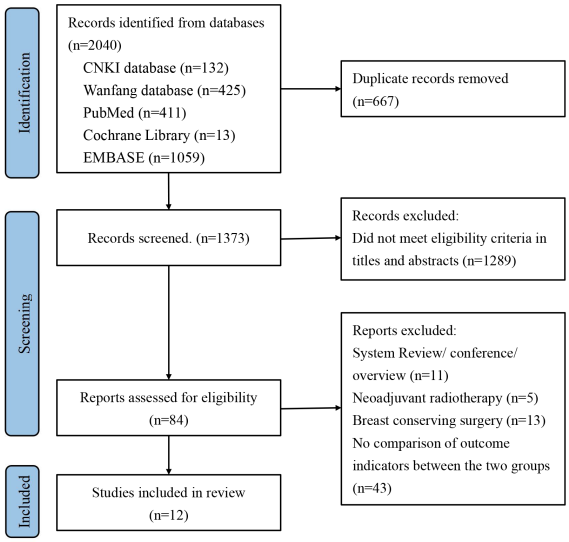

FIGURE 1
Preferred Reporting Items for Systematic Review and Meta-Analysis of Diagnostic Test Accuracy Studies (PRISMA) flow diagram for study selection.

TABLE 1 Basic characteristics of the included studies.

First author, year	Study type	Study time	Country	MT +IR/ MT(n)	Match the propensity scores	Operation program of MT+IR group	Outcomes	Median follow-up	NOS score
Gouy 2005 (33)	R	1985-1995	France	48/181	no	MT	LRFS/DMFS	10 years	6
Golshan 2011 (34)	P	2004-2008	USA	13/24	no	MT	Complication	1 year	7
Prabhu 2012 (35)	R	1997-2010	USA	40/60	no	SSM	Complication	31.6 months/30 months	8
Kansal 2013 (36)	P	2007-2010	USA	62/57	yes	MT	Complication	1 year	7
Abt 2014 (37)	R	2005-2011	USA	820/2876	no	MT	Complication	30 days	6
Aurilio 2014 (38)	R	1995-2006	Italy, Europe	59/74	no	MT	OS/DFS	8.2 years	9
Gerber 2014 (39)	R	2007-2010	Germany, Switzerl	54/142	no	MT	Complication	12 weeks	6
Ryu 2017 (40)	R	2008-2015	Korea	31/85	yes	NSM/SSM	OS/DFS/ DMFS/LRFS	29.2 months/38.8 months	9
Vieira 2019 (41)	R	2005-2011	Brazil	48/96	yes	NSM/SSM	OS/DFS/LRFS	75.9 months/67 months	8
Wu 2020 (42)	R	2010-2016	Korea	323/323	yes	NSM/SSM	OS/DFS/ DMFS/LRFS	67 months/ 68 months	9
Park 2021 (43)	R	2008-2014	Korea	345/1354	no	MT	OS	30.1 months	8
Wu 2022 (44)	R	2010-2016	Korea	209/209	yes	NSM	OS/DFS/ DMFS/LRFS	70 months/ 74months	9

R, Retrospective cohort study; P, Prospective cohort study; MT, mastectomy; IR, immediate reconstruction; NSM, nipple-sparing mastectomy; SSM, skin sparing mastectomy; OS, overall survival; DFS, disease free survival; LRFS, local recurrence free survival; DMFS, distant metastasis free survival; NOS, Newcastle–Ottawa scale.

Subgroup analysis of surgical complications in the MT+IR and IR groups was performed according to whether the propensity score matched. There were no significant differences in surgical complications, regardless of propensity score matching (Supplementary Figure 1).

3.4 Survival

3.4.1 OS

Six studies compared postoperative OS between the two groups (38, 40–44), including 982 MT+IR patients and 2028 MT patients. Meta-analysis using a fixed effect model showed no significant difference in the OS between the two groups [HR=0.91, 95% CI (0.72, 1.16), P=0.45] (Figure 4A).

3.4.2 DFS

Five studies compared postoperative DFS between the two groups (38, 40–42, 44), including 670 MT+IR patients and 787 MT patients. Meta-analysis using a fixed effect model showed no significant difference in the DFS between the two groups [HR=1.06, 95% CI (0.87, 1.29), P=0.54] (Figure 4B).

3.4.3 LRFS

Five studies compared postoperative LRFS between the two groups (33, 40–42, 44), including 659 MT+IR patients and 894 MT patients. Meta-analysis using a fixed effect model showed no significant difference in the LRFS between the two groups [HR=1.02, 95% CI (0.62, 1.65), P=0.95] (Figure 4C).

3.4.4 DMFS

Four studies compared postoperative DMFS between the two groups (33, 40, 42, 44), including 611 MT+IR patients and 798 MT patients. Meta-analysis using a fixed effect model showed no significant difference in the DMFS between the two groups [HR=0.97, 95% CI (0.76, 1.22), P=0.77] (Figure 4D).

3.4.5 Subgroup analysis of survival

Subgroup analysis of OS, DFS, LRFS, and DMFS in the MT+IR and IR groups was performed according to whether the propensity score matched. Among each subgroup, there were no significant differences in OS, DFS, LRFS, and DMFS between the two groups (Supplementary Figures 2-5).

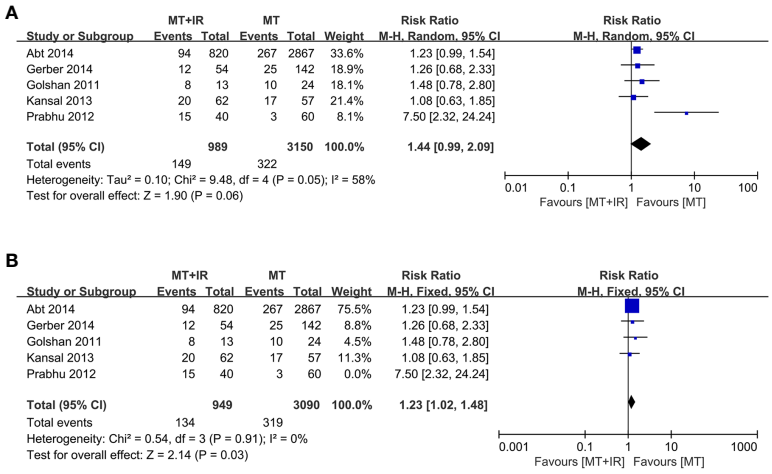

FIGURE 2
Forest plot of surgical complication in two groups. **(A)** All of five studies was included. **(B)** The study of Prabhu et al. was excluded. MT, Mastectomy; IR, Immediate reconstruction.

3.5 Sensitivity analysis

We conducted a sensitivity analysis by excluding one study at a time. When the survey of Prabhu et al. (35) was excluded, the statistical heterogeneity of the meta-analysis results decreased significantly (I^2 = 0%, P=0.91). The results significantly differed in the incidence of surgical complications between the MT+IR group and the MT group [RR=1.23, 95% CI (1.02, 1.48), P=0.03] (Figure 2B).

4 Discussion

Breast reconstruction has been widely accepted as a mean to enhance breast cancer patients' quality of life, mental well-being, and aesthetics degree post-surgery as evidenced by recent studies (45, 46). Our study provides valuable information that MT+IR in breast cancer patients after NAC may bring more short-term surgical complications than MT. The results of previous studies have been controversial on whether IR increases surgical complications. Mortenson et al. (47) and Lee et al. (48) both observed an increased incidence of wound complications when IR was combined with MT. The study of Hamahata et al. (49) yielded reports of a 10.0% postoperative complication rate in the IR group versus 6.1% in the non-IR group. A network meta-analysis of 51 studies revealed that the risk of overall complications and surgical site infection was more significant in the MT+IR group than in the MT group (50). Conversely, other studies found no significant difference in the incidence of complications between the two groups (51, 52).

A meta-analysis investigated the incidence of complications between MT+IR after NAC and adjuvant chemotherapy after MT +IR. There was no significant difference in the incidence of complications between the two groups (27). However, when the implant reconstruction subgroup was analyzed, there was some evidence suggesting that implant losses were more likely to occur in patients post-NAC compared to those in control groups (27). Another meta-analysis included 26 studies comparing surgical complications in breast cancer patients with or without NAC who

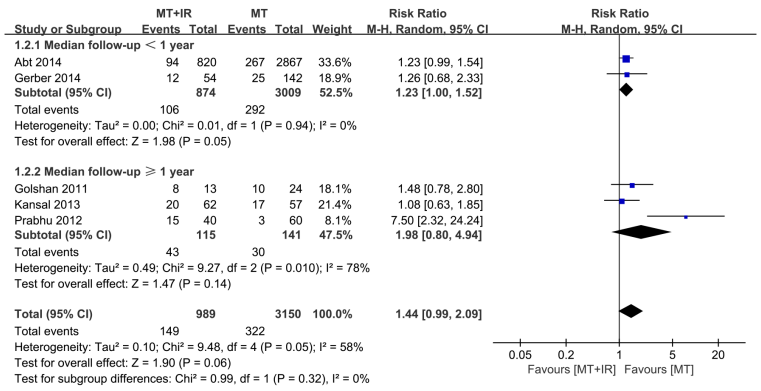

FIGURE 3
Subgroup analysis of different follow-up time on surgical complications.

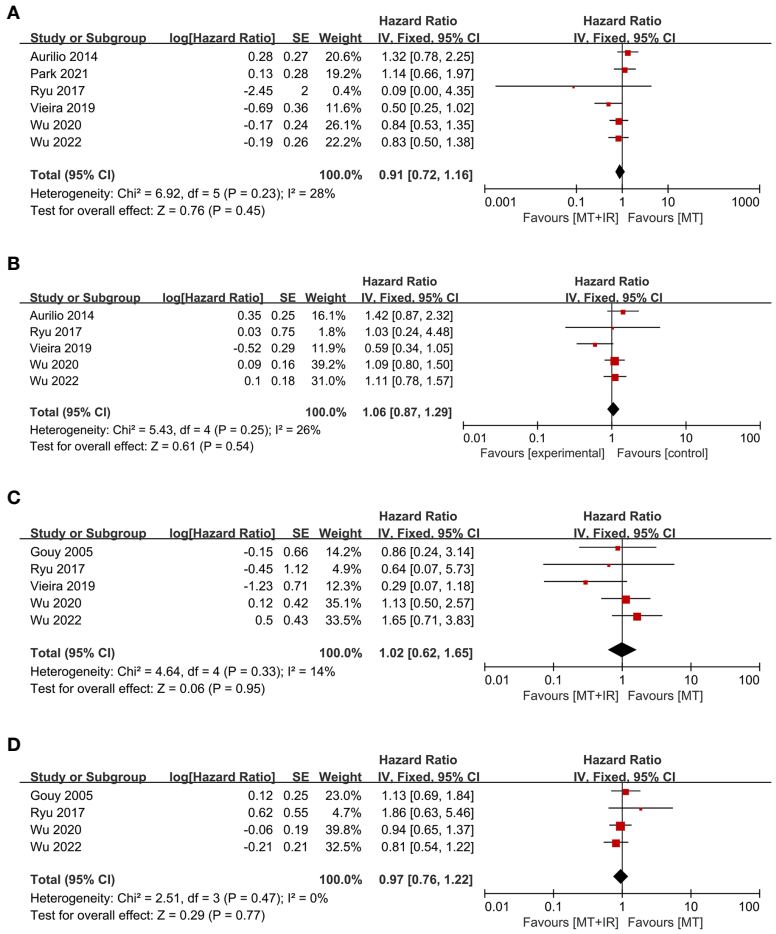

FIGURE 4
Forest plot of postoperative survival condition in two groups. **(A)** Overall survival; **(B)** Disease-free survival; **(C)** Local recurrence-free survival; **(D)** Distant metastasis-free survival. MT, Mastectomy; IR, Immediate reconstruction.

underwent any breast surgery (29). In that study, it was found that NAC did not increase the risk of certain complications, including seroma, wound complications, skin or nipple necrosis, flap ischemia or loss, and implant loss (29). However, these studies have limited reference significance for patients who have completed or underwent NAC when formulating the following surgery scheme. Matar et al. (53) showed that compared with MT+IR, delayed reconstruction (DR) after MT has a lower incidence of surgical complications, especially hematoma and postoperative infection. Although there is no significant correlation between the occurrence of surgical complications and the recurrence rate and mortality of breast cancer, DR may be a better alternative for patients afraid of complications (54). Among the five studies that investigated complications we included, only Abt et al. (37) studied wound and systemic complications containing Accordion Expanded grades 1 to 6 but did not report detailed numbers of occurrence of each complication (55, 56). The other four studies examined only wound complications that included complications of Accordion Expanded grades 1 to 4 (34–36, 39).

Without considering the influence of NAC, several previous meta-analyses proved that there was no significant difference in postoperative DFS, OS, and local recurrence rate between the MT +IR group and the MT group (57, 58). However, Shen et al. (50) conducted a Bayesian analysis and concluded that the OS of the MT +IR group was more advantageous than that of the MT group. Generally, there is a biased selection in the MT+IR group, for the patients may be younger or have higher schooling, some of them have a lower clinical stage and a better response to NAC (41, 59). Baseline characteristics of patients before NAC and the response to NAC can affect the prognosis of patients (60, 61). Based on this selective factor, some studies showed that the MT+IR group had higher OS and LRFS and a lower recurrence rate (62, 63). However, when propensity score matching was used, the survival rate between the two groups did not show significant differences in many studies. Lee et al. (64, 65) compared DMFS and breast cancer-specific survival rates between the two groups after propensity score matching, and the results showed no significant difference. Yi et al. (66) found no significant difference in the DFS between the two groups after adjusting for the clinical TNM staging. A study by Song et al. (67) showed that in patients with tumor sizes greater than 3 cm, the DFS of the MT group was higher than the MT+IR group, especially in HER2-positive and triple-negative patients. We performed subgroup analyses of propensity-matched studies that were matched for age, clinical stage, molecular type, and response to

NAC (40–42, 44). Similar to other studies, our study showed no significant difference between the two groups in OS, DFS, LRFS and DMFS, regardless of propensity score matching (Supplementary Figures 2-5).

There is no suitable report to provide a reference for the conclusion of the effect of IR on prognosis in post-NAC patients. Although no difference in prognosis was observed in our study, the accuracy is also limited by the bias caused by retrospective analysis. Liu et al. (28) demonstrated the same OS benefits for both NAC and non-NAC cases in patients with breast cancer receiving MT+IR. However, some studies suggest that MT+IR patients who received NAC had worse OS than MT+IR patients without NAC (68). It is necessary to consider the patient's response to NAC, as patients with pathologic complete response after NAC have a better prognosis than patients with limited or no response (41, 69, 70). Only a few studies have matched this factor, which could decrease the influence of different factors. After matching patients in the MT +IR and MT groups based on their responsiveness to NAC, Vieira et al. (41) found no statistically significant difference in DFS and LRFS between the two groups. However, the MT+IR group had a better OS and cancer-related survival, which they still attributed to selecting patients with a better response to NAC for IR. Ryu et al. (40) proved that OS, DFS, DMFS, and LRFS did not differ significantly between the two groups, whose matched variables included age, clinical stage before NAC, response to NAC, and pathologic stage after NAC. Two studies from Korea matched the response to NAC and also found no significant differences in OS, DFS, DMFS, and LRFS between the two groups, even in patients with locally advanced breast cancer (42, 44). In addition, some studies have shown that the best operation time after NAC is 4-8 weeks because it is related to increased OS and DFS and reduced complications (71, 72). However, due to the lack of relevant data, this study did not further analyze subgroups.

The heterogeneity test results comparing surgical complications between the two groups revealed significant heterogeneity among the studies. When the study of Prabhu et al. (35) was excluded, the heterogeneity decreased significantly, suggesting that this study may be one of the sources of heterogeneity. Further data analysis indicated that the patients had locally advanced breast cancer, and the surgical method in the MT+IR group was skin-sparing mastectomy (SSM). In contrast, other studies employed nipple-sparing mastectomy (NSM), SSM, and traditional MT as surgical methods in the MT+IR group. SSM/NSM retains a portion of the native breast structure, resulting in better breast appearance and quality of life for the patients. However, it may also bring about more surgical complication (73). Future research needs to analyze the specific surgical scheme after differentiation.

This study has the following limitations: (1) the investigation was conducted with a limited number of studies, which may present a risk of publication bias; (2) most of the included studies were retrospective studies, which may have selection bias and retrospective bias; (3) the long-term cosmetic effects of the two groups were not studied; (4) because the radiotherapy data in each study could not be extracted, our study did not consider radiotherapy, which may introduce bias; and (5) it is necessary to organize criteria related to complications of breast surgery as the number of patients submitted to IR is increasing, and the complications are decreasing yearly.

It is impossible to perform prospective randomized studies related to oncoplastic surgery because we can not randomize the type of breast surgery, and matched studies represent the best study form. It is necessary to take more studies matched by the response to NAC and other baseline characteristics with adequate follow-up to evaluate the long-term results of MT+IR after NAC. Further standardization of surgical complications and IR categories must be studied to obtain the most suitable and safe reconstruction method for breast cancer patients after NAC. The long-term cosmetic and symmetrization rates of IR in post-NAC patients need further evaluation.

5 Conclusion

Our meta-analysis demonstrated that compared with the MT, MT+IR does not affect the postoperative OS, DFS, LRFS, and DMFS in post-NAC breast cancer patients, accompanied by a mild increase in short-term surgical complications, but no significant difference in long-term complications.

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.

Author contributions

GL: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Software, Validation, Visualization, Writing – original draft, Writing – review and editing, Funding acquisition, Resources. HJ: Writing – original draft, Writing – review and editing, Conceptualization, Data curation, Funding acquisition, Investigation, Methodology, Resources, Software, Validation, Visualization. JL: Conceptualization, Writing – review and editing, Investigation, Supervision. LX: Writing – review and editing, Conceptualization, Investigation, Supervision. ZC: Writing – review and editing, Conceptualization, Data curation, Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Validation.

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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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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2023.1288744/full#supplementary-material

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Pathologic complete response prediction in breast cancer lesion segmentation and neoadjuvant therapy

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Objectives: Predicting whether axillary lymph nodes could achieve pathologic Complete Response (pCR) after breast cancer patients receive neoadjuvant chemotherapy helps make a quick follow-up treatment plan. This paper presents a novel method to achieve this prediction with the most effective medical imaging method, Dynamic Contrast-enhanced Magnetic Resonance Imaging (DCE-MRI).

Methods: In order to get an accurate prediction, we first proposed a two-step lesion segmentation method to extract the breast cancer lesion region from DCE-MRI images. With the segmented breast cancer lesion region, we then used a multi-modal fusion model to predict the probability of axillary lymph nodes achieving pCR.

Results: We collected 361 breast cancer samples from two hospitals to train and test the proposed segmentation model and the multi-modal fusion model. Both segmentation and prediction models obtained high accuracy.

Conclusion: The results show that our method is effective in both the segmentation task and the pCR prediction task. It suggests that the presented methods, especially the multi-modal fusion model, can be used for the prediction of treatment response in breast cancer, given data from noninvasive methods only.

KEYWORDS

PCR, DCE-MRI, neoadjuvant chemotherapy, multi-modal fusion model, breast cancer, lesion segmentation

1 Introduction

The incidence of breast cancer has been increasing in recent years, and breast cancer is one of the most common malignant cancers in women. In 2023, it is estimated that there will be 297,790 new cases of invasive breast cancer diagnosed and 43,170 women will die from breast cancer in the U.S. (1). At present, neoadjuvant chemotherapy (NAC) plays an important role in breast cancer treatment, and research (2–5) shows that whether axillary lymph nodes achieve

pathologic Complete Response (pCR) is an important prognostic predictor for breast cancer patients who receive NAC, and that pCR indicates a lower risk of local recurrence and a better long-term prognosis for patients. Therefore, it is of great importance if we can predict whether axillary lymph nodes will achieve pCR after patients receive NAC; this helps make a follow-up treatment plan and improve patients' prognosis.

As a non-invasive method, imaging examination plays an important role in the clinical diagnosis and treatment of cancer. Specifically, in the evaluation of treatment response to NAC in breast cancer, Magnetic Resonance Imaging (MRI) is the most commonly used imaging evaluation method in clinical practice (6). However, based on radiologists' subjective evaluation of imaging features, MRI shows high sensitivities (83–92%) and intermediate specificities (47–63%) in preoperative diagnosis of axillary lymph nodes achieving pCR after NAC (7). Nevertheless, recently, artificial intelligence has shown great promise in analyzing medical images, helping to identify image information beyond the ability of the naked eye, and providing objective quantitative evaluation to support clinical decision-making (6). Specifically, deep neural networks, especially convolutional networks, attract great attention in the field of medical imaging analysis (8). Thus, the objective of this paper is to utilize deep neural networks to process MRI images of breast cancer in order to predict whether axillary lymph node metastasis in breast cancer could achieve pCR after patients receive NAC.

Compared with other types of medical imaging technologies, such as Computed Tomography (CT) and Positron Emission Tomography (PET), MRI provides better imaging capability for soft tissues and is widely adopted in breast cancer diagnosis and treatment. In our work, we use Dynamic Contrast-enhanced Magnetic Resonance Imaging (DCE-MRI), which provides a high-quality image for soft tissues with better quality of blood flow around the lesion, which facilitates higher accuracy and earlier detection in breast cancer diagnosis. Despite the above, due to the nature of medical imaging technology, a common DCE-MRI image for breast cancer diagnosis (Figure 1A), contains a large amount of redundant information, so we need to extract only the lesion region of interest for further processing in order to achieve better performance. Image segmentation is widely used in medical imaging analysis, where pixels from specific regions are segmented from the background. With the prevalence of deep learning, models such as the Fully Convolutional Network (FCN) (9) and UNet (10) are applied in medical image segmentation and achieve great performance. It is also proven that neural networks are effective and efficient in breast tumor segmentation tasks (11). In our work, considering the fact that breast cancer lesions are close to the chest wall and vary in size and distribution, we propose a two-step lesion segmentation method using nnUNet (12) as shown in Figure 1: (1) segmentation of the mammary gland region; (2) segmentation of the breast cancer lesion region within the mammary gland region. When training medical image segmentation models, transferability should be taken into consideration because DCE-MRI images collected from different centers may vary in resolution, scanner used, protocol, and image quality. Hence, we apply a histogram matching method (13) to augment the training samples in order to improve the model transferability.

Usually, after acquiring the model representation of breast cancer lesions, we can directly train a neural network to predict the probability of pCR after NAC. However, as pointed out by Ramos-Vara (14), immunohistochemical detection can greatly help in the diagnosis of breast cancer, invasion and metastasis of tumors, and prognosis of breast cancer, so together with MRI data, we coordinate four common types of molecular typing data in breast cancer treatment to construct a multi-modal fusion model to predict whether axillary lymph nodes could achieve pCR. Our experiments show that the proposed multi-modal fusion model outperforms the predictive model with only MRI data.

In order to train and evaluate the proposed two-step lesion segmentation method and the multi-model fusion model, we collected 361 breast cancer samples from two hospitals: 246 samples from Guangdong Provincial People's Hospital using the Philips Achieva 1.5 T MRI system, and 115 samples from Henan Renmin Hospital using the Discovery MR750 3.0 T MRI system. Each sample comes with DCE-MRI imaging and molecular typing data, and each DCE-MRI image is labeled and verified by radiologists with more than 5 years of breast cancer experience.

In this paper, we make the following three contributions: First, we propose a two-step lesion segmentation method to extract breast cancer lesion regions from DCE-MRI images. In the model training, considering the different sources of DCE-MRI images, we apply a simple histogram matching method to improve the model

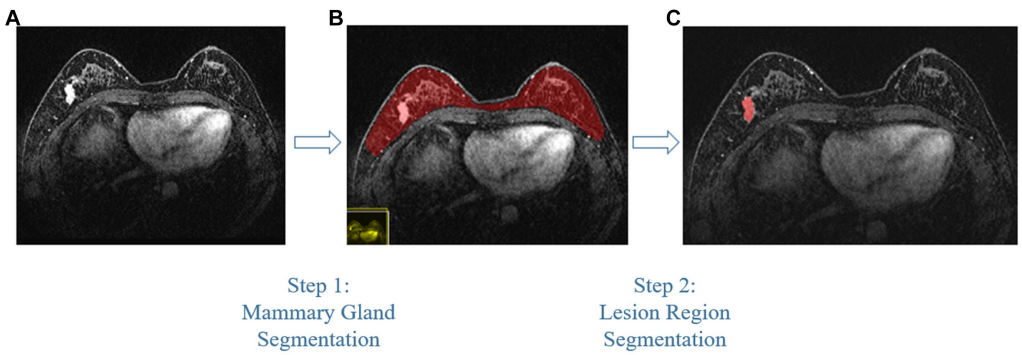

FIGURE 1
The proposed two-step breast cancer lesion segmentation method. **(A)** is a DCE-MRI image sample for breast cancer diagnosis, which contains irrelevant regions, such as the heart; **(B)** shows the segmented mammary gland region in red; **(C)** shows the breast cancer lesion region in red.

transferability. Second, we propose a multi-modal (i.e., segmented DCE-MRI image and molecular typing data) fusion model to predict the probability of axillary lymph nodes achieving pCR after patients receive neoadjuvant therapy. Finally, we evaluate our model through extensive ablation studies and experiments on a collected breast cancer dataset, and we show the promising performance of the proposed method.

The studies involving human participants were reviewed and approved by the Ethics Board of Guangdong Provincial People's Hospital and the Ethics Board of Henan Renmin Hospital. Written informed consent to participate in this study was provided by the participants.

2 Related works

2.1 Convolutional neural network

Convolutional neural networks (CNN) have achieved great success in medical imaging analysis. CNN was first introduced to process medical images by Lo et al. (15), and with the rapid development of CNN (16, 17), it has been considered one of the most effective methods to process medical images. ResNet (18), as one of the most classic CNNs, is widely adopted in all kinds of neural networks; with 152 layers of networks, it outperformed other models in the ImageNet Large Scale Visual Recognition Challenge (ILSVRC) 2015 by a large margin. Compared with AlexNet (16) and VGGNet (19), ResNet achieves smaller training errors and better testing accuracy, so in our proposed models, we chose ResNet as the backbone network.

2.2 Medical image segmentation

With the rapid development and popularization of medical imaging devices and technologies, including MRI, CT, PET, etc., the amount of medical images produced by these devices is increasing; it is reported that medical images account for one-fifth of all images generated worldwide. Thus, it is urgent to process medical images effectively, and medical image segmentation is the first important step in image analysis. Among all medical imaging technologies, MRI is the most widely adopted one. With MRI, professionals can vary the image contrast to show different image intensities to reflect the difference between soft tissue, parenchyma, and fluid (20, 21).

With the assistance of CNN, various medical image segmentation methods have been developed. In 2015, FCN (9) was proposed to implement pixel-level classification to solve the semantic segmentation problem; it accepts images of arbitrary sizes. FCN was one of the first deep learning techniques that were applied to medical image processing, but the segmentation performance is not satisfactory. Based on FCN, Olaf et al. introduced U-Net (10) for cell image segmentation; its surprising performance soon made it a standard backbone network. Later, 3D U-Net (22), V-Net (23), Res-UNet (24), and other variants of U-Net (25–30) were proposed. Aside from FCN and U-Net, Recurrent Neural Networks (RNNs) are also utilized for medical image segmentation (31, 32).

2.3 Pathologic complete response prediction

Over the last decade, many methods have been developed in academia to predict pCR, including radiomics, machine learning, and deep learning. In radiomics, pre-designed features are extracted to build a predictive model, but these pre-designed features are complex (33). Traditional machine learning methods such as SVM and AdaBoost also need well-designed features for prediction. In (34), 13,950 imaging features are extracted from CT and MRI data for machine learning. Compared with traditional radiomics and machine learning methods, the predictive model based on deep learning provides an end-to-end training and inferring method that can be directly applied to medical images (35). In our work, we use MRI images of breast cancer lesion regions, along with four types of molecular typing data commonly used in breast cancer treatment, to construct a multi-modal fusion model to predict whether or not the patient can achieve pCR.

3 Methods

In this section, we introduce the proposed method of processing MRI images of breast cancer with neural networks in order to predict whether axillary lymph node metastasis in breast cancer could achieve pCR after patients receive neoadjuvant therapy. We have divided this section into two parts: the first part gives details on how we extract the breast cancer lesion region from a common DCE-MRI breast cancer image; the second part introduces the multi-modal fusion model for pCR prediction.

3.1 Breast cancer lesion segmentation

As introduced in Section 1, and referring to Figure 1A, a common DCE-MRI image for breast cancer diagnosis contains a large amount of information that is irrelevant, so we needed to extract only the concerned lesion region for later processing in order to achieve better performance. Another notable reason for breast cancer lesion segmentation is that there is similar imaging intensity in the heart region in DCE-MRI images, as shown in Figure 2, so it is preferable to remove the heart region in order to reduce the probability of false positives. In the following, we elaborated on the proposed two-step lesion segmentation method to extract breast cancer lesion regions based on nnUNet and introduced a simple histogram matching method to augment the training samples in order to improve the model transferability between different centers.

3.1.1 Backbone network for image segmentation

As the DCE-MRI data collected for training is three-dimensional, we chose nnUNet (12) as the backbone network for the breast cancer lesion segmentation task. We specified the nnUNet as follows:

3.1.1.1 Pre-processing

Re-sampling and normalization were implemented at this stage. As the spatial resolution of each MRI image varied, which means one pixel of the image may represent a different size of physical space, the

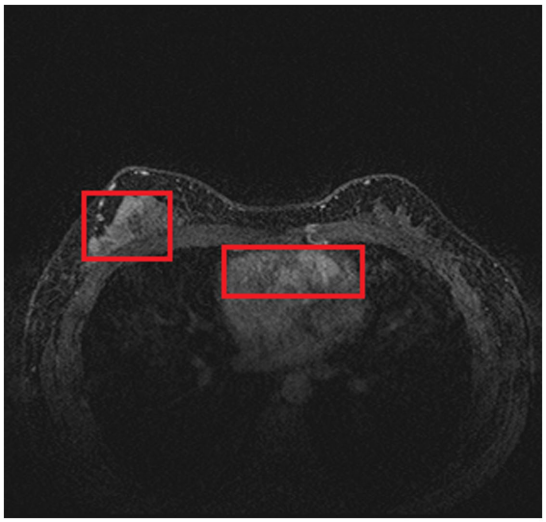

FIGURE 2
Two red rectangles show similar imaging intensity in the breast and heart regions.

MRI image needs to be re-sampled according to the median of the spatial resolution of all data. Z-score normalization was done independently for each patient's imaging data.

Data augmentation was also implemented. Augmentation techniques include random rotation, random scaling, random elastic transformation, gamma correction, and inversion.

3.1.1.2 Loss function

During training, we utilized the Cross-entropy loss and the Dice loss as follows:

$$L_{total} = L_{dice} + L_{ce} \tag{1}$$

where the Cross-entropy loss L_{ce} is defined as follows:

$$L_{ce} = -\frac{1}{N}\sum_{i}\sum_{k}^{K} v_{ik}\log\left(u_{ik}\right) \tag{2}$$

Dice loss was first introduced in (23) to solve the imbalance between positive and negative samples. Dice loss is different from Cross-entropy loss: it helps minimize segmentation error and obtain more stable segmentation performance (36). The Dice loss equation is as follows:

$$L_{dice} = -\frac{2}{|K|}\sum_{k\in K}\frac{\sum_{i\in \mathrm{I}} u_i^k v_i^k}{\sum_{i\in I} u_i^k + \sum_{i\in \mathrm{I}} v_i^k} \tag{3}$$

In Eqs. (2) and (3), u is the model's predictive probability, v is the ground truth one-hot code, K is the number of classes, and I is the representation vector of the image. Empirically, Cross-entropy loss makes the model focus on the global representation, i.e., each pixel of the image, while Dice loss pays more attention to the positive region, so L_{total} takes advantage of both global and local information.

3.1.1.3 Inference

Image segmentation inference was then performed on patches of MRI images. An image was divided into patches with an overlap of *size/2* pixels, where *size* is the size of the stride. Due to the lack of neighbor information, the segmentation accuracy of the edges of each patch will be relatively lower, so when fusing the segmentation result for pixels along the edges, we decreased the weight of edge pixels while increasing the weight of pixels close to the center.

3.1.1.4 Post-processing

After obtaining a segmentation result, we found the largest connected contour and, in the meantime, neglected other smaller ones. This post-processing step can effectively reduce the occurrence of false positives.

3.1.2 Two-step lesion segmentation

In order to reduce the probability of false positives, we utilized a two-step lesion segmentation method to extract the breast cancer lesion region. As shown in Figure 1, given a DCE-MRI sample for breast cancer diagnosis, we first segmented the mammary gland region, based on which we then segmented the breast cancer lesion region.

3.1.2.1 Mammary gland segmentation

The pre-processing described in Section 3.1.1 was applied to the original DCE-MRI samples, and the backbone network, i.e., nnUNet, was utilized to implement the first step "mammary gland segmentation" task.

3.1.2.2 Breast cancer lesion segmentation

After getting the result from the first segmentation step, we continued to segment the breast cancer lesion region. The mammary gland region was pre-processed only by Z-score normalization and is fed to the second segmentation step. We used the same backbone network to implement the "breast cancer lesion segmentation" task.

The details of the training are explained in Section 4, and the performance of our proposed two-step lesion segmentation method is also shown in the following section.

3.1.3 Domain adaptation

As our dataset was collected from two different centers, there will inevitably be a model transfer issue when training on samples from one center and testing on another. This is a common issue in medical image analysis because different medical imaging devices with different imaging protocols, methods, and different operators produce MRI images that vary in resolution, quality, etc.; therefore, many methods have been proposed to mitigate this issue (13, 37, 38). With respect to the specific differences between DCE-MRI samples, we designed a domain adaptation method, i.e., simple histogram matching (13), to improve the transferability of the model. Another advantage of histogram matching is that it only requires the gray-level distribution of the DCE-MRI images; thus, it does not reveal any personal information about the patient.

3.1.3.1 Histogram matching

At this point, we applied a simple histogram matching method (13) to augment training samples in order to improve transferability. More specifically, we introduced the gray-level distribution to augment training samples, each of which was augmented by matching the gray-level histogram computed with samples from other centers. The histogram matching is implemented as follows:

$$S_k = \frac{L-1}{M*N}\sum_{j=0}^{k} n_j * k = 0,1,2\ldots,L-1 \quad (4)$$

where L is the maximum gray-level value of the target histogram, M and N are the width and height of the image, and n_j is the gray-level value of pixel j.

As for the segmentation task, we first implemented the mammary gland segmentation without histogram matching. We then computed a gray-level histogram for each sample in the test dataset (in our experiment, samples from Henan Renmin Hospital are used as the test dataset) and then applied histogram matching to each sample in the training dataset (in our experiment, samples from Guangdong Provincial People's Hospital are used as the training dataset) with a randomly selected gray-level histogram from the test dataset. After the training dataset was augmented, it was fed to nnUNet for breast cancer lesion segmentation training.

3.2 Pathologic complete response prediction

Among all treatments for breast cancer, NAC is emerging as a new and effective method. As introduced in Section 1, utilizing imaging examination as a non-invasive method, together with four types of molecular typing data commonly used in breast cancer treatment, we proposed a multi-modal fusion model to predict whether axillary lymph nodes could achieve pCR after patients receive NAC.

3.2.1 Multi-modal fusion

Although one can use the MRI data of the breast cancer lesion to directly predict the probability of pCR after neoadjuvant therapy, it has been proven that immunohistochemical detection can also help in breast cancer prognosis (14). Thus, we propose to utilize common types of molecular typing data extracted by immunohistochemical detection of breast cancer. More specifically, we chose the following four common types of molecular typing data in breast cancer treatment: Human Epidermal Growth Factor Receptor 2 (HER2), Estrogen Receptor (ER), Progesterone Receptor (PR), and Ki-67.

HER2 protein is negative in normal breast tissue, and the amplification of HER2 is highly related to the growth, proliferation, transfer, and invasion of tumor cells; thus, it can be treated as one of the prognostic indicators of clinical treatment monitoring. ER and PR are nuclear hormone receptors; the expression of ER/PR indicates that tumor cells retain the characteristics of hormone-dependent growth and is significant in the prognosis judgment of breast cancer. Ki-67 is a monoclonal antibody; high expression of Ki-67 indicates a poor prognosis.

In our work, we used the above four types of molecular typing data, together with a DCE-MRI image of breast cancer lesions, to train the multi-modal (i.e., text and image) fusion model to predict pCR.

3.2.2 Network structure

We used conventional ResNet (18) as the backbone network to construct the prediction model as a common practice; more specifically, ResNet34 was selected, and we justify this choice in Section 4. The network structure is shown in Figure 3:

As shown in Figure 3, non-imaging features and MRI data were processed by two separate network branches. The molecular

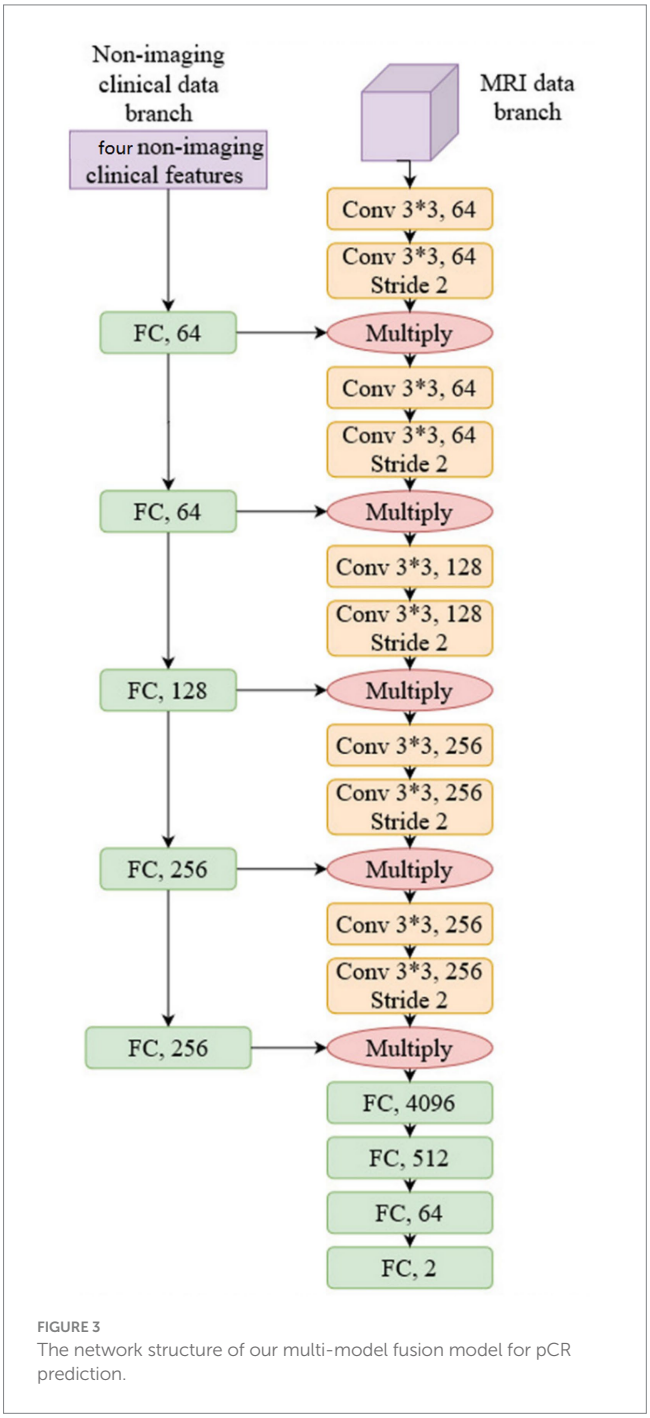

FIGURE 3
The network structure of our multi-model fusion model for pCR prediction.

typing data was processed by five Fully Connected (FC) layers, while the MRI image was processed by five convolutional network layers. It should be noted that the output of each FC layer in the non-imaging clinical data branch is fused with the output of each CNN layer in the MRI data branch by multiplication. This structure balances the weight of non-imaging data and MRI data to compute the model representation and makes the model utilize both molecular typing data and a DCE-MRI image of a breast cancer lesion to predict pCR. The proposed network is trained by the conventional Cross-entropy loss function.

4 Experiments and analysis

4.1 Experiment setting

4.1.1 Dataset

In our work, we used DCE-MRI data for breast cancer lesion segmentation and pCR prediction. DCE-MRI can provide a high-quality image for soft tissues with better quality of blood flow around the lesion region, which facilitates higher accuracy and earlier detection in breast cancer diagnosis. Therefore, DCE-MRI is the most widely adopted imaging method in breast cancer diagnosis and treatment.

In order to train and test the proposed method, we collected 361 breast cancer samples from two hospitals: 246 samples from Guangdong Provincial People's Hospital and 115 samples from Henan Renmin Hospital. Each DCE-MRI image was labeled and verified by professionals. A labeled DCE-MRI sample is shown in Figure 4. We also collected the four types of molecular typing data commonly used in breast cancer treatment: HER2, ER, PR, and Ki-67, for each of the 361 samples.

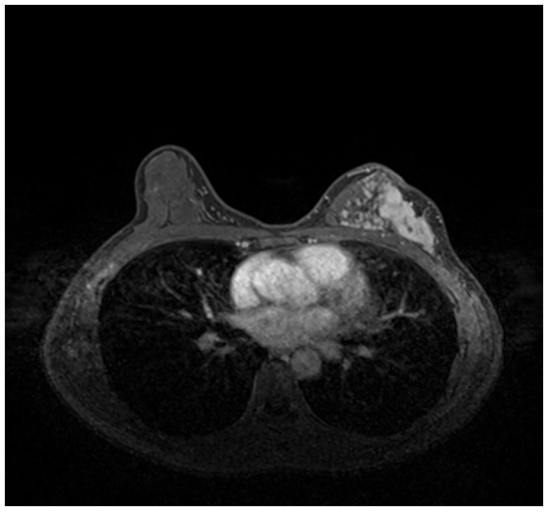

FIGURE 4
An example of the 361 labeled DCE-MRI samples in our dataset.

4.1.2 Network training setup

For breast cancer lesion segmentation, the network was trained by Adam optimizer (39) with a learning rate of 3e-4 for 1,000 epochs. The learning rate was decayed by 5 if the decrease in the average training loss over 30 epochs was less than 5e-3. The model convergence criteria are: the decrease in the average training loss over 60 epochs must be less than 5e-3, or the learning rate must be less than 1e-6. For pCR prediction, after acquiring the segmentation result, the breast cancer lesion images were resampled to a size of 128*128*128. The initial learning rate was set to 1e-4, and the network was trained for 200 epochs.

4.2 Ablation studies

4.2.1 Effect of histogram matching

As introduced in Section 3.1.3, we used a simple histogram matching method to augment the training dataset in order to improve the transferability of the model. Here, we conducted an ablation study to show the effect of this domain adaptation method. As shown in Figure 5, for an MRI image (a) from the training dataset (i.e., samples from Guangdong Provincial People's Hospital), we randomly picked a target image (b) from Henan Renmin Hospital and applied gray-level histogram matching to the original training image so as to obtain an augmented sample (c).

We show the results of the proposed segmentation model with and without domain adaptation in Table 1. It is apparent that after applying the proposed domain adaptation method, i.e., histogram matching, the segmentation IoU increased by 7%. We also note that the training curve oscillates more than it does without histogram matching, as shown in Figure 6. This is because the gray-level distribution of the target dataset is introduced into the training samples.

4.2.2 ResNet depth

Normally, a deeper network implies stronger modeling ability; however, this is not always true in medical image processing models because of the higher risk of overfitting. We conducted an ablation study to show how the depth of the ResNet affects the model's performance. We trained the pCR prediction model with conventional ResNet18, ResNet34, and ResNet50, respectively, and the result is shown in Table 2. We can see that the performance does not change much between models with different ResNet depths. Based on this, we chose ResNet43 in the experiments that follow.

4.2.3 Effect of the surrounding mammary gland

The performance of the prediction model is directly affected by the correlation between the input data and the prediction target. As for pCR

TABLE 1 Performance of the breast cancer lesion region segmentation task with and without domain adaptation.

Task	Domain Adaptation	Dice	IoU
Breast cancer lesion region segmentation	No	0.78	0.65
	Yes	0.83	0.72

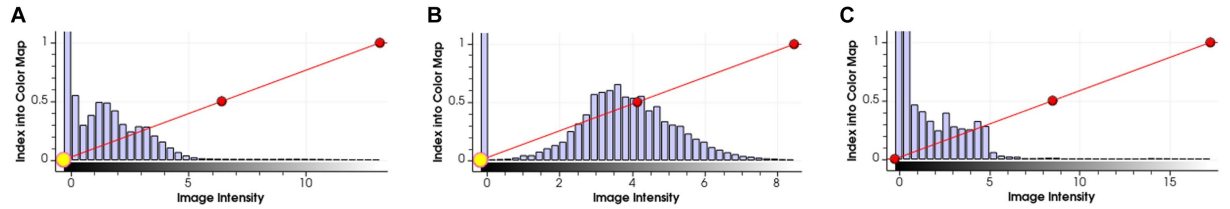

FIGURE 5
Example of gray-level histogram matching. **(A)** is a sample from Guangdong Provincial People's Hospital; **(B)** is a randomly picked sample from Henan Renmin Hospital; and **(C)** is the result of applying histogram matching to **(A)**.

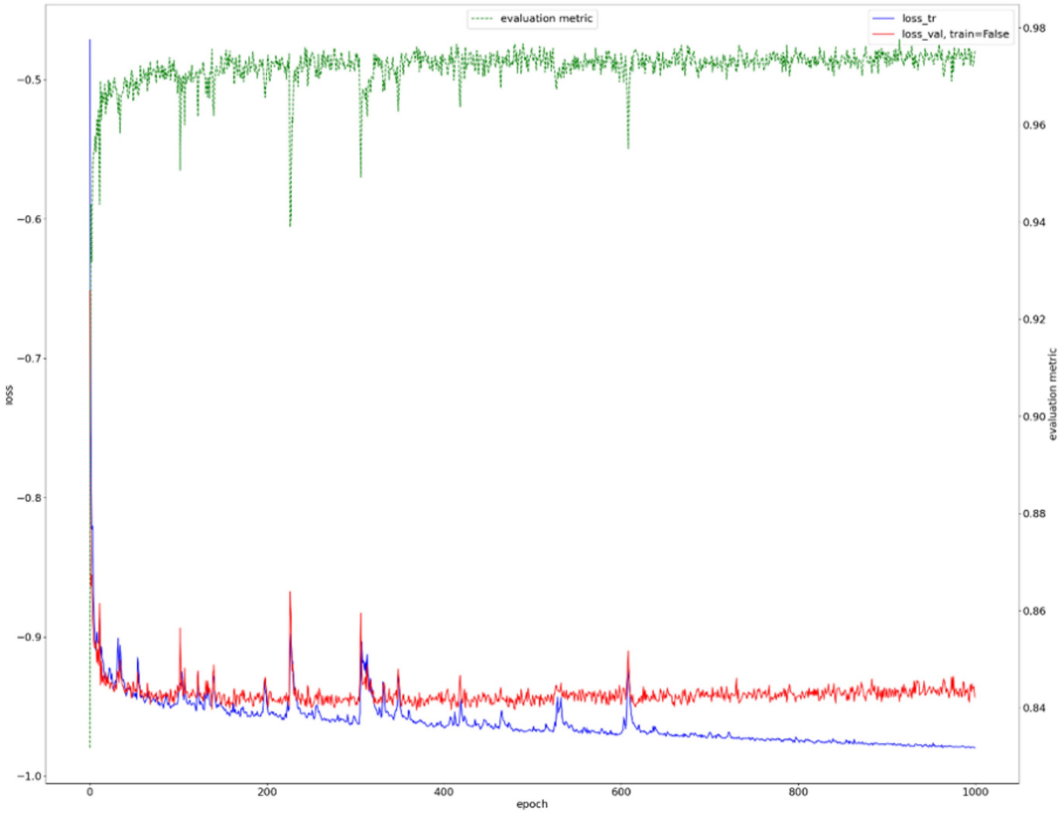

FIGURE 6
Training curve of mammary gland segmentation.

TABLE 2 Result of pCR prediction with ResNet of different depths.

Task	ResNet depth	Accuracy	AUC
pCR prediction	ResNet18	0.70	0.68
	ResNet34	0.72	0.69
	ResNet50	0.71	0.69

prediction tasks, as pointed out in (40), the mammary gland provides certain information when determining preoperative lymph node metastasis in breast cancer. Also, as pointed out by professionals, the MRI data of the mammary gland may contain abnormal information that may be related to patient prognosis. Thus, we conducted an ablation to test the influence of the surrounding mammary gland in predicting pCR. After acquiring the segmentation result of the breast cancer lesion, we expanded the periphery by using an expansion algorithm with kernels of three sizes, i.e., 5 pixels, 10 pixels, and 15 pixels. An example is shown in Figure 7. We used a circular expansion kernel in order to maintain the original shape of the segmented lesion. Then the expanded DCE-MRI data of the lesion region was used to train the proposed pCR prediction model, and the result is shown in Table 3. It is quite obvious that the surrounding gland information does not help at all in pCR prediction, so we used the segmented lesion region directly for pCR prediction in the following experiments.

4.2.4 Effects of multi-modal fusion

We also conducted an ablation study to show the effect of multi-modal fusion. We present the performance of pCR prediction with only DCE-MRI data of the segmented lesion and with both DCE-MRI data and four common types of molecular typing data (i.e.,

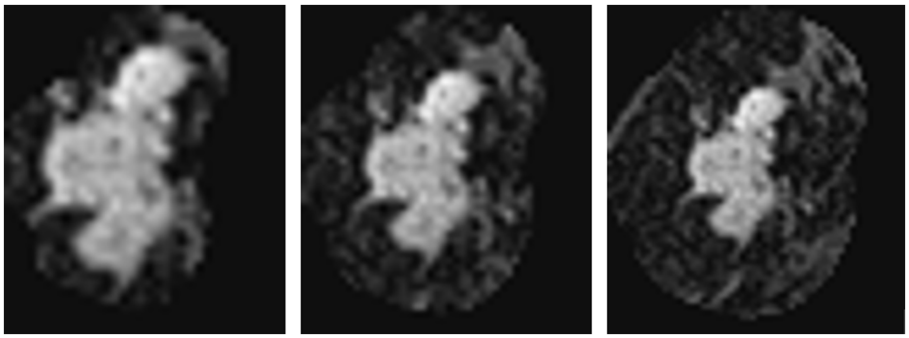

FIGURE 7
Example of expanding a segmented lesion region by 5, 10 and 15 pixels, respectively, from left to right.

TABLE 3 Result of pCR prediction with different expanding kernel sizes.

Task	Kernel size (pixel)	Accuracy	AUC
pCR prediction	-	0.72	0.69
	5	0.42	0.60
	10	0.57	0.77
	15	0.42	0.76

TABLE 4 Result of pCR prediction with DCE-MRI data only and with multi-modal fusion.

Task	Model	Accuracy	AUC
pCR prediction	ResNet34	0.72	0.69
	Multi-modal fusion	0.85	0.81

multi-modal fusion) in Table 4. It is noted that the multi-modal fusion model provides a 13% increase in accuracy, which proves that the proposed model is effective.

4.3 Experiment results

In this section, we present the results of the two-step lesion segmentation and pCR prediction. It should be noted that the experiments were conducted according to the method introduced in Section 3, and as explained in Section 4.2, the experiments were performed with domain adaptation, with ResNet34, without the surrounding mammary gland data of the lesion, and with multi-modal fusion.

4.3.1 Two-step lesion segmentation

4.3.1.1 Mammary gland segmentation.

The training curve is shown in Figure 6 and examples of segmented mammary glands are shown in Figure 8.

The performance of the proposed method for mammary gland segmentation is shown in Table 5. We achieved 93% IoU in the first segmentation task.

4.3.1.2 Breast cancer lesion segmentation.

Results from the first segmentation step, for example, Figure 8B, were used as input for the second segmentation step.

TABLE 5 Performance of the two-step lesion segmentation task.

Task	Dice	IoU	HD95
Mammary gland segmentation	0.96 ± 0.01	0.93 ± 0.02	3.73 ± 2.02
Breast cancer lesion segmentation	0.83	0.72	-

The training curve is shown in Figure 9, and the performance of the proposed method for breast cancer lesion segmentation is shown in Table 5.

4.3.2 Pathologic complete response prediction

We used a multi-modal fusion model to predict whether axillary lymph nodes could achieve pCR after patients receive neoadjuvant therapy. DCE-MRI data of the segmented breast cancer lesion region and four types of molecular typing data commonly used in breast cancer treatment (i.e., HER2, ER, PR, and Ki-67) were utilized as input to the proposed multi-modal fusion model. The performance of pCR prediction by the proposed model is shown in Table 4. The multi-modal fusion model achieved an accuracy of 85%, which is significantly high for pCR prediction of breast cancer with only non-invasive methods.

In addition, we performed McNemar's test of the two pCR prediction methods, one with DCE-MRI data only and the other with multi-modal fusion. We also performed a Chi-square goodness-of-fit test between each of the two methods and the ground truth. We randomly selected 200 samples to test each of the two methods, and the statistics of the pCR prediction results are shown in Tables 6, 7, respectively. The McNemar's test showed that there exists a statistical difference between the two pCR prediction methods, while the Chi-square goodness-of-fit test revealed that the pCR prediction result by the multi-modal fusion method is more consistent with the ground truth distribution.

5 Conclusion

In this paper, we presented a two-step lesion segmentation method to extract breast cancer lesion regions from DCE-MRI images, and in this process, we applied a simple histogram matching method to improve the transferability of the model. Then, we proposed a multi-modal (i.e., segmented DCE-MRI image and molecular typing data) fusion model to predict the probability of

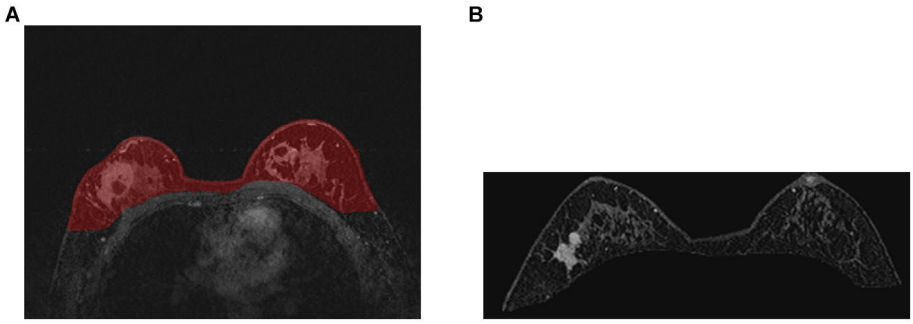

FIGURE 8
Examples of segmented mammary gland. **(A)** shows the mammary gland region in red, **(B)** shows a segmented mammary gland.

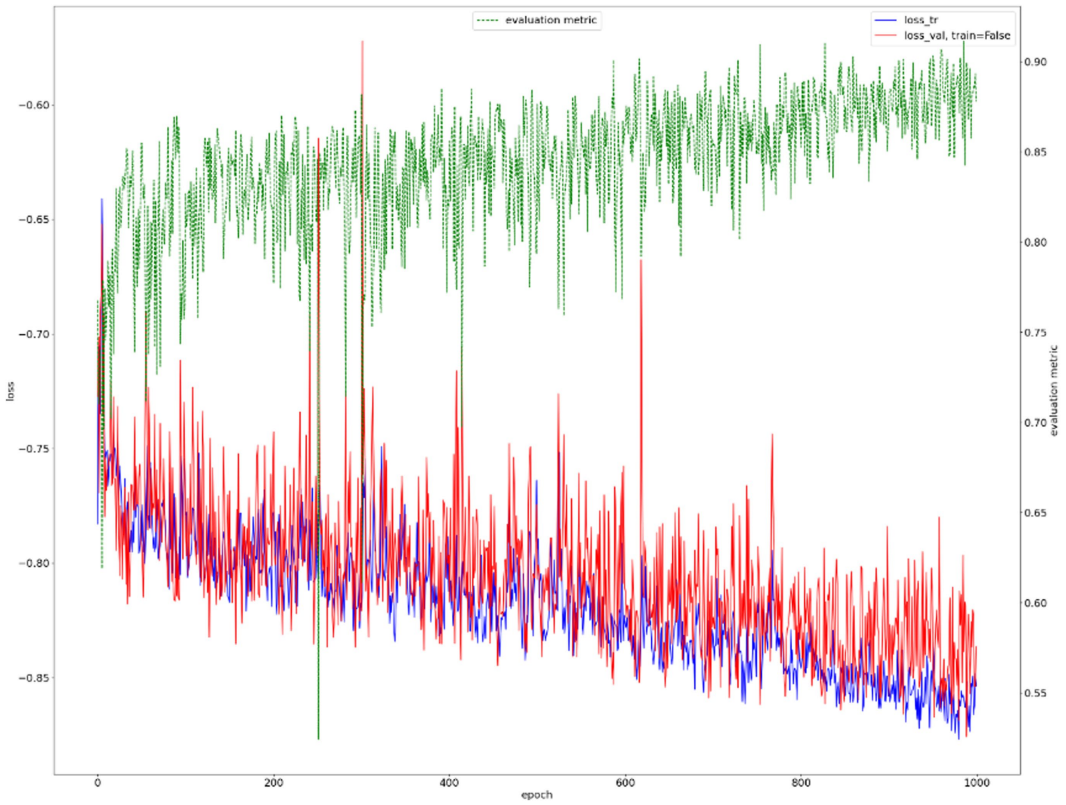

FIGURE 9
Training curve of breast cancer lesion segmentation.

axillary lymph nodes achieving pCR after patients receive NAC. We collected 361 breast cancer samples from two hospitals to train and test the proposed segmentation method and the multi-modal fusion model. We demonstrated that our method achieves 93 and 72% IoU in mammary gland segmentation and breast cancer lesion segmentation tasks, respectively. We also showed that our multi-modal fusion model is effective and reaches 85% accuracy in pCR prediction using only data collected in a non-invasive manner. Although the IoU of breast cancer lesion segmentation is not very high (72%), it was used in the multi-modal fusion model and reached 85% accuracy in pCR prediction. This suggests that the presented method can be used for the prediction of treatment responses in breast cancer.

5.1 Limitations

The 361 breast cancer samples we collected for this study only include patients with solid tumors; therefore, this study focuses on lesion region segmentation of solid tumors and cannot be directly applied to other types of lesions, e.g., non-mass lesions or different breast parenchyma compositions. If the proposed

TABLE 6 Result of McNemar's test of two pCR prediction methods.

Prediction with DCE-MRI	Prediction with Multi-modal		Total	χ^2	p
	pCR	non-pCR			
pCR	63	1	64	9.31	0.0023
non-pCR	12	124	136		
Total	75	125	200		

TABLE 7 Result of the Chi-square goodness-of-fit test between each of the two pCR prediction methods and the ground truth, respectively.

	pCR	non-pCR	χ^2	p
Prediction with DCE-MRI	64	136	7.43	0.0064
Prediction with Multi-modal	75	125	1.32	0.2509
Ground truth	83	117		

method is to be used in other cases, it needs to be re-trained with enough specific data samples. Additionally, the proposed pCR prediction method requires a two-step process where we need to segment the breast cancer lesion from the DCE-MRI image, only then can we perform the final pCR prediction with the multi-model fusion model.

Data availability statement

The data analyzed in this study is subject to the following licenses/restrictions: The image and clinical medical data used to support the findings of this study are restricted by the Ethics Board of Guangdong Provincial People's Hospital in order to protect patient privacy. Data are available from Gang Fang, gangf@gzhu.edu.cn for researchers who meet the criteria for access to confidential data. Requests to access these datasets should be directed to Gang Fang, gangf@gzhu.edu.cn.

Ethics statement

The studies involving human participants were reviewed and approved by the Ethics Board of Guangdong Provincial People's Hospital and Ethics Board of Henan Renmin Hospital. Written informed consent to participate in this study was provided by the participants.

Author contributions

GF designed and supervised the study. YL carried out the whole study. ZC assisted the whole study, conducted extra experiments. JC and ZS wrote the code for the study. All authors contributed to the article and approved the submitted version.

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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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Prognostic analysis of cT1-3N1M0 breast cancer patients who have responded to neoadjuvant therapy undergoing various axillary surgery and breast surgery based on propensity score matching and competitive risk model

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Background: Sentinel lymph node biopsy (SLNB) in breast cancer patients with positive clinical axillary lymph nodes (cN1+) remains a topic of controversy. The aim of this study is to assess the influence of various axillary and breast surgery approaches on the survival of cN1+ breast cancer patients who have responded positively to neoadjuvant therapy (NAT).

Methods: Patients diagnosed with pathologically confirmed invasive ductal carcinoma of breast between 2010 and 2020 were identified from the Surveillance, Epidemiology, and End Results (SEER) database. To mitigate confounding bias, propensity score matching (PSM) analysis was employed. Prognostic factors for both overall survival (OS) and breast cancer-specific survival (BCSS) were evaluated through COX regression risk analysis. Survival curves were generated using the Kaplan-Meier method. Furthermore, cumulative incidence and independent prognostic factors were assessed using a competing risk model.

Results: The PSM analysis matched 4,890 patients. Overall survival (OS) and BCSS were slightly worse in the axillary lymph node dissection (ALND) group (HR = 1.10, 95% CI 0.91-1.31, p = 0.322 vs. HR = 1.06, 95% CI 0.87-1.29, p = 0.545). The mastectomy (MAST) group exhibited significantly worse OS and BCSS outcomes (HR = 1.25, 95% CI 1.04-1.50, p = 0.018 vs. HR = 1.37, 95% CI 1.12-1.68, p = 0.002). The combination of different axillary and breast surgery did not significantly affect OS (p = 0.083) but did have a significant impact on BCSS (p = 0.019). Competing risk model analysis revealed no significant difference in the cumulative incidence of breast cancer-specific death (BCSD) in the axillary surgery group (Grey's test, p = 0.232), but it showed a higher cumulative incidence of BCSD in the MAST group (Grey's test, p = 0.001). Multivariate

analysis demonstrated that age ≥ 70 years, black race, T3 stage, ER-negative expression, HER2-negative expression, and MAST were independent prognostic risk factors for both OS and BCSS (all $p < 0.05$).

Conclusion: For cN1+ breast cancer patients who respond positive to NAT, the optimal surgical approach is combining breast-conserving surgery (BCS) with SLNB. This procedure improves quality of life and long-term survival outcomes.

KEYWORDS

neoadjuvant therapy, sentinel lymph node biopsy, breast-conserving surgery, propensity score matching, SEER database

Introduction

To assess the prognosis of breast cancer patients and guide their treatment, it is crucial to determine the status of axillary lymph nodes (ALN). For patients with early-stage breast cancer who have negative ALN and present clinically low risk, guidelines recommend the use of sentinel lymph node biopsy (SLNB) (1–3). When sentinel lymph node (SLN) shows no evidence of tumor, axillary lymph node dissection (ALND) can be omitted, streamlining surgical procedures, reducing hospitalization duration, and minimizing complications like upper limb lymphedema and dysfunction, all without compromising survival (4, 5). In patients with early-stage breast cancer where ALN are negative and clinical risk is low, even if SLN indicates the presence of 1 or 2 macro metastases, ALND can still be avoided by opting for breast-conserving surgery (BCS) combined with radiotherapy (RT) (5).

In order to preserve both the axillary and breast regions, neoadjuvant therapy (NAT) is typically administered as the initial treatment for cN1+ breast cancer, particularly in patients with HER-2-positive breast cancer and triple-negative breast cancer. Concurrently, the use of precise *in vivo* drug sensitivity testing can identify high-risk groups for escalated treatment, ultimately enhancing patient prognosis (1, 2, 6–10). After receiving NAT, the percentage of breast cancer patients with clinically positive lymph nodes (cN1+) that transitioned to clinically negative lymph nodes (cN0) was as high as 46% to 91%. Consideration of SLNB is warranted if positively identified nodes with a locator clip are excised during the operation, or if SLN is identified using a dual tracer and at least three SLN are detected. With negative test results, 30.3% to 56.5% of patients can avoid ALND (7, 11–18).

However, cN1+ patients who respond positive to NAT may face challenges in preserving both the breast and axillary regions due to various factors (12, 19–24). Firstly, several factors can obstruct lymphatic drainage in the breast, affecting the detection of SLN, such as tumor cell necrosis, non-bacterial inflammation, and lymphatic fibrosis. Second, tumor regression may occur in an irregular pattern, resulting in unacceptable false-negative and margin-positive rates. Additionally, a higher false-negative rate (8.4%-17%) is observed in patients who do not use dual tracers or marker clips to locate the SLN. Lastly, there is a lack of robust long-term survival data. While SLNB is performed for cN1+ breast cancer patients who respond positive to NAT, if the SLNs are positive, the standard treatment still involves supplementary ALND and local RT (1, 2, 6).

Although cN1+ patients who respond positive to NAT may encounter various challenges, including different degrees of false negative rates, performing SLNB remains an acceptable approach to avoid ALND (1, 2, 6, 11–17, 19, 20). However, it's worth noting that the majority of studies in this area are non-randomized, single-center, and characterized by small sample sizes, limited biopsy techniques, short follow-up periods, and a lack of long-term survival data. Consequently, the experimental conclusions need further validation. The SEER program, hosted by the National Cancer Institute, encompasses nearly half of the U.S. population and provides invaluable research data for the prevention and management of cancer patients. In light of this, the present study retrospectively analyzed patients with cT1-3N1M0 breast non-specific infiltrating duct carcinoma who responded positive to NAT between 2010 and 2020 in the SEER database. The objective was to investigate the impact of various axillary and breast surgical approaches on survival, thereby furnishing critical clinical evidence for the reasonable selection of axillary and breast surgery.

Materials and methods

Data collection

In this study, the SEER database data were obtained by searching the SEER database [Incidence-SEER Research Data, 17 Registries, Nov 2022 Sub (2000–2020)] with software SEER*Stat v8.4.1.2 (download from https://seer.cancer.gov/data-software/)

and account numbers (access code is: #89bMxdH, obtained from https://seer.cancer.gov/data/access.html). The SEER data obtained did not contain any personally identifiable patient information. As a result, this study was exempt from ethical review by the Ethics Committee of the Affiliated Sanming First Hospital of Fujian Medical University.

Patient cohort

Patients included in this study were females with a confirmed pathological diagnosis of nonspecific infiltrating duct carcinoma of the breast (ICD-0-3 = 8500/3) from 2010 to 2020. The collected data encompassed various factors such as age, marital status, race, laterality, histological grade, TNM classification, molecular subtypes, primary cancer details, records of radiotherapy and chemotherapy, surgical records, count of regional lymph node examinations, treatment sequencing, follow-up duration, survival status, and cause of death. In accordance with AJCC 8th edition guidelines, data for T1, T2, T3, and N1 patients were integrated from 2010 to 2020, and M0(i+) was considered as M0. The exclusion criteria consisted of the following: [1] absence of chemotherapy records, non-NAT, and ineffectiveness in NAT; [2] non-primary cancer; [3] survival data is 0; [4] unknown surgical methods and count of regional lymph node examinations; [5] indeterminate or missing information regarding laterality, ER, PR, HER2, and molecular subtypes; and [6] age < 18. Figure 1 illustrates the detailed design process of this study.

The age variable was stratified into four groups based on the onset of breast cancer: < 35, 35-54, 55-69, and ≥ 70. Marital status was categorized into three groups: married, single, and other. Race was divided into three groups: white, black, and other. Due to a substantial amount of data with unknown histological grading, this subset was retained and treated as a separate variable, further divided into three groups: grade I-II, grade III-IV, and unknown. Given that the SEER database did not distinguish between specific axillary procedures, making it difficult to differentiate between SLNB and ALND, this study followed the axillary dissection definition for breast cancer as outlined by AJCC and supported by relevant literature (25, 26). In this study, regional lymph node detection numbering between 1-5 was classified as SLNB, while detection of 6 or more nodes was classified as ALND. Additionally, following guidelines provided by the SEER database Breast Surgery Code Manual, codes 20-24 were identified as indicative of BCS for breast cancer, whereas codes 30 and 40-75 were associated with MAST procedures for breast cancer. In order to provide more tailored guidance for clinical practice, the study conducted a survival analysis of combined axillary and breast surgeries (BCS +SLNB, BCS+ALND, MAST+SLNB, and MAST+ALND).

Observation indicators

The observational analysis in this study focused on several key indicators, including overall survival (OS), breast cancer-specific survival (BCSS), breast cancer-specific death (BCSD), and death from other causes (OCSD). OS was defined as the duration from diagnosis to either death from any cause or the last follow-up. BCSS and BCSD measured the period from diagnosis to death attributed specifically to breast cancer or until the last follow-up. OCSD

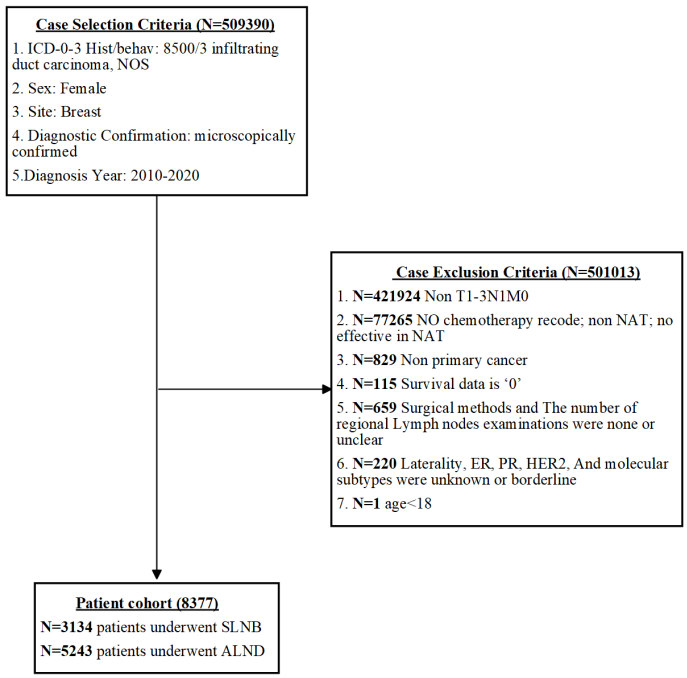

FIGURE 1
The screening process of the patient cohort in this study.

denoted the interval between diagnosis and death resulting from reasons other than breast cancer.

Statistical analysis

In this study, all variables were categorical and expressed as percentages. Chi-square tests were employed to assess differences between groups of variables. Propensity score matching (PSM) analysis was conducted using the R package "MatchIt". The nearest neighbor matching algorithm was implemented with a matching ratio of 1:1 and a caliper value of 0.001. This aimed to balance variables that exhibited significant differences between the SLNB group and the ALND group, thereby reducing potential confounding biases in this retrospective study. Kaplan-Meier survival analysis, facilitated by the R packages "survival" and "Survminer", was utilized to estimate survival probabilities and generate survival curves. Inter-group comparisons were conducted using the log-rank test. Univariate and multivariate Cox proportional hazard regression models were applied to analyze independent prognostic risk factors for OS and BCSS, with results presented in forest plots. The R package "cmprsk" was utilized for competing risk model analysis to mitigate estimation bias related to deaths from other causes. The Fine-Gray test was employed to obtain cumulative incidence data for different axillary and breast surgeries. A multivariate analysis of the competitive risk model was performed using the R package "mstate". This facilitated the construction of a COX regression model and the creation of a nomogram. All statistical analyses were conducted using R Studio (R 2023.06.0 + 421, downloaded from https://posit.co/downloads/).A significance level of $p < 0.05$ was considered statistically meaningful.

Results

Patient clinicopathological characteristics

Before propensity score matching (PSM), a total of 8,377 eligible breast cancer patients were included, with 3,134 in the SLNB group and 5,243 in the ALND group. In comparison to the ALND group, the SLNB group exhibited higher incidences of left breast tumors (52.3%), unknown histological grade (58.0%), T1 staging (25.5%), ER-negative expression (39.9%), PR-negative expression (53.7%), HER2 positive expression (40.7%), HR +/HER2+ subtype (27.0%), and a higher proportion of BCS (48.8%), with all differences being statistically significant (all $p < 0.05$). After PSM, a total of 4,890 eligible breast cancer patients were included, with 2,445 in the SLNB group and 2,445 in the ALND group. After matching, there were no statistically significant differences between the two groups across all variables (all $p > 0.05$). This indicates a successful matching outcome. Detailed baseline characteristics of patients before and after PSM are presented in Table 1.

Survival analysis

During a median follow-up period of 32 months (ranging, 1-131 months), there were 215 deaths in the SLNB group, of which 185 (86.0%) were attributed to breast cancer. In the ALND group, there were 266 deaths, with 219 (82.3%) being due to breast cancer. Kaplan-Meier survival analysis revealed that for cT1-3N1M0 breast cancer patients, those treated with ALND demonstrated slightly lower OS and BCSS compared to those treated with SLNB. However, these differences did not reach statistical significance (HR=1.10, 95% CI 0.91-1.31, P=0.322 vs. HR=1.06, 95% CI 0.87-1.29, P=0.545) (Figures 2A, B). When comparing the MAST group to the BCS group, patients in the MAST group exhibited significantly worse OS and BCSS (HR=1.25, 95% CI 1.04-1.50, P=0.018 vs. HR=1.37, 95% CI 1.12-1.68, P=0.002) (Figures 2C, D).

There was no statistically significant difference in the impact of different combinations of axillary and breast surgeries (BCS+SLNB, BCS+ALND, MAST+SLNB, and MAST+ALND) on OS ($p = 0.083$) (Figure 3A). However, after excluding breast cancer-related deaths caused by other factors, it was observed that various combinations of axillary and breast surgeries did have a significant effect on BCSS. Specifically, MAST combined with ALND showed the poorest BCSS and this difference was statistically significant ($p = 0.019$) (Figure 3B). Additionally, the use of BCS+SLNB in combination with radiotherapy was associated with improved OS in cT1-3N1M0 breast cancer patients ($p = 0.038$) (Supplementary Figure S1A). Both BCS+SLNB and ALND combined with radiotherapy demonstrated improvements in BCSS ($p = 0.042$, $p = 0.031$) (Supplementary Figure S1B).

Univariate and multivariate Cox regression analysis

In the univariate Cox regression analysis, various factors including different age groups, marital status, race, histological grade, T stage, ER expression, PR expression, HER2 expression, molecular typing, and type of breast surgery were found to be significantly correlated with both OS and BCSS, establishing them as independent prognostic predictors (all $p < 0.05$). However, laterality, axillary surgery, and radiotherapy were not found to be associated with OS and BCSS (all $p > 0.05$) (Table 2). Following the removal of two collinear variables (molecular subtypes and combined axillary operation with breast operation), statistically significant variables identified in the univariate analysis were included in the multivariate Cox proportional risk regression model analysis, and a forest plot model was constructed. The results indicated that age ≥ 70, being of black race, T3 staging, ER-negative expression, HER2 negative expression, and undergoing mastectomy were identified as independent prognostic risk

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TABLE 1 The clinicopathological characteristics of patients before and after PSM.

Characteristics	Before PSM				After PSM			
	All patients (n=8377) N(%)	SLNB (n=3134) N(%)	ALND (n=5243) N(%)	P value	All patients (n=4890) N(%)	SLNB (n=2445) N(%)	ALND (n=2445) N(%)	P value
Age				0.134				0.349
<35	651 (7.8)	248 (7.9)	403 (7.7)		342 (7.0)	175 (7.2)	167 (6.8)	
35-54	4496 (53.7)	1631 (52.0)	2865 (54.6)		2660 (54.4)	1323 (54.1)	1337 (54.7)	
55-69	2645 (31.6)	1031 (32.9)	1614 (30.8)		1544 (31.6)	789 (32.3)	755 (30.9)	
>=70	585 (7.0)	224 (7.1)	361 (6.9)		344 (7.0)	158 (6.5)	186 (7.6)	
Marital status				0.094				0.426
Married	5004 (59.7)	1915 (61.1)	3089 (58.9)		3015 (61.7)	1529 (62.5)	1486 (60.8)	
Single	1748 (20.9)	619 (19.8)	1129 (21.5)		961 (19.7)	473 (19.3)	488 (20.0)	
Other	1625 (19.4)	600 (19.1)	1025 (19.5)		914 (18.7)	443 (18.1)	471 (19.3)	
Race				0.127				0.305
White	5914 (70.6)	2225 (71.0)	3689 (70.4)		3576 (73.1)	1806 (73.9)	1770 (72.4)	
Black	1266 (15.1)	444 (14.2)	822 (15.7)		670 (13.7)	335 (13.7)	335 (13.7)	
Other	1197 (14.3)	465 (14.8)	732 (14.0)		644 (13.2)	304 (12.4)	340 (13.9)	
Laterality				0.013				0.391
Left	4230 (50.5)	1638 (52.3)	2592 (49.4)		2541 (52.0)	1286 (52.6)	1255 (51.3)	
Right	4147 (49.5)	1496 (47.7)	2651 (50.6)		2349 (48.0)	1159 (47.4)	1190 (48.7)	
Grade				<0.001				0.535
I-II	1622 (19.4)	489 (15.6)	1133 (21.6)		830 (17.0)	408 (16.7)	422 (17.3)	
III-IV	2568 (30.7)	827 (26.4)	1741 (33.2)		1417 (29.0)	696 (28.5)	721 (29.5)	
Unknown	4187 (50.0)	1818 (58.0)	2369 (45.2)		2643 (54.0)	1341 (54.8)	1302 (53.3)	
T stage				0.003				0.993
T1	2043 (24.4)	798 (25.5)	1245 (23.7)		1172 (24.0)	585 (23.9)	587 (24.0)	
T2	4665 (55.7)	1771 (56.5)	2894 (55.2)		2831 (57.9)	1415 (57.9)	1416 (57.9)	
T3	1669 (19.9)	565 (18.0)	1104 (21.1)		887 (18.1)	445 (18.2)	442 (18.1)	
ER status				0.023				0.640
Positive	5163 (61.6)	1882 (60.1)	3281 (62.6)		2953 (60.4)	1485 (60.7)	1468 (60.0)	
Negative	3214 (38.4)	1252 (39.9)	1962 (37.4)		1937 (39.6)	960 (39.3)	977 (40.0)	
PR status				0.003				0.668
Positive	4057 (48.4)	1451 (46.3)	2606 (49.7)		2356 (48.2)	1170 (47.9)	1186 (48.5)	
Negative	4320 (51.6)	1683 (53.7)	2637 (50.3)		2534 (51.8)	1275 (52.1)	1259 (51.5)	
HER2 status				<0.001				0.062
Positive	3206 (38.3)	1277 (40.7)	1929 (36.8)		1945 (39.8)	940 (38.4)	1005 (41.1)	
Negative	5171 (61.7)	1857 (59.3)	3314 (63.2)		2945 (60.2)	1505 (61.6)	1440 (58.9)	
Breast subtype				<0.001				0.291
HR+/HER2+	2124 (25.4)	847 (27.0)	1277 (24.4)		1286 (26.3)	620 (25.4)	666 (27.2)	
HR+/HER2-	3240 (38.7)	1112 (35.5)	2128 (40.6)		1776 (36.3)	912 (37.3)	864 (35.3)	

(Continued)

TABLE 1 Continued

Characteristics	Before PSM				After PSM			
	All patients (n=8377) N(%)	SLNB (n=3134) N(%)	ALND (n=5243) N(%)	P value	All patients (n=4890) N(%)	SLNB (n=2445) N(%)	ALND (n=2445) N(%)	P value
HR-/HER2+	1082 (12.9)	430 (13.7)	652 (12.4)		659 (13.5)	320 (13.1)	339 (13.9)	
HR-/HER2-	1931 (23.1)	745 (23.8)	1186 (22.6)		1169 (23.9)	593 (24.3)	576 (23.6)	
Breast surgery				<0.001				0.300
BCS	3340 (39.9)	1528 (48.8)	1812 (34.6)		2147 (43.9)	1055 (43.1)	1092 (44.7)	
MAST	5037 (60.1)	1606 (51.2)	3431 (65.4)		2743 (56.1)	1390 (56.9)	1353 (55.3)	
Radiation				0.057				0.502
YES	6192 (73.9)	2354 (75.1)	3838 (73.2)		3723 (76.1)	1851 (75.7)	1872 (76.6)	
NO	2185 (26.1)	780 (24.9)	1405 (26.8)		1167 (23.9)	594 (24.3)	573 (23.4)	

PSM, propensity-score matching; SLNB, sentinel lymph node biopsy; ALND, axillary lymph node dissection; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; BCS, breast-conserving surgery; MAST, Mastectomy.

factors for both OS and BCSS, with all differences being statistically significant (all $p < 0.05$) (Table 3). Furthermore, having a marital status categorized as "other" emerged as an independent prognostic factor for overall survival (HR=1.27, 95% CI 1.01-1.59, p = 0.040). The forest plots depicting the results of the multivariate Cox regression models for both BCSS and OS can be found in Figure 4 and Supplementary Figure S2, respectively.

Competing risk model analysis

To mitigate the influence of non-breast cancer-related deaths on survival analysis, a competitive risk model was employed for the analysis. The results of the Fine-Gray test indicated no significant difference in the cumulative incidence of BCSD (Grey's test, $p = 0.619$) and OCSD (Grey's test, P=0.232) between the ALND

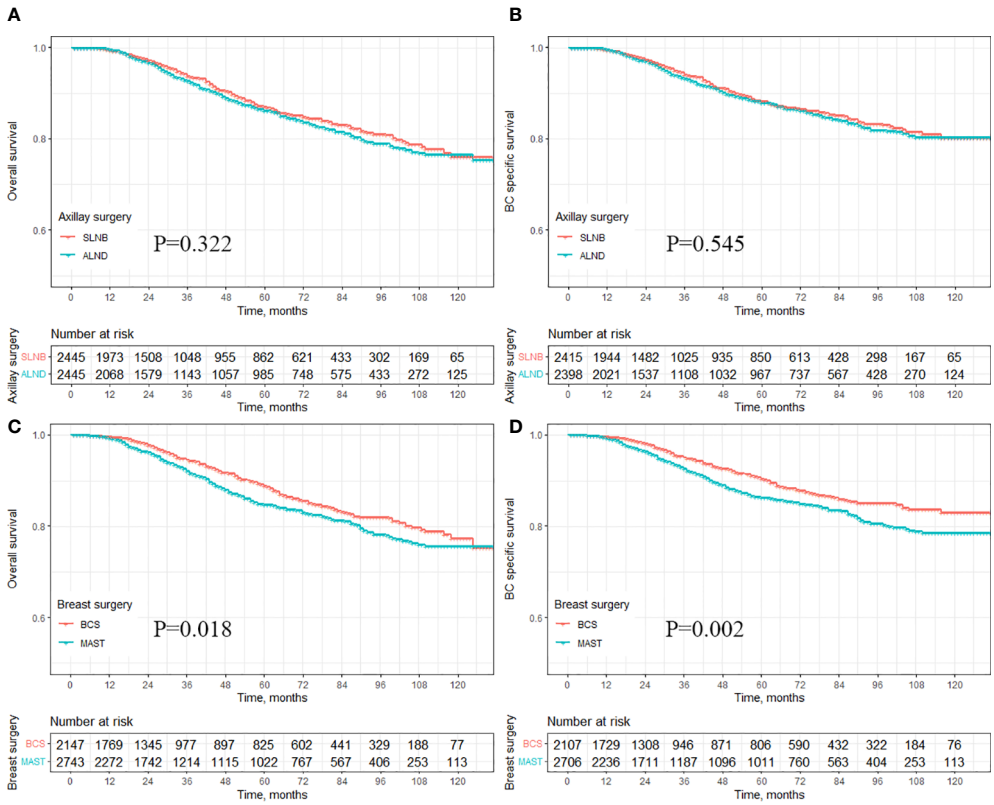

FIGURE 2
Survival analysis of different axillary and breast surgeries for OS and BCSS of breast cancer patients. **(A)** OS in the axillary surgery group, **(B)** BCSS in the axillary surgery group, **(C)** OS in the breast surgery group, **(D)** BCSS in the breast surgery group.

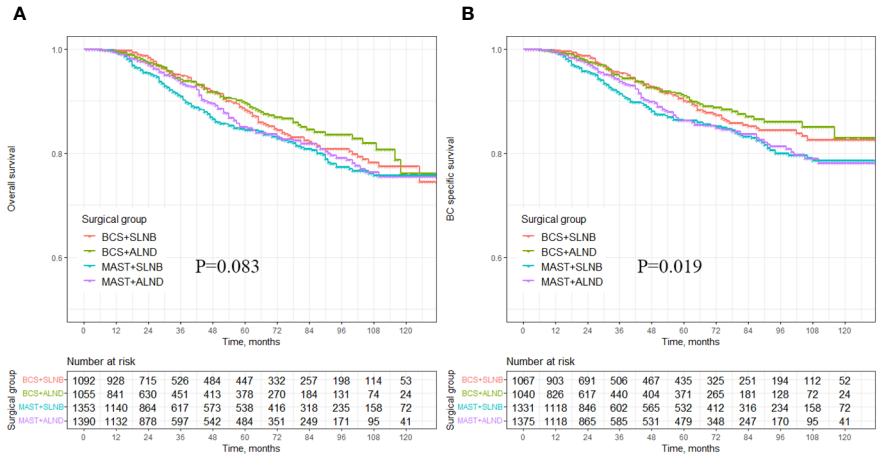

FIGURE 3
Survival analysis of OS and BCSS in breast cancer patients with different axillary surgery combined with different breast surgery. **(A)** OS in the different axillary surgery combined with different breast surgery, **(B)** BCSS in the different axillary surgery combined with different breast surgery.

TABLE 2 Univariate Cox prognostic analysis of OS and BCSS.

Characteristics	OS		BCSS	
	HR[95% CI]	P value	HR[95% CI]	P value
Age				
<35	Reference		Reference	
35-54	0.71 (0.51-0.98)	0.036	0.68 (0.48-0.95)	0.024
55-69	0.95 (0.68-1.32)	0.742	0.84 (0.59-1.2)	0.339
>=70	1.8 (1.2-2.69)	0.004	1.39 (0.89-2.19)	0.148
Marital status				
Married	Reference		Reference	
Single	1.3 (1.04-1.63)	0.023	1.3 (1.02-1.65)	0.037
Other	1.54 (1.23-1.91)	<0.001	1.38 (1.08-1.77)	0.010
Race				
White	Reference		Reference	
Black	1.52 (1.2-1.93)	0.001	1.56 (1.21-2.03)	0.001
Other	1.07 (0.81-1.41)	0.627	1.2 (0.9-1.6)	0.216
Laterality				
Left	Reference		Reference	
Right	1.13 (0.94-1.35)	0.181	1.15 (0.95-1.4)	0.157
Grade				
I-II	Reference		Reference	
III-IV	1.28 (1.04-1.59)	0.021	1.31 (1.04-1.66)	0.022
Unknown	1.04 (0.79-1.38)	0.759	1.02 (0.75-1.38)	0.922
T stage				
T1	Reference		Reference	

(Continued)

TABLE 2 Continued

Characteristics	OS		BCSS	
	HR[95% CI]	P value	HR[95% CI]	P value
T2	1.1 (0.87-1.4)	0.416	1.16 (0.89-1.52)	0.271
T3	1.76 (1.35-2.29)	<0.001	1.96 (1.46-2.62)	<0.001
ER status				
Postive	Reference		Reference	
Negative	1.8 (1.51-2.16)	<0.001	1.81 (1.49-2.2)	<0.001
PR status				
Postive	Reference		Reference	
Negative	1.65 (1.37-1.98)	<0.001	1.69 (1.38-2.07)	<0.001
HER2 status				
Postive	Reference		Reference	
Negative	2.18 (1.77-2.69)	<0.001	2.46 (1.94-3.11)	<0.001
Breast subtype				
HR+/HER2+	Reference		Reference	
HR+/HER2-	2.17 (1.61-2.93)	<0.001	2.35 (1.69-3.27)	<0.001
HR-/HER2+	1.77 (1.23-2.54)	0.002	1.64 (1.08-2.48)	0.020
HR-/HER2-	3.9 (2.9-5.25)	<0.001	4.23 (3.05-5.87)	<0.001
Breast surgery				
BCS	Reference		Reference	
MAST	1.25 (1.04-1.5)	0.019	1.37 (1.12-1.68)	0.002
Axillay surgery				
SLNB	Reference		Reference	
ALND	1.1 (0.91-1.31)	0.322	1.06 (0.87-1.29)	0.545
Radiation				
YES	Reference		Reference	
NO	0.98 (0.8-1.2)	0.851	1.02 (0.81-1.27)	0.889
Surgical group				
BCS+ALND	Reference		Reference	
BCS+SLNB	0.89 (0.67-1.19)	0.444	0.93 (0.67-1.29)	0.668
MAST+ALND	1.23 (0.97-1.58)	0.092	1.37 (1.04-1.8)	0.023
MAST+SLNB	1.13 (0.88-1.46)	0.335	1.28 (0.97-1.7)	0.080

OS, overall survival; BCSS, breast cancer-specific survival; HR, hazard ratio; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; BCS, breast-conserving surgery; MAST, Mastectomy; SLNB, sentinel lymph node biopsy; ALND, axillary lymph node dissection.

and SLNB groups (Figure 5A). When comparing the MAST group to the BCS group, the cumulative incidence of BCSD was notably higher (Grey's test, $p = 0.001$), signifying a statistically significant difference. However, the cumulative incidence of OCSD in the MAST group did not show statistical significance (Grey's test, P=0.121) (Figure 5B). Furthermore, in comparison to the combination of BCS with SLNB or ALND, the MAST group combined with SLNB or ALND exhibited a significantly higher cumulative incidence of BCSD (Grey's test, $p = 0.014$), while the cumulative incidence of OCSD was not statistically significant (Grey's test, $p = 0.278$) (Figure 5C). The multivariate analysis conducted with the competitive risk model identified age ≥ 70, being of black race, T3 staging, ER-negative expression, HER2-negative expression, and undergoing mastectomy as independent prognostic risk factors, all demonstrating statistically significant differences (all $p < 0.05$) (Supplementary Table S1). The nomogram illustrating the competitive risk model is presented in Supplementary Figure S3.

TABLE 3 Multivariate Cox prognostic analysis of OS and BCSS.

Characteristics	OS		BCSS	
	HR[95% CI]	P value	HR[95% CI]	P value
Age				
<35	Reference		Reference	
35-54	0.83(0.6-1.16)	0.277	0.82(0.58-1.16)	0.261
55-69	1.19(0.84-1.7)	0.332	1.13(0.78-1.64)	0.528
>=70	2.25(1.46-3.45)	<0.001	1.86(1.15-2.99)	0.011
Marital status				
Married	Reference		Reference	
Single	1.24(0.99-1.57)	0.065	1.23(0.96-1.58)	0.109
Other	1.27(1.01-1.59)	0.040	1.17(0.91-1.51)	0.230
Race				
White	Reference		Reference	
Black	1.36(1.06-1.74)	0.015	1.37(1.04-1.79)	0.023
Other	1.17(0.88-1.54)	0.278	1.28(0.96-1.71)	0.092
Grade				
I-II	Reference		Reference	
III-IV	1.03(0.82-1.3)	0.778	1.04(0.81-1.33)	0.777
Unknown	0.86(0.65-1.15)	0.311	0.83(0.61-1.14)	0.250
T stage				
T1	Reference		Reference	
T2	1.13(0.89-1.44)	0.326	1.15(0.88-1.51)	0.300
T3	1.74(1.33-2.28)	<0.001	1.86(1.39-2.5)	<0.001
ER status				
Postive	Reference		Reference	
Negative	1.61(1.25-2.08)	<0.001	1.55(1.18-2.05)	0.002
PR status				
Postive	Reference		Reference	
Negative	1.12(0.86-1.46)	0.403	1.19(0.9-1.59)	0.225
HER2 status				
Postive	Reference		Reference	
Negative	2.19(1.77-2.7)	<0.001	2.48(1.96-3.14)	<0.001
Breast surgery				
BCS	Reference		Reference	
MAST	1.32(1.09-1.59)	0.005	1.42(1.15-1.75)	0.001

OS, overall survival; BCSS, breast cancer-specific survival; HR, hazard ratio; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2; BCS, breast-conserving surgery; MAST, Mastectomy.

Discussion

BCS combined with SLNB has been performed in cN1+ breast cancer patients effectively treated with NAT. This approach has been a subject of ongoing debate in clinical practice, particularly due to the limited evidence on long-term survival outcomes from extensive real-world data. In this retrospective study, we analyzed data from 8377 patients diagnosed with non-specific infiltrating duct carcinoma of cT1-3N1M0 breast cancer in the SEER database between 2010 and 2020. After meticulous matching using PSM to minimize confounding

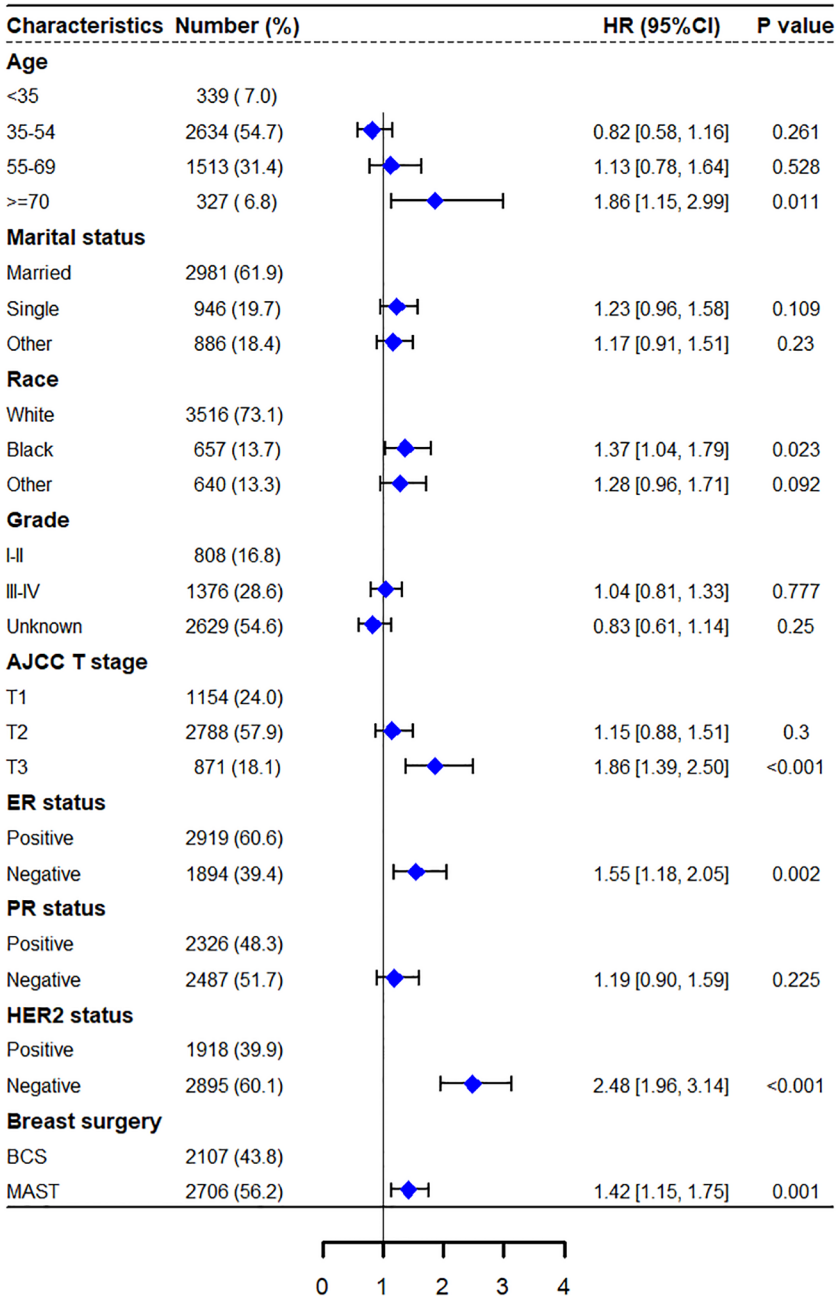

FIGURE 4
Multivariate Cox regression model forest graph for BCSS.

bias, a total of 4890 patients were included in the final analysis. The results revealed that the benefits of SLNB on both OS and BCSS were comparable to those of ALND. Moreover, patients who underwent BCS demonstrated significantly better OS and BCSS compared to those who underwent MAST. Additionally, combining BCS with either SLNB or ALND led to improved survival outcomes. We further employed Fine-Gray competitive risk analysis and Cox proportional risk regression models to account for the impact of deaths from other causes on survival outcomes. These analyses revealed a higher cumulative incidence of BCSD in patients who underwent MAST combined with either SLNB or ALND. Based on our findings, we recommend the combination of BCS and SLNB for patients who meet the criteria for breast and axillary preservation.

In this study, it was observed that 37.4% of patients with cN1+ breast cancer underwent SLNB. Existing literature reports a wide range of SLNB proportions in cN1+ breast cancer patients effectively treated with NAT, varying from 14.6% to 56.5%. Simultaneously, the rate of ALND decreased from 100% to 29.4% (11, 13, 17). Various factors have been associated with the reduction in ALND rates after NAT, including breast cancer molecular subtype (11, 13), higher histological grade (11), residual breast lesions, and vascular infiltration (11, 19). However, Weber et al.

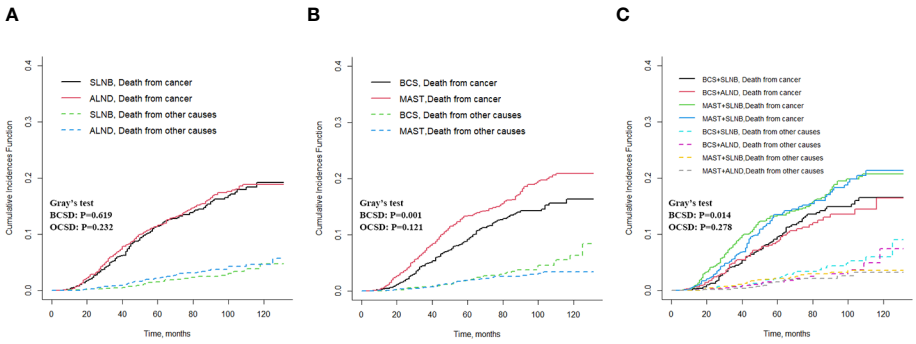

FIGURE 5
Cumulative incidence of BCSD and OCSD for different axillary and breast surgeries. **(A)** BCSD and OCSD in the axillary surgery group, **(B)** BCSD and OCSD in the breast surgery group, **(C)** BCSD and OCSD in the different axillary surgery combined with different breast surgery.

presented data indicating that the ALND rate in cN1+ breast cancer patients who effectively responded to NAT remained as high as 49% Interestingly, their study found no correlation between the acceptance of ALND and the proportion or treatment regimen of adjuvant therapy after NAT (27).

SLN staging after NAT has demonstrated greater accuracy in reflecting prognosis compared to the initial axillary status. Most studies support the implementation of SLNB after NAT (1, 13, 15, 19, 21). It is recommended to utilize the dual tracer method or positioning clip for marking positive lymph nodes, with SLN detection rates ranging from 80.1% to 96%, and false negative rates from 6.8% to 17% (1, 12, 16, 19–24). To further minimize the false negative rate, axillary lymph nodes can be labeled with radioactive iodine seeds, resulting in detection rates of SLN ranging from 98.2% to 100%, false negative rates of 2-4%, negative prediction rates of 92-97%, and an 82% reduction in the need for ALND. However, the practice of implanting guidewires under ultrasound guidance to locate suspicious lymph nodes before NAT is not recommended, as it yields a detection rate of only 70.8% (24, 28–30). Additionally, in order to decrease the false negative rate of detected SLNs, it is recommended to increase the number of SLNs examined and employ immunohistochemical techniques. With three or more SLNs examined, the false negative rate is notably low, ranging from 0-9% (11, 12, 16, 21, 23).

In this study, we observed no significant difference in OS and BCSS between the SLNB group and the ALND group. This finding aligns with the results reported in the majority of literature. For instance, Martelli et al. demonstrated that in cT2N0/1 breast cancer patients receiving NAT, the 10-year OS in the SLNB group was 89% with a 10-year Disease-Free Survival (DFS) of 79%, showing no significant difference in survival outcomes compared to the SLNB +ALND group (14). Similarly, Kahler-Ribeiro-Fontana et al. found that cN1+ breast cancer patients who underwent SLNB after NAT exhibited a 5-year OS rate of 89.8% and a 10-year OS rate of 80.1% (31). In a study by Kim et al., N+ breast cancer patients who received NAT were stratified into five groups based on surgical approach and pathological axillary lymph node results, revealing no disparities in OS or axillary local recurrence rate among the groups (20). Moreover, Piltin et al. reported that among breast cancer patients who underwent SLNB after NAT and were followed for a median of 34 months, recurrence occurred in only 1 out of 159 patients, in contrast to 16 out of 443 patients who underwent ALND (17).

In this study, we observed that nearly 44% of patients with cN1+ breast cancer opted for BCS, resulting in an improved appearance and enhanced psychological well-being for these patients. After NAT, the rate of breast preservation in patients has shown a consistent upward trend, reaching 53.2% to 90% (8–10). BCS is deemed feasible even for patients with multifocal or multicentric lesions, provided there is no residual tumor at the surgical margin. Studies have demonstrated that there are no significant differences in local recurrence, disease-free survival, and overall survival when the surgical margin exceeds 2mm or 1mm, as compared to margins less than 2mm or 1mm (32, 33). The success of transitioning to BCS is associated with factors like the molecular subtype of breast cancer, larger tumor size, positive axillary lymph nodes, and the presence of breast calcification (9). Among breast cancer patients who underwent breast-preserving surgery following NAT, the 10-year local recurrence rate in the breast was 6.5%, while the 10-year recurrence rate in the axillary region of the breast was 10.3%. In comparison to mastectomy, there were no statistically significant differences in terms of distant recurrence, BCSD, and OCSD, although the local recurrence rate was slightly higher. High local recurrence was associated with ER-negativity, cN1+ status, non-pathological complete response in axillary lesions, and pN2-3 staging. To mitigate the risk of local recurrence, it is imperative to implement measures such as meticulous local and pathological evaluation, precise tumor localization, intraoperative removal of breast markers, accurate determination of the volume of the lesion to be resected, and the consideration of adjuvant radiotherapy (7, 34). Sang et al. corroborated that following NAT, breast cancer patients who underwent BCS exhibited a significantly improved overall survival rate compared to those who opted for mastectomy. This finding aligns with the conclusions drawn in the present study, where no statistically significant disparities were observed in terms of disease-free survival and local recurrence between the two groups (10).

The study results indicate that combining BCS with SLNB or ALND leads to improved survival outcomes. Additionally, the inclusion of postoperative radiotherapy to both the breast and axillary regions is recommended to further enhance these outcomes (1, 2, 6, 15). In this study, cN1+ breast cancer patients

who responded effectively to NAT and underwent BCS in combination with SLNB demonstrated significantly improved OS and BCSS benefits after receiving postoperative supplemental radiation therapy. It's worth mentioning that Rusthoven et al.'s findings suggested that, following mastectomy after NAT, radiotherapy improved OS across all postoperative axillary lymph node subgroups (ypN0, ypN1, and ypN2-3). Interestingly, in patients undergoing BCS, regardless of axillary lymph node status, radiotherapy to the whole breast and regional lymph nodes did not lead to improved OS, which contrasts with the conclusions of this study (35). In line with the majority of literature, this study identified age ≥ 70, black race, T3 stage, ER-negative expression, and HER2-negative status as independent prognostic risk factors for BCSS, further corroborating existing evidence.

This study benefits from an extensive dataset comprising nearly 510,000 patients of breast cancer over an 11-year period, sourced from the SEER database. PSM analysis was effectively utilized to mitigate potential confounding variables, enhancing the robustness of the conclusions. The extended follow-up period of more than 10 years from the date of diagnosis further strengthens the reliability of the findings. However, the study does possess certain limitations. Firstly, it is a retrospective study without a predefined experimental design, resulting in the absence of specific variables related to axillary surgery methods, such as SLNB procedure codes, number of SLNs detected, SLN tracing methods, and precise chemoradiotherapy protocols. This could introduce bias and limits further in-depth analysis. Secondly, despite the study's extended duration, the median follow-up time of 32 months suggests that a majority of enrolled cases are recent, potentially resulting in fewer recorded death events and influencing the analysis of survival outcomes to some degree. Finally, various factors impacting survival outcomes, including targeted medications, endocrine treatments, genetic testing, and underlying patient conditions, are not included in the SEER database, preventing further analysis. Despite these constraints, the study's findings still offer valuable evidence for guiding the selection of axillary breast surgery for breast cancer patients who respond effectively to NAT. Nevertheless, confirmation through large-scale, multi-center prospective cohort studies is warranted.

Conclusion

Utilizing SEER data, we investigated the prognostic implications of distinct axillary and breast surgical approaches in cT1-3N1M0 breast cancer patients exhibiting responsiveness to NAT. Among cN1+ breast cancer patients effectively treated with NAT, the combined approach of BCS and SLNB emerged as the optimal surgical strategy for those meeting criteria for axillary and breast-sparing surgery. This approach demonstrated superior long-term quality of life and survival outcomes.

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 in the article/Supplementary Material.

Author contributions

MZ: Data curation, Investigation, Writing – review & editing. YS: Conceptualization, Data curation, Writing – review & editing. HSW: Data curation, Formal analysis, Writing – review & editing. JX: Investigation, Methodology, Writing – review & editing. WC: Investigation, Methodology, Writing – review & editing. HW: Validation, Visualization, Writing – review & editing. BY: Validation, Visualization, Writing – review & editing. HL: Writing – review & editing, Validation, Visualization.

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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.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2024.1319981/full#supplementary-material

SUPPLEMENTARY FIGURE S1
Survival analysis of breast cancer patients treated with different axillary and breast surgeries combined with radiotherapy.

SUPPLEMENTARY FIGURE S2
Multivariate Cox regression model forest graph for OS.

SUPPLEMENTARY FIGURE S3
Nomogram of multivariate competitive risk regression model analysis.

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A nomogram for predicting pathologic node negativity after neoadjuvant chemotherapy in breast cancer patients: a nationwide, multicenter retrospective cohort study (CSBrS-012)

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Purpose: This study aimed to investigate the factors associated with pathologic node-negativity (ypN0) in patients who received neoadjuvant chemotherapy (NAC) to develop and validate an accurate prediction nomogram.

Methods: The CSBrS-012 study (2010–2020) included female patients with primary breast cancer treated with NAC followed by breast and axillary surgery

in 20 hospitals across China. In the present study, 7,711 eligible patients were included, comprising 6,428 patients in the primary cohort from 15 hospitals and 1,283 patients in the external validation cohort from five hospitals. The hospitals were randomly assigned. The primary cohort was randomized at a 3:1 ratio and divided into a training set and an internal validation set. Univariate and multivariate logistic regression analyses were performed on the training set, after which a nomogram was constructed and validated both internally and externally.

Results: In total, 3,560 patients (46.2%) achieved ypN0, and 1,558 patients (20.3%) achieved pathologic complete response in the breast (bpCR). A nomogram was constructed based on the clinical nodal stage before NAC (cN), ER, PR, HER2, Ki67, NAC treatment cycle, and bpCR, which were independently associated with ypN0. The area under the receiver operating characteristic curve (AUC) for the training set was 0.80. The internal and external validation demonstrated good discrimination, with AUCs of 0.79 and 0.76, respectively.

Conclusion: We present a real-world study based on nationwide large-sample data that can be used to effectively screen for ypN0 to provide better advice for the management of residual axillary disease in breast cancer patients undergoing NAC.

KEYWORDS

breast cancer, neoadjuvant chemotherapy, pathologic nodal response, prediction nomogram, pathologic complete response

Introduction

With the recognition of the importance of biology and systematic therapy in local control, we gradually agree that larger surgery does not cure bad biology in breast cancer (1). The adoption of a true multidisciplinary treatment approach, rather than the sequential use of different therapies, decreases the extent of surgery and its associated morbidity (2, 3).

Axillary lymph node dissection (ALND) has traditionally been used as routine axillary surgical management for breast cancer patients (4). Multiple prospective, randomized trials led by the American College of Surgeons Oncology Group (ACOSOG) Z0011 trial (5) demonstrated that sentinel lymph node biopsy (SLNB) can replace ALND in patients with low nodal burden disease because of noninferior local control and survival, but with lower surgical morbidity. Neoadjuvant chemotherapy (NAC) results in frequent downstaging of tumors in both the breast and axilla, which can lead to fewer surgeries in patients with larger tumors at diagnosis. The implementation of NAC has enabled selected women to undergo breast-conserving surgery (BCS) in the last two decades; however, for patients who received NAC, the chance of de-escalated axillary surgery has not improved (6). The National Comprehensive Cancer Network (NCCN) breast cancer guidelines recommend SLNB for patients with cN0 to ycN0 disease after NAC, but ALND is still recommended for patients who are converted from cN+ to cN0, and SLNB is usually considered a relative contraindication due to its low identification rate and high false-negative rate (FNR) (7, 8). In the SENTinel NeoAdjuvant (SENTINA) study (9), the detection rate of SLNB after NAC in patients with cN+ to cN0 disease was 80.1% (95% CI 76.6–83.2), and the false-negative rate was 14.2% (95% CI 9.9–19.4). However, approximately 74% of breast cancer patients with cN0 disease are sentinel lymph node-negative, and postoperative complications still occur even after SLNB (10, 11).

Patients with a low risk of residual axillary involvement after NAC could benefit from omitting axillary surgical intervention if there are accurate tools for nodal response prediction (12). Currently, the commonly used clinical imaging methods for evaluating the axillary region include ultrasound, mammography, magnetic resonance imaging (MRI), and positron emission tomography CT (PET-CT) (13–15). Nevertheless, the accuracy of these techniques remains low, and there are no unified guidelines for axillary imaging evaluation of NAC response (16). The ACOSOG Z1071 (Alliance) trial reported that axillary ultrasound (AUS) after NAC can identify abnormal nodes, guide patient selection for SLN surgery instead of ALND, and reduce the FNR of SLNB to less than 10%. However, the accuracy of AUS after NAC was low; only 43.2% of patients who were negative for AUS were confirmed to have nodal pCR by ALND (16). Investigators also

attempted to decrease the FNR by marking positive lymph nodes at diagnosis before NAC. However, clips can be found during surgery in only half of the patients (17). Imaging-guided localization (IGL) of the clipped node was introduced to increase the likelihood of clip removal. The lowest FNR was achieved when IGL was added to SLN biopsy, a procedure called targeted axillary dissection (TAD) (18, 19). However, it did not significantly change the performance of tailored axillary surgery, which left ≥2 positive nodes behind in 47.6% of the patients (20, 21). In all these explorations, the prediction model based on clinical and pathological factors still has clinical value and application prospects. The present study aimed to identify factors that are predictive of ypN0 and construct a novel nomogram that can effectively predict nodal negativity and thus potentially avoid axillary surgery, which can reduce women's loss of function and lymphedema.

Methods

Study population

The Chinese Society of Breast Surgery (CSBrS-012) is a nationwide, multicenter, 10-year retrospective clinical epidemiological study conducted across 20 hospitals in China. The CSBrS-012 study included female primary breast cancer patients who received NAC and underwent standard breast and axillary surgery after NAC between January 2010 and December 2020. The 20 hospitals are located in central, northern, eastern, northwestern, northeastern, and southwestern China, and represent different levels of breast cancer burden. After excluding patients with incomplete data, 7,711 patients were enrolled in the study. Hospitals were randomly assigned to two groups comprising 6,428 patients in the primary cohort from 15 hospitals and 1,283 patients in the external validation cohort from five hospitals. We then randomized the patients in the primary cohort at a 3:1 ratio into the training and internal validation sets (Figure 1). The study was performed in accordance with the Declaration of Helsinki and approved by the Ethical Review Committee of the First Hospital of Jilin University (No. 2021–066). As this was a retrospective study and all data analyses were performed anonymously, the requirement for informed consent from the patients was waived.

Patient characteristics

Variables included age, clinical tumor (cT) and clinical nodal (cN) stages before NAC, tumor histology, ER, PR, HR, HER2, Ki-67, biological subtypes, NAC regimen, NAC treatment cycle, and pCR status. Immunohistochemistry (IHC) was used to detect the expression of ER, PR, HER2, and Ki-67. ER and PR were defined as positive if ≥1% of cells were positive. HR was defined as positive if the ER and/or PR were positive. HER2 expression was defined as

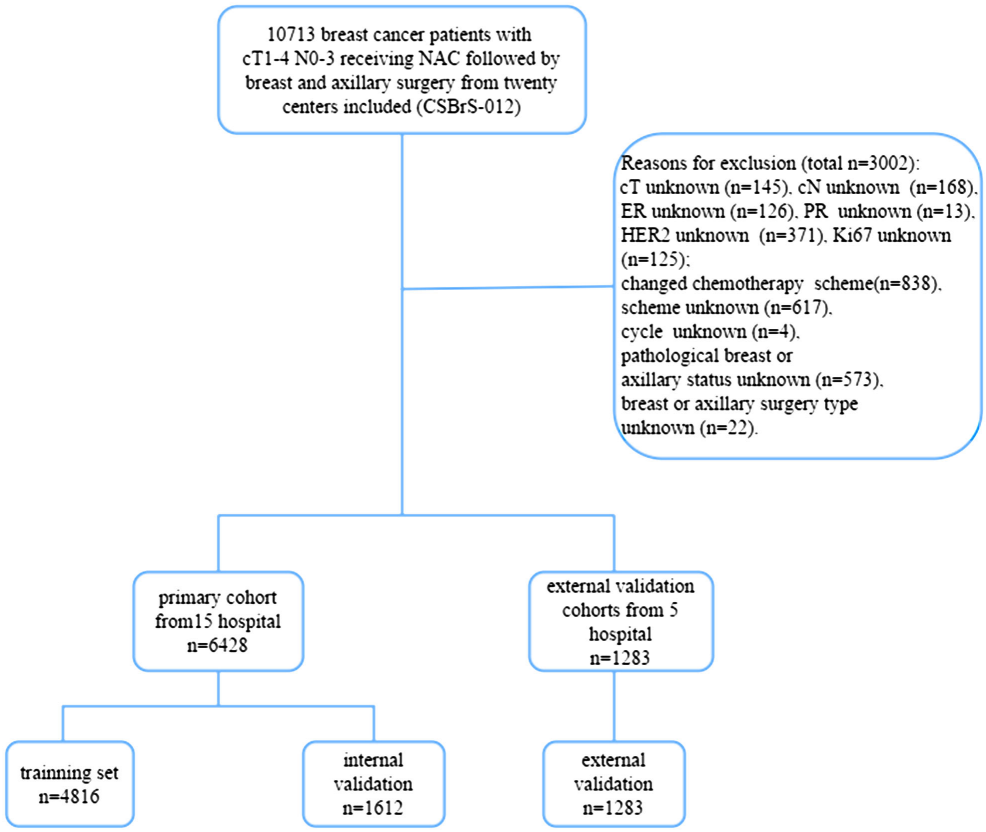

FIGURE 1
Flow diagram of the study. NAC, neoadjuvant chemotherapy; CSBrS-012: The Chinese Society of Breast Surgery study (2010–2020).

positive if 3+ by IHC or 2+ by IHC and positive by *in situ* hybridization. Tumor subtypes were categorized according to St. Gallen criteria (22): HR+/HER2−, HR+/HER2+, HR−/HER2+, and TNBC. The T and N stages were defined according to the 8th edition of the American Joint Committee on Cancer (AJCC) (23). cN0 was defined as no suspicious lymph nodes on axillary ultrasound or suspicious lymph nodes on axillary ultrasound but negative on either fine needle aspiration cytology or core needle biopsy or negative on SLNB prior to NAC. Suspicious lymph nodes were considered in cases of a hypoechoic round shape, focally thickened cortex, or absent fatty hilum. pCR was defined as the absence of residual invasive or *in situ* carcinoma in the breast or axillary lymph nodes (ypT0/ypN0). NAC and surgery were performed in accordance with the Chinese Society of Clinical Oncology (CSCO) Breast Cancer Guidelines and the National Comprehensive Cancer Network (NCCN) Breast Cancer Guidelines. In our study, we divided NAC regimens into three categories: (1) anthracycline combined with taxane, (2) taxane combined with platinum, and (3) other regimens.

Statistical analysis

Statistical analyses were performed using SPSS version 21.0 (Inc., Chicago, IL, USA) and R 4.2.2 (R Project for Statistical Computing) software. The differences in clinicopathological parameters between the training and internal validation sets were evaluated using Pearson's χ^2 test. Univariate logistic regression and backward stepwise selection were used for the final multivariate model. A predictive nomogram for ypN0 was established based on independent risk factors identified via multivariate analysis. The predictive value of the model was appraised using receiver operating characteristic (ROC) curves and calibration curves. The AUC (area under the receiver operating characteristic curve) was calculated.

Results

Patient characteristics and NAC response

A total of 7,711 female breast cancer patients, with a median age of 49 years, were enrolled. The baseline characteristics of the patients are summarized in Table 1. The proportion of patients with initial stage cT1–2 tumors was 79.8%, and that with initial stage cT3–4 tumors was 20.2%. The proportion of patients with cN0–1 stage disease in the study population was greater than that of patients with cN2–3 stage disease (81.5% vs. 18.5%). Most patients had invasive ductal cancer (6,971 [90.4%]). Anthracyclines and taxanes were the most common NAC treatments (76.3%). Approximately half of the HER2+patients received targeted

TABLE 1 Baseline patient characteristics.

Characteristic	Training set (n = 4,816)	Internal validation set (n = 1,612)	p-value	External Validation set (n = 1,283)
Age			0.155	
≤35	482 (10.0)	181 (11.2)		134 (10.4)
≥56	1,216 (25.2)	379 (23.5)		374 (29.2)
36–45	1,265 (26.3)	401 (24.9)		320 (24.9)
46–55	1,853 (38.5)	651 (40.4)		455 (35.5)
cT			0.712	
T1	583 (12.1)	174 (10.8)		205 (16.0)
T2	3,234 (67.2)	1,096 (68.0)		859 (67.0)
T3	749 (15.5)	256 (15.9)		173 (13.4)
T4	250 (5.2)	86 (5.3)		46 (3.6)
cN			0.551	
N0	1,390 (28.9)	450 (28.0)		318 (24.7)
N1	2,590 (53.8)	871 (54.0)		666 (52.0)
N2	338 (7.0)	174 (10.8)		210 (16.4)
N3	498 (10.3)	117 (7.2)		89 (6.9)
Histology			0.032	
IDC	4,306 (89.4)	1,472 (91.3)		1,193 (93.0)
Others	510 (10.6)	140 (8.7)		90 (7.0)

(Continued)

TABLE 1 Continued

Characteristic	Training set (n = 4,816)	Internal validation set (n = 1,612)	p-value	External Validation set (n = 1,283)
Biologic Subtype			0.034	
HR−/HER2−	858 (17.8)	239 (14.8)		241 (18.8)
HR−/HER2+	703 (14.6)	232 (14.4)		160 (12.5)
HR+/HER2−	2,290 (47.5)	815 (50.6)		626 (48.8)
HR+/HER2+	965 (20.0)	326 (20.2)		256 (20.0)
HER2			0.308	
Negative	3,148 (65.4)	1,054 (65.4)		867 (67.6)
Positive no target	873 (18.1)	301 (18.7)		163 (12.7)
Positive + single agent HER2 blockade	590 (12.3)	176 (10.9)		165 (12.9)
Positive + dual HER2 blockade	205 (4.3)	81 (5.0)		88 (6.9)
Ki67			0.497	
<20%	682 (14.2)	240 (14.9)		193 (15.0)
≥20%	4,134 (85.8)	1,372 (85.1)		1,090 (85.0)
NAC regimen			0.873	
Anthracyclines + Taxanes	3,758 (78.0)	1,263 (78.3)		860 (67.0)
Taxanes + Platinums	448 (9.3)	143 (8.9)		187 (14.6)
Others	610 (12.7)	206 (12.8)		236 (18.4)
Cycle			0.405	
4	580 (12.0)	219 (13.6)		377 (29.4)
6	1,936 (40.2)	656 (40.7)		507 (39.5)
8	1,592 (33.1)	521 (32.3)		287 (22.4)
>8	306 (6.4)	93 (5.8)		24 (1.9)
Others	402 (8.3)	123 (7.6)		88 (6.9)
bpCR			0.061	
No	3,801 (78.9)	1,308 (81.1)		1,044 (81.4)
Yes	1,015 (21.1)	304 (18.9)		239 (18.6)

cT, clinical tumor stage before neoadjuvant chemotherapy; cN, clinical tumor stage before neoadjuvant chemotherapy; IDC, invasive ductal carcinoma; ER, estrogen receptor; PR, progesterone receptor; HR, hormone receptor; HER2, human epidermal growth factor receptor 2; bpCR, breast pathologic complete response.

therapy, among which single-agent HER2 blockade was more than twice as frequent as dual HER2 blockade.

As shown in Table 2, 3,560 patients (46.2%) achieved ypN0, and 1,558 patients (20.3%) achieved bpCR. Among the patients who achieved bpCR, 75.3% had ypN0, whereas 38.7% did not (p <0.001). The pathological responses of the breast and axillary lymph nodes according to the biological subtype are summarized in Table 3. Responses to NAC in the different subgroups were generally consistent between the breast and axillary regions. In both the breast and axilla, HR-negative patients showed a better response to NAC than HR-positive patients (p <0.001). In both the breast and axilla, HR+/HER2− subtypes exhibited relatively poor responses to NAC compared to the other subtypes (p <0.001). The ypN0 rate for all subtypes was significantly higher than the bpCR rate (p <0.05).

Associations between ypN0 and clinicopathologic parameters

According to the univariate logistic regression analyses of the training set, cN stage, ER, PR, HER2, Ki67, NAC treatment cycle, and bpCR were associated with ypN0. All of the above parameters were subjected to multivariate logistic regression using backward selection analysis, and a lower cN stage, ER-negative status, PR-

TABLE 2 Pathologic response of breast and axillary to NAC in whole study population.

Response	ypN0	ypN+	total
bpCR	1,173 (75.3)	385 (24.7)	1,558 (20.3)
non-bpCR	2,387 (38.7)	3,766 (61.3)	6,153 (79.7)
total	3,560 (46.2)	4,151 (53.8)	7,711

ypN0, pathologic node negative after neoadjuvant chemotherapy; ypN+, pathologic node positive after neoadjuvant chemotherapy; bpCR, breast pathologic complete response; non-bpCR, not achieved breast pathologic complete response.

negative status, HER2-positive status with targeted therapy, Ki67 level ≥20, more NAC treatment cycles, and bpCR were confirmed to be independent predictors of ypN0 (Table 4).

Nomogram for predicting ypN0

A nomogram to predict ypN0 was developed based on multivariate logistic regression results. Points were assigned to each variable and summed to obtain the total number of points. Finally, the probability of ypN0 was determined by drawing a vertical line from the total score to the bottom row (Figure 2A). For example, a patient with HER2-amplified breast cancer with cN1 and Ki67 >20 who received eight cycles of NAC with single targeted therapy and achieved bpCR had a total of 188 points, so the possibility of ypN0 after NAC for this patient was 88% (Figure 2B), and a patient with triple-negative breast cancer with cN1 and Ki67 >20 who received eight cycles of NAC and did not achieve bpCR had a total of 88 points, so the possibility of ypN0 after NAC for this patient was 40% (Figure 2C).

The discriminatory ability of the nomogram to predict ypN0 status was investigated using receiver operating characteristic (ROC) curve analysis. The AUCs of the training, internal validation, and external validation sets were 0.80, 0.79, and 0.76, respectively, indicating that the nomogram had potentially promising predictive power. The calibration plots presented excellent agreement between the training and validation sets and showed no significant difference between the predicted and actual probabilities of ypN0 (P = 1.000) (Figures 3–5).

Discussion

Among patients with cN0 breast cancer, approximately 74% do not have axillary lymph node metastasis (24). This means that even SLNB represents overtreatment and causes unnecessary complications, with few advantages for many patients. However, the St. Gallen Consensus Panel in 2017 (25) and the German AGO recommendation in 2022 (26) recommend SLNB as the standard surgical procedure for patients who present with cN0 before and after NAC. In patients who are cN+ and achieved nodal pCR after NAC, ALND is still performed in clinical practice in some cases because of the unacceptable identification rate and FNR of SLNB (7–9, 27).

Recently, the 5-year survival results of the SOUND trial were published (28). This was a prospective non-inferiority phase III randomized clinical trial that enrolled 1,463 patients with small breast tumors (<2 cm) and a cN0 stage. Patients were randomized in a 1:1 ratio to either the SLNB group or the no axillary surgery group. Interestingly, omission of axillary surgery was not inferior to SLNB in terms of the 5-year DFS and OS. This was a study of patients who underwent upfront surgery. For patients who receive NAC, multiple prospective trials investigating whether axillary surgery can be safely abandoned in selected patients are underway. The European Breast Cancer Research Association of Surgical Trialists (EUBREAST)-01 is a prospective clinical trial in which axillary surgery will be eliminated completely (no SLNB) for initially cN0 patients with radiological complete remission and breast pCR in the lumpectomy specimen (29). The ASICS trial is a non-inferiority, single-arm trial open to both breast-conserving and mastectomy patients in which no SLNB is performed in cN0, triple-negative, or HER2-positive breast cancer patients with a radiological complete response on MRI (30). The results of these trials are expected in to continue for the next 5 years. Meanwhile, the prediction model for axillary nodal burden based on clinical and pathological factors has clinical value and application prospects. In the present study, we presented and validated a model based on nationwide multicenter data of breast cancer patients to predict the possibility of ypN0 disease after NAC. Moreover, to prove its universality, we externally validated the nomogram using patient information from different hospitals.

Researchers at the MD Anderson Cancer Center first proposed that breast pCR is strongly correlated with nodal status after NCT (31). In the present study, 46.2% of patients achieved ypN0 and 20.3% of patients achieved bpCR, and the rate of ypN0 was greater on patients who achieved bpCR than in the nonbpCR group (75.3% vs. 38.7%). Tumor response to NAC was significantly related to tumor subtype. Barron et al. (32) reported 30,821 patients with cT1/cT2 cN0/cN1 breast cancer treated with NAC from the American National Cancer Database and reported breast pCR rates of 37.2%, 58.2%, 37.2%, and 13.1%, respectively. The ypN0 rates were 78.6%,

TABLE 3 Pathological response of breast and axillary lymph node according to biologic subtype.

Subtypes	ypN0	ypN+	bpCR	non-bpCR	total
HR−/HER2−	793 (59.3)	545	422 (31.6)	916	1,338
HR−/HER2+	657 (60.0)	438	350 (32.0)	745	1,095
HR+/HER2−	1,268 (34.0)	2,463	437 (11.8)	3294	3,731
HR+/HER2+	842 (54.5)	705	349 (22.6)	1,198	1,547

HR, hormone receptor; HER2, human epidermal growth factor receptor; ypN0, pathologic node negative after neoadjuvant chemotherapy; ypN+, pathologic node positive after neoadjuvant chemotherapy; bpCR, breast pathologic complete response; non-bpCR, not achieved breast pathologic complete response.

TABLE 4 Univariate and multivariate logistic analysis of factors predict the lymph node positivity after NAC in the training set.

Variables	Univariate Analysis			Multivariable Analysis		
	OR	95% CI	P-value	OR	95% CI	P-value
Age						
≤35	reference					
46–55	1.01	0.80–1.28	0.934			
36–45	1.16	0.91–1.49	0.231			
≥56	0.91	0.71–1.18	0.512			
cT						
T1	reference					
T2	1.05	0.86–1.30	0.619			
T3	1.02	0.79–1.33	0.830			
T4	0.77	0.54–1.10	0.152			
cN						
N0	reference			reference		
N1	0.18	0.16–0.22	<0.001	0.19	0.16–0.22	<0.001
N2	0.11	0.08–0.15	<0.001	0.11	0.08–0.14	<0.001
N3	0.09	0.07–0.12	<0.001	0.09	0.07–0.12	<0.001
Tumor Histology						
IDC	reference					
Others	1.13	0.91–1.41	0.281			
ER						
Negative	reference					
Positive	0.63	0.52–0.76	<0.001	0.62	0.51–0.75	<0.001
PR						
Negative	reference					
Positive	0.77	0.64–0.93	0.006	0.78	0.65–0.94	0.010
HER2						
Negative	reference					
Positive no target	1.44	1.21–1.72	<0.001	1.42	1.19–1.68	<0.001
Positive + single agent HER2 blockade	2.39	1.80–3.17	<0.001	2.40	1.94–2.97	<0.001
Positive + dual HER2 blockade	2.28	1.51–3.45	<0.001	2.32	1.64–3.32	<0.001
Ki67						
<20%	reference			reference		
≥20%	1.45	1.19–1.78	<0.001	1.46	1.20–1.78	<0.001
NAC regimen						
Anthracyclines + Taxanes	reference					
Taxanes + Platinums	1.02	0.71–1.46	0.914			
Others	1.00	0.81–1.23	0.983			

(Continued)

TABLE 4 Continued

Variables	Univariate Analysis			Multivariable Analysis		
	OR	95% CI	P-value	OR	95% CI	P-value
NAC cycle						
4	reference					
6	1.20	0.96–1.50	0.107	1.19	0.96–1.48	0.117
8	1.26	1.01–1.60	0.044	1.25	1.00–1.56	0.052
>8	1.97	1.42–2.77	<0.001	1.95	1.40–2.71	<0.001
Others	1.24	0.92–1.67	0.156	1.24	0.92–1.66	0.161
bpCR						
No	reference			reference		
Yes	4.62	3.86–5.53	<0.001	4.65	3.90–5.57	<0.001

Only variables with P-values <0.05 were included in the multivariate analysis. OR, odds ratio; 95% CI, 95% confidence interval; cT, clinical tumor stage before neoadjuvant chemotherapy; cN, clinical tumor stage before neoadjuvant chemotherapy; IDC, invasive ductal carcinoma; ER, estrogen receptor; PR, progesterone receptor; HR, hormone receptor; HER2, human epidermal growth factor receptor 2; bpCR, breast pathologic complete response.

84.5%, 75.3%, and 47.0% for TNBC, HR−/HER2+, HR+/HER2+, and HR+/HER2− subtypes, respectively. In our study, the distribution of tumor subtypes was consistent with that in the above study; however, the rates of bpCR and ypN0 were low because we included cT3–4 and cN2–3 patients. In addition, the pCR and ypN0 rates of HER2+ patients were not significantly high in the current study, possibly because only approximately half of the patients with HER2+ status (50.5%, 1,335/2,642) received

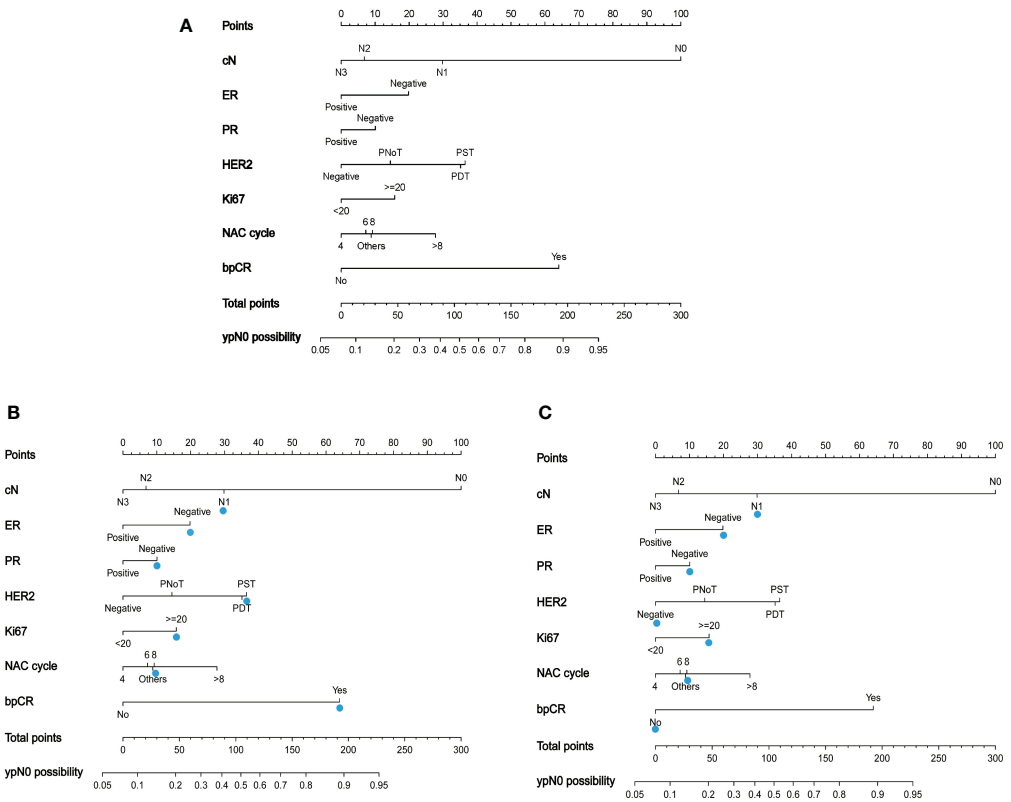

FIGURE 2
(A) A nomogram to predict the probability of ypN0 in breast cancer patients receiving neoadjuvant chemotherapy. PNoT, HER2 positive without targeted therapy; PST, HER2 positive with single agent HER2 blockade; PDT, HER2 positive with dual HER2 blockade. **(B)** The blue triangle demonstrates usage of the model: a patient with HER2-amplified breast cancer with cN1 and Ki67 >20 who received eight cycles of NAC with single-targeted therapy and achieved bpCR had a total of 188 points, and the possibility of ypN0 after NAC for this patient was 88%; **(C)** a patient with triple-negative breast cancer with cN1 and Ki67 >20 who received eight cycles of NAC and did not achieve bpCR had a total of 88 points. The possibility of ypN0 after NAC was 40% for this patient.

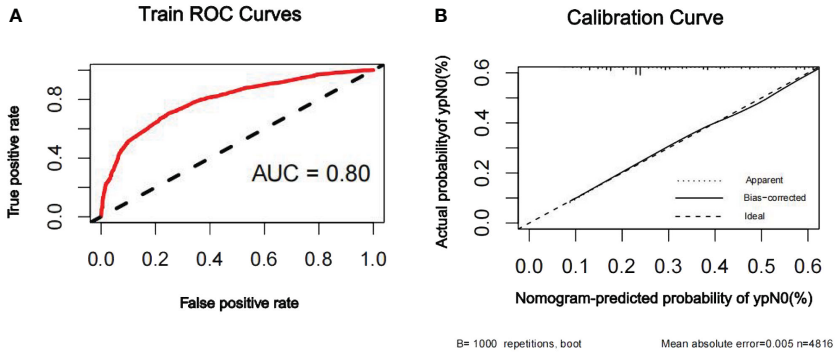

FIGURE 3
ROC curve **(A)** and calibration curve **(B)** are shown for the prediction model of ypN0 in the training cohort. The ROC curve for the training set indicated an AUC of 0.80. ROC, receiver operating characteristic curve; AUC, area under the curve.

molecular-targeted therapy because the targeted drugs were not covered by medical insurance in the early years.

As expected, clinical nodal stage and breast tumor response strongly predicted ypN0. To avoid the influence of receptors on molecular subtypes, we did not include subtypes in the analysis. We found that patients with ER-negative, PR-negative, and HER2-positive disease had a higher ypN0. Ki67 is a proliferation marker, and patients with higher Ki67 levels showed greater sensitivity to chemotherapy in previous studies (33, 34), which was consistent with our study. In the present study, multivariate analysis revealed that more treatment cycles were associated with ypN0, independent of the tumor histology and treatment regimen. Clinical tumor size has been shown to be a predictor of lymph node status in operable breast cancer patients in several previous studies (35–37); however, in the context of NAC, the relationship between cT and ypN0 was not significant in our study.

We developed a nomogram based on multivariate logistic regression results. In contrast to previous nomograms that predicted axillary pCR in initially cN+ patients (38–40) or in specific subtypes (41, 42), the current nomogram predicted ypN0 in all patients with stage cT1–4N0–3 disease. The AUC of the nomogram in the ROC curve analysis was 0.80, 0.79, and 0.76 in the training, internal, and external validation cohorts, respectively, and showed good discrimination in the prediction of ypN0. The advantage of our prediction nomogram is that most breast cancer patients who receive NAC can be assessed, and the indicators for building the nomogram can be easily acquired by surgeons. Moreover, as mentioned above, our findings are consistent with those of previous studies in a global context in terms of pCR for different subtypes, which indicates that our nomogram can also be applied to patients in different countries.

There are several limitations in our study. First, histological grade was found to be an independent prognostic factor for pCR in patients with breast cancer in previous studies (43, 44). In our study, we could not analyze this factor because it was not included in the initial database. Second, if we put this nomogram into practice for the omission of any axillary surgery, it should be determined before surgery, but bpCR is available after surgery. However, multiple studies have explored methods to detect bpCR without surgery (45–48). A prospective trial showed that image-guided vacuum-assisted core biopsy (VACB) of the primary breast tumor bed following NAC can identify patients who are very likely to have a bpCR with an FNR of <5% (49). Another potential limitation of this study was its retrospective nature. Our study, which reflects the current clinical practices across the country, will facilitate the design of prospective clinical trials in the future.

Future Directions: The developed nomogram may help clinicians weigh the lymph node tumor burden after NAC more appropriately. However, if our research conclusions are extended to

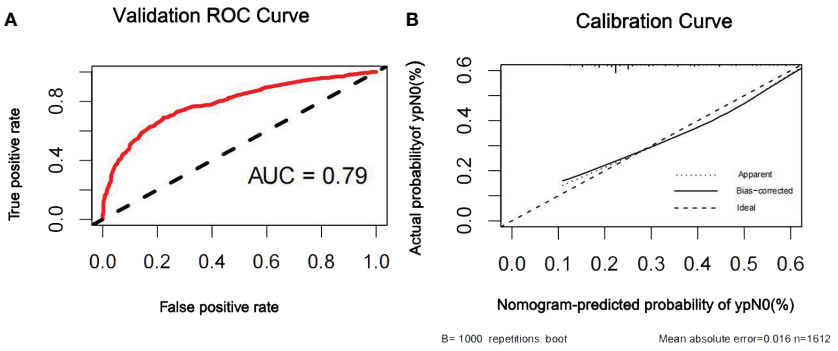

FIGURE 4
ROC curve **(A)** and calibration curve **(B)** are shown for the prediction model of ypN0 in the internal validation cohort. For discrimination in the internal validation set, the ROC curve indicated an AUC of 0.79. ROC, receiver operating characteristic curve; AUC, area under the curve.

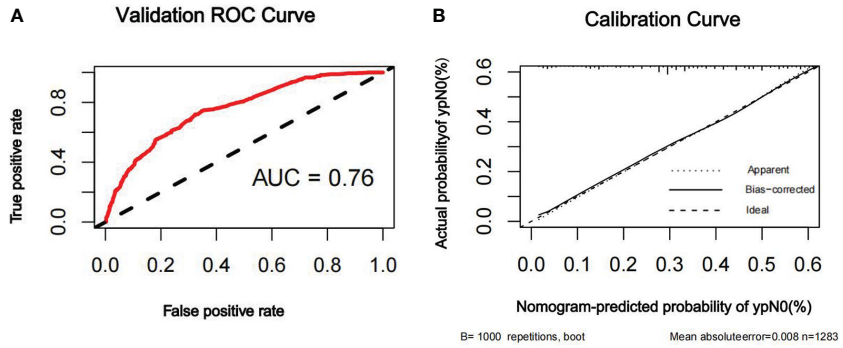

FIGURE 5
ROC curve **(A)** and calibration curve **(B)** are shown for the prediction model of ypN0 in the external validation cohort. For discrimination in the external validation set, the ROC curve indicated an AUC of 0.76. ROC, receiver operating characteristic curve; AUC, area under the curve.

clinical work, further clinical trials using this nomogram are required to determine the survival and local recurrence rates of patients who avoid axillary surgery following NAC. The authors expected that related studies of the nomogram could lead to more feasible progress, and that the nomogram could be well connected with targeted axillary dissection, including the clipped node.

Conclusions

We present a real-world study based on nationwide large sample data and construct a nomogram model that can effectively screen ypN0 to provide better advice for the management of residual axillary disease in breast cancer patients receiving NAC.

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 authors.

Ethics statement

The studies involving humans were approved by Ethical Review Committee of the First Hospital of Jilin University (No. 2021-066). The studies were conducted in accordance with the local legislation and institutional requirements. The ethics committee/institutional review board waived the requirement of written informed consent for participation from the participants or the participants' legal guardians/next of kin because as this was a retrospective study and all data analyses were performed anonymously.

Author contributions

AM: Conceptualization, Formal Analysis, Methodology, Software, Validation, Writing – original draft, Investigation. YiJL: Data curation, Formal Analysis, Methodology, Software, Validation, Writing – review & editing. NC: Data curation, Writing – review & editing. ZL: Data curation, Writing – review & editing. RL: Data curation, Writing – review & editing. YZ: Data curation, Writing – review & editing. HY: Data curation, Writing – review & editing. YuJL: Data curation, Writing – review & editing. KL: Data curation, Writing – review & editing. JZ: Data curation, Writing – review & editing. DM: Data curation, Writing – review & editing. ZY: Data curation, Writing – review & editing. YHL: Data curation, Writing – review & editing. PF: Data curation, Writing – review & editing. JW: Data curation, Writing – review & editing. HJ: Data curation, Writing – review & editing. ZZ: Data curation, Writing – review & editing. XT: Data curation, Writing – review & editing. ZC: Data curation, Writing – review & editing. KW: Data curation, Writing – review & editing. AS: Data curation, Writing – review & editing. FJ: Data curation, Writing – review & editing. PW: Formal Analysis, Writing – review & editing. JH: Conceptualization, Project administration, Resources, Supervision, Visualization, Writing – review & editing. ZF: Conceptualization, Data curation, Resources, Supervision, Writing – review & editing. HZ: Conceptualization, Funding acquisition, Investigation, Methodology, Project administration, Supervision, Visualization, Writing – review & editing.

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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.

Publisher's note

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Surgery paradigm for locally advanced breast cancer following neoadjuvant systemic therapy

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Locally advanced breast cancer (LABC) remains a significant clinical challenge, particularly in developing countries. While neoadjuvant systemic therapy (NST) has improved the pathological complete response (pCR) rates, particularly in HER2-positive and triple-negative breast cancer patients, surgical management post-NST continues to evolve. The feasibility of omitting surgery and the increasing consideration of breast-conserving surgery, immediate reconstruction in LABC patients are important areas of exploration. Accurate assessment of tumor response to NST through advanced imaging and minimally invasive biopsies remains pivotal, though challenges persist in reliably predicting pCR. Additionally, axillary lymph node management continues to evolve, with emerging strategies aiming to minimize the extent of surgery in patients who achieve nodal downstaging post-NST. Minimizing axillary lymph node dissection in favor of less invasive approaches is gaining attention, though further evidence is needed to establish its oncological safety. The potential for personalized treatment approaches, reducing surgical morbidity, and improving quality of life are key goals in managing LABC, while maintaining the priority of achieving favorable long-term outcomes.

KEYWORDS

locally advanced breast cancer, individualized treatment, neoadjuvant systemic therapy, surgery, pathological complete response

Introduction

LABC is commonly referred to inoperable cancers which surgical resection is impossible without systemic therapy and absence of distant metastases. In general, clinically stage III breast cancer was included (1, 2).

The implementation of a comprehensive breast cancer screening program has resulted in a comparatively low prevalence of LABC in developed nations (3). It still remains a big challenge in developing countries. For instance, in India, 47% of breast cancer cases are diagnosed at stage III (4). Despite the elevated risk of recurrence and metastasis, LABC can still be curable if local control is attained. Due to the use of dual human epidermal growth factor receptor 2 (HER2) blockade and platinum-based neoadjuvant chemotherapy, the rate of pCR rate in HER2 positive (HER2+) or triple-negative breast cancer (TNBC) patients has increased to more than 30% (5). Mastectomy and axillary lymph node dissection (ALND) are commonly employed as the standard surgical procedures for patients diagnosed with LABC. Surgery is performed with the objective of completely excising the primary tumor, as well as any adjacent skin or muscular involved. As the treatment approach for breast cancer transitions from "maximum tolerable" to "minimum effective" treatment, it is important to consider if there are

additional surgical options available for patients with LABC, while considering the pretreatment stage and response to NST. This review seeks to investigate the potential for omitting breast surgery and the viability of breast-conserving surgery (BCS) or immediate reconstruction (IR) without compromising oncological safety for LABC. Additionally, as well as to identify targeted patients for ALND exemption, thus promoting individualized surgical options for LABC patients.

Ways to evaluate the effectiveness of NST and possibility of omitting surgery

Assessing the response of breast cancer patients to NST before surgery is essential for tailoring personalized surgical plans and treatment strategies. In cases where patients achieve a clinical complete response (cCR), meaning no detectable cancer is found through physical examination and imaging, it may even be possible to consider omitting surgery (6). Magnetic resonance imaging (MRI) is more accurate in predicting pCR and residual disease compared to clinical examination, ultrasound and mammography (7, 8). However, MRI can either overestimate or underestimate residual disease. Overestimation may occur due to fibrosis, necrotic tumors, or residual benign masses, while underestimation can be caused by no mass lesions, invasive lobular carcinoma, hormone receptor-positive (HR+) tumors, nonconcentric shrinkage patterns, antiangiogenic therapy, or late-enhancing foci (9). Therefore, the accuracy of MRI is still falling short of clinical expectations. Moreover, the accuracy varies significantly across different molecular subtypes, with the highest sensitivity observed in TNBC and the lowest in HR+/HER2- subtypes (10). Therefore, relying solely on imaging results is insufficient. In recent years, multiple trials have explored the predictive value of image-guided minimally invasive biopsy (MIB) techniques, such as core needle biopsy (CNB), vacuum-assisted biopsy (VAB), and fine-needle aspiration (FNA), for determining breast pCR following NST. For example, the study by Sutton et al. (11) found that MRI-guided VAB can increase the accuracy of predicting pCR to 95%. However, Hemert et al. (12) found that small residual lesions (4–7 mm) are often tended to be missed in biopsy procedures. A meta-analysis (13) of nine trials involving 1,030 breast cancer patients found that, while the pooled sensitivity and specificity of MIB were 0.72 [95% confidence interval (CI): 0.61–0.81] and 0.99 [95% CI: 0.89–1.00], respectively, current image-guided MIB methods are still not accurate enough for reliably predicting breast pCR after NST.

The question of whether patients achieving cCR or pCR through MIB can be exempted from breast surgery has been addressed in previous retrospective studies by Ring (14) and Clouth (15), which included patients with stage III breast cancer. Their findings indicate that omitting breast surgery does not affect survival outcomes in the long run. However, there are no studies specifically examining the exemption of surgery in LABC. A multicenter phase II clinical trial (NCT02945579) (16) led by MD Anderson Cancer Center is exploring the possibility of omitting surgery after NST, but it has excluded LABC patients. Despite the pooled analysis published in *Lancet* (17) showing that patients who achieve pCR exhibit improved long-term survival rates, a recent meta-analysis (18) of 54 clinical studies found only a weak association between pCR and both disease-free survival (DFS) and overall survival (OS). The meta-analysis concluded that pCR should not be considered the primary endpoint in trials of NST for breast cancer. Currently, there are no effective methods available for accurately assessing pCR. Moreover, pCR cannot be considered a primary endpoint in research, as patients with LABC who achieve pCR are not yet exempt from surgery.

Breast surgery

Feasibility and safety of BCS in LABC patients

Is BCS considered a safe treatment option for LABC patients who exhibit positive response to NST? This paragraph explores the influence of tumor shrinkage patterns on the feasibility of BCS, evaluates the criteria for selecting patients for BCS, and discusses the implications of different margin definitions on clinical outcomes. The crucial aspect of BCS is to achieve a negative pathological margin, so it's important to understand the pattern of tumor regression. The tumor shrinkage patterns following NST predominantly exhibit concentric and non-concentric characteristics. Wang et al. (19) classified residual tumor morphology into three categories: isolated residual tumors (61%), multifocal and patchlike (33%), and main residues with satellite lesions (6%). Most tumors exhibited isolated concentric shrinkage, while the other two types demonstrated non-concentric shrinkage. The primary tumor's size directly influenced its concentric shrinkage pattern, with larger tumors more often showing non-concentric shrinkage, which complicates the attainment of negative margins. The application of BCS after NST is theoretically limited to tumors exhibiting concentric shrink patterns. For multiple lesions in the same quadrant, BCS can be attempted. The primary tumor in LABC is typically large and prone to be non-concentric. As a result, it is necessary to conduct imaging comparisons before and after NST in order to comprehensively assess the patterns of tumor shrinkage. Bi et al. (20) conducted a study on 3D MRI reconstruction of residual tumors, suggesting that a 50% reduction in the longest diameter and a size of ≤2 cm post-NST could qualify patients for BCS. This criterion could potentially expand the BCS-eligible patient population. After a median follow-up of 77 months, the rate of recurrence or metastasis was 7.1%. The National Comprehensive Cancer Network and St. Gallen consensus (21, 22) define negative margins for BCS after NST as "no ink on tumor," consistent with criteria for BCS without NST. However, a 2022 meta-analysis in the *British Medical Journal* (23) challenged this standard, finding that close margins (defined as no tumor on ink but <2 mm) were linked to a higher risk of local recurrence and metastasis compared to negative margins (≥2 mm), even when accounting for adjuvant chemotherapy and radiotherapy ($P < 0.001$).

This raises concerns about the adequacy of the "no tumor on ink" criterion for BCS post-NST. The safety of applying non-NST margin criteria to NST cases remains inconclusive due to insufficient high-level evidence.

The rate of BCS after NST in LABC patients ranged from 12.5% to 43.4% in several retrospective studies (24–27). BCS was found to be oncologically safe for LABC patients who responded well to NST. Younger patients, those with smaller tumors, and those achieving pCR were more frequently selected for BCS. Additionally, patients in the NST-BCS group were more commonly found to have HER2+/HR- or TNBC (24, 27), as well as non-invasive lobular carcinoma, compared to the mastectomy group (25, 26).

Sun et al. (28) conducted a meta-analysis of 16 studies, finding no significant difference in local recurrence-free survival (LRFS) between the BCS and mastectomy groups ($P = 0.26$). However, DFS and OS were higher in the BCS group ($P < 0.01$). This may be attributed to the higher pCR rates in the BCS group (29), which is associated with improved DFS and OS. While these results imply that BCS maybe safe for LABC patients who have a favorable response to NST, it should be noted that the studies referenced are all retrospective. Therefore, high-quality medical evidence is still needed to confirm these conclusions.

Feasibility and safety of IR after NST

Breast reconstruction offers patients who cannot undergo BCS an opportunity for a more aesthetically pleasing breast shape and can help mitigate some of the negative effects of total mastectomy. Considerations include the benefits of immediate reconstruction (IR) versus delayed reconstruction (DR), the oncological safety of different reconstruction techniques, and the effects of combining these procedures with NST and radiation therapy.IR is associated with higher physical and psychological satisfaction compared to DR, and patients desiring reconstruction may opt for IR without compromising safety (30). Procedures such as nipple-sparing, skin-sparing, or skin-reducing mastectomies allow for IR, with nipple-sparing mastectomies requiring a negative margin at the posterior of the nipple-areola complex (31). There is a lack of high-quality evidence confirming the oncological safety of nipple-sparing mastectomy combined with reconstruction. However, several retrospective studies indicate that IR after NST does not increase the risk of local recurrence or negatively impact long-term survival. For instance, Meli et al. (32) found that there is no significant difference in local recurrence or survival between patients who undergo nipple-sparing mastectomy with or without NST, suggesting that IR is a viable and safe option. Wu et al. (33) found no significant differences in long-term outcomes including 5-year LRFS, DFS, or OS between patients who had IR after NST and those who had NR. This indicates that opting for IR does not compromise long-term survival, thus reinforcing the safety and desirability of IR. However, some caution is advised. A study by Song et al. (34) highlighted those patients with tumors exceeding 3 cm who received IR had a lower 5-year DFS compared to those who had no reconstruction, suggesting that IR may be more appropriate for smaller tumors (≤3 cm). For stage T4 breast cancer, particularly inflammatory breast cancer, Pawloski et al. (35) found that IR significantly increased the likelihood of postoperative complications and delayed the start of radiotherapy, often by more than 8 weeks. Due to these complications and the observation that the average time until the first recurrence was 18 months within a median follow-up of 4.2 years, the study recommended postponing reconstruction for at least 18 months after surgery. Wu et al. (36) reported no significant differences in LRFS, DFS, or OS between patients with poor responses to NST who underwent nipple-sparing or skin-sparing IR and those who had mastectomy alone. This suggests that the response to NST should not solely determine the choice of IR. A meta-analysis (37) of 17 studies involving 3,249 patients examined the effect of NST on postoperative complications associated IR. The analysis found that neoadjuvant NST did not significantly raise the overall risk of postoperative complications ($P = 0.34$). The analysis did show a statistically significant rise in the rate of implant or expander loss ($P = 0.03$). This suggests that while NST does not broadly elevate the risk of complications, it may specifically heighten the risk of implant-related issues.

There is widespread agreement that postmastectomy radiation therapy can lead to skin discoloration and reduction in size of the nipple-areola complex (38). In the meantime, the 2022 recommendations from the Oncoplastic Breast Consortium (39) generally agree that post-mastectomy radiation therapy (PMRT) raises the risk of complications in all forms of implant-based breast reconstruction. Most experts in the field concur that PMRT carries a lower overall long-term risk of complications after immediate autologous reconstruction compared to implant-based reconstruction. In order to avoid delaying PMRT after IR, a reverse sequence (RS) of NST, preoperative radiotherapy, mastectomy and IR has been proposed. Paillocher et al. (40) included 111 patients with RS, with a median follow-up of 31.6 months. The 5-year DFS and OS were 93.2% and 98.3%, respectively, and patient satisfaction was high (17/20). In this study, radiotherapy was feasible 4 weeks after the end of NST in the RS group, while immediate autologous latissimus dorsi breast reconstruction surgery was feasible 6–8 weeks following the conclusion of radiotherapy in the standard sequence (SS) group, and RS could shorten the treatment time. Maire et al. (41) compared the RS and SS approaches using the autologous latissimus dorsi flap with or without an implant. With a median follow-up of 61.7 months, there was no significant difference between the groups in OS ($P = 0.44$) or RFS ($P = 0.30$). Postoperative morbidity also did not differ significantly between the two groups ($P = 0.51$). In the RS group, the average time from the end of radiotherapy to surgery was 5.9 weeks, compared to 8.4 weeks in the SS group from surgery to the start of radiotherapy, indicating that RS could significantly shorten treatment time ($P < 0.001$). To further explore the optimization of treatment timelines, the ongoing single-arm clinical trial NCT05412225 (42) is investigating the feasibility of preoperative radiotherapy followed by total mastectomy and autologous IR in LABC patients. This approach aims to avoid delays in radiotherapy after IR.

For LABC patients, doctors should guide them to fully understand the process, risks and benefits of reconstructive surgery, and be clear about the expected results of surgery. Patients with original large tumor, IR should be performed with great cautiousness. T4 stage, especially inflammatory breast cancer, IR is not recommended. Patients who are willing to reconstruct and need radiation therapy can receive radiation therapy before surgery after NST to shorten the treatment time and at the same time maintain the aesthetics of the breast after reconstruction.

Axillary lymph node management after NST

The use of NST has significantly changed the approach to axillary lymph node management in breast cancer. Traditionally, ALND was performed for patients with clinically positive nodes (cN+), but recent efforts have explored less invasive alternatives. The primary goal is to strike a balance between reducing surgical morbidity and maintaining oncological safety for these patients. A meta-analysis (43) including 33 studies revealed that axillary lymph node pCR rates by breast cancer subtypes in patients with cN+ were 60%, 45%, 48%, and 18% for HR-/HER2+, HR+/HER2+, HR-/HER2-, and HR+/HER2-, respectively. This suggests that patients with HER2+ and TNBC may be eligible for less extensive axillary surgery. Data from the Netherlands Cancer Registry (44) revealed that between 2006 and 2016, there was a notable increase in the rate of patients with initially negative axillary lymph nodes with non-invasive diagnostic methods (cN0) who underwent sentinel lymph node biopsy (SLNB) after NST, rising from 33% to 62%. Additionally, the rate of patients with cN+ who underwent ALND decreased from 99% to 63% ($P < 0.01$). There is ongoing debate about the conditions under which ALND can be safely omitted after NST. This discussion is particularly relevant when lymph nodes initially assessed as positive before treatment (cN+) are found to be negative upon pathological examination after treatment, as determined through SLNB (ypN0). The European Breast Cancer Research Association of Surgical Trialists (EUBREAST) conducted a global survey (45) in 2020, highlighting differing expert opinions on axillary management post-NST. Key points of contention include whether ALND can be omitted for patients whose positive nodes become negative (cN+→ ypN0) and the appropriate treatment for patients with sentinel lymph nodes (SLNs) showing isolated tumor cells (ypN0[i+]) or micrometastases (ypN1[mi]).

Data from large clinical trials (46–48) have found that NST potentially increase the FNR of SLNB due to its effects on axillary lymphatic reflux patterns, disruption of lymphatic structures, and induction of fibrosis. Several meta-analyses have also confirmed that the use of dual-tracer sampling and removing a minimum of three SLNs are effective in reducing FNR (49, 50). In addition, a strategy that involves marking nodes with biopsy-confirmed metastases prior to initiating NST and subsequently performing SLNB with targeted axillary dissection (TAD) has been shown to effectively reduce FNR. Anderson Cancer Center (51) revealed FNR of 10.1% and 1.4% for SLNB and SLNB in combination with TAD, respectively ($P = 0.03$).

Safety of cN+→ ypN0 exemption from ALND

There is some controversy in the guidelines as to whether cN+→ypN0 patients should be spared from ALND. Barrio et al. (52) conducted an analysis on a cohort of 610 patients diagnosed with cN1. Among those patients, 91% who were ypN0 underwent SLNB alone. It was found that 42% of these patients had three or more SLNs removed, and 70% of them received regional nodal irradiation (RNI). At a median follow-up of 40 months, recurrence in the axillary nodes was noted in just one patient, who did not undergo RNI. This study suggested that cN1→ ypN0 patients, and who had three or more SLNs identified through SLNB, may not require ALND. Tinterri et al. (53) studied 291 patients who were ypN0 after SLNB, including 131 who were cN0 and 160 who were cN+ before treatment. After a median follow-up of 43 months, the local recurrence rates in the axillary nodes were 2.3% for patients with cN0 and 1.3% for those with cN+. There were no significant differences in DFS and OS between the cN0 and cN+ groups or between those who had SLNB and those who had ALND. Similarly, Kahler et al. (54) analyzed 688 ypN0 patients after SLNB, with a median follow-up of 9.2 years. They observed local axillary recurrence rates of 1.8% for cN0 patients and 1.5% for cN1-2 patients, with no significant difference in DFS and OS between the groups. These retrospective studies consistently show that cN+ → ypN0 patients do not necessarily need ALND. However, some limitations exist, such as Tinterri et al.'s lack of detailed information about cN+ patients and Kahler et al.'s inclusion of only 12 cases of cN2 patients. In contrast, Park et al. (55) analyzed data from 22,156 cN2-3 patients in the National Cancer Database. Of these, 2,190 (9.9%) underwent SLNB. After adjusting for relevant factors, the study found that ALND was linked to a reduced risk of mortality compared to SLNB, even in patients who achieved pCR. In a study conducted by Lim et al. (56), 477 patients with cN1→ ypN0 were analyzed. At a median follow-up of 65 months, patients who underwent ALND had worse DFS ($P = 0.011$) and OS ($P = 0.0476$) compared to those who had only SLNB. They noted that the ALND group had a higher number of patients with larger tumors (T3-4). However, in the subgroup of patients with smaller tumors (cT1–2), there was no significant difference in DFS and OS between the two groups. The details of the corresponding retrospective studies are provided in Table 1.

The AXSANA trial (57), a multi-center prospective study, aims to recruit a total of 3,000 patients by the year 2030. The aim of this study is to evaluate the feasibility and safety of various surgical techniques, including ALND, SLNB, and TAD, in patients with positive lymph nodes. In summary, for LABC patients, particularly those achieving ypN0 status, it may be appropriate to consider less invasive surgical options like SLNB, especially when dealing with smaller tumors and fewer affected

TABLE 1 Summary of retrospective studies on cN+→ ypN0 patients.

Study	Enrollment	Surgical technique	Follow-up	Primary outcome
Barrio et al. (52)	555cN1	234 SLNB 321 ALND (no ypN0 or <3 negative SLNs)	40 months	Nodal recurrence:1 (refuse NRT).
Tinterri et al. (53)	131 cN0 160 cN+	226 ypN0: SLNB 65 ypN0: ALND	43 months	No statistically differences in DFS、OS between cN0 and cN+ nor between SLNB only or ALND.
Kahler et al. (54)	466 cN0 211 cN1 11 cN2	428 ypN0: SLNB 40 ypN+: SLNB 220 ypN+: ALND	9.2 years	Among 428 ypN0 patients, LRFS、OS、DFS has no difference between cN0 and cN1/2 groups.
Park et al. (55)	15176 cN2 6979 cN3	2190 SLNB 19966 ALND		ALND was associated with improved survival ($p < 0.001$) even for patients who achieved ypN0.
Lim et al. (56)	477 cN1	314 SLNB (17.5% cT3-4) 163 ALND (27.6% cT3-4)	65 months	ALND patients had significantly worse DFS ($P = 0.011$) and OS ($P = 0.0476$) but not in the cT1-2 group.

lymph nodes. However, for patients with more extensive disease, ALND may still be warranted until the final results of the AXSANA trial are available.

Axillary lymph node management for ypN0(i+) and ypN1(mi)

The management of ypN0(i+) or ypN1(mi) remains a topic of debate. Wong et al. (58) showed that the 5-year DFS of ypN0(i+) and ypN1(mi), ypN0 patients in the Dana-Farber/Brigham and Women's Cancer Center (DFBWCC) was 73.5%, 74.7%, and 88.4% ($P < 0.001$); the 5-year OS in the NCDB database was 82.8%, 79.5%, and 88.9% ($P < 0.001$). Subgroup analyses indicated that ypN0(i+) and ypN1(mi) exhibited a poorer prognosis compared to ypN0, particularly in cases of HER2+ and TNBC. Pending results from large clinical trials, this study suggested that patients with ypN0(i+) and ypN1(mi) should undergo ALND. In contrast, a retrospective study (59) conducted in the Netherlands revealed that there was no difference in the 5-year OS ($P = 0.889$) or DFS ($P = 0.613$) rates between patients with ypN0(i+) and ypN1(mi) compared to those with ypN0. The potential explanation for this disparity, aside from population variation, could be attributed to the fact that 70.4% of ypN0(i+) and 80.3% of ypN1(mi) cases included in the DFBWCC study ultimately underwent ALND, whereas in the Netherlands study, all patients underwent ALND. Kantor et al. (60) analyzed 4,496 patients with HR+/HER2-, finding no statistically difference between ypN0 or ypN+ in LRFS, OS, and DFS between those who underwent ALND and patients who did not. Based on these findings, the study suggested that ypN0(i+) and ypN1(mi) patients may not need ALND after neoadjuvant endocrine therapy. The international multicenter retrospective OPBC-05/ICARO study (61) examined 583 patients with ypN0(i+). Among them, 182 patients received ALND, while 401 did not. Among those who underwent ALND, 30% were found to have additional positive nodes. There was no significant difference in the 5-year rate of any oncologic outcomes. Consequently, the study suggests that routine ALND may not be necessary for this patient population. Existing studies present conflicting findings regarding the potential exemption of ypN0(i+) and ypN1(mi) from ALND. In the EUBREAST survey (45), it was found that 32.3% of the experts recommended no additional treatment for ypN0(i+) patients, while 33.1% suggested RNI. A total of 34.8% of the experts recommended ALND for ypN1(mi) patients, while 30.4% expressed a preference for RNI. The prevailing viewpoint among experts at the 2021 St. Gallen Conference (22) was in favor of RNI as opposed to ALND for patients with ypN0(i+), ypN1(mi). However, definitive guidelines are pending the results of ongoing clinical trials. The OT1-3-02 (62) and NSABP B-51/RTOG 1,304 (63) clinical trials were conducted to enroll patients with ypN0(i+) in order to examine the potential benefits of RNI. The Alliance A11202 (64) and TAXIS (65) phase III trials are evaluating the safety of omitting ALND in patients with ypN1(mi). The details of the corresponding retrospective studies are provided in Table 2.

Possibility of ALND omission in ypN+ patients

ALND is commonly used as a standard treatment for breast cancer patients with positive SLNs, but it is associated with significant morbidity. Recently, there has been interest in finding less invasive alternatives that maintain oncological safety. Efforts have been made to investigate the potential of SLNB and RNI as a safe alternative to ALND in certain cases. The ACOSOG Z0011 study (66) included 892 female patients with T1 or T2 breast cancer who underwent BCS and had metastases in one or two SLNs without palpable axillary lymphadenopathy, were followed for a median of 9.3 years. The results indicated that SLN alone was not inferior to that of patients treated with ALND. The AMAROS Trial (67) included 1,425 patients with cT1-2, node-negative breast cancer and a positive sentinel node biopsy, who were randomly assigned to either ALND or NRT. The 10-year analysis shows that both treatments resulted in a low axillary recurrence rate, with no significant differences in OS, DFS, or locoregional control. Though these two clinical trials did not include patients who received NST, they still provide a potential option for patients with LABC. Efforts have been made to find less invasive procedures for ypN+ patients.

The retrospective study conducted by Almahariq et al. (68) included patients with cT1-3N1 who were converted to ypN1 after NST from the NCDB. Out of the total sample, 1,313

TABLE 2 Summary of retrospective studies on ypN0(i+) and ypN1(mi) patients.

Study	Enrollment	Surgical technique	Follow-up	Primary outcome
Wong et al. (58)	967 cT1-4 N0-1	524 ypN0 (37.6%ALND) 27 ypN0(i+) (70.4%ALND) 61 ypN1(mi) (80.3%ALND) 221ypN1 (94.1%ALND) 134 ypN2-3 (100%ALND)	5 years	ypN0(i+) and ypN1(mi) exhibited a poorer prognosis compared to ypN0 and ALND is recommended.
Nijnatten et al. (59)	1347 cN+	299 ypN0 (SLNB) 51 ypNi/mi (ALND) 997 ypN1-3 (ALND)	5 years	No differences in DFS、OS between ypN0(i+) and ypN1(mi) compared to ypN0.
Kantor et al. (60)	4495 cT1-3 N0-1 (HR+/HER2-)	2510 ypN0 99 ypN0(i+) 257ypN1(mi) 948ypN+ (32.1% ALND)	5 years	No difference between ypN0 or ypN+ in LRFS, OS, and DFS between those who underwent ALND and patients who did not. ALND can be avoided.

patients underwent ALND and 304 patients underwent SLNB. All patients received RNI. The study found a statistically significant difference in 5-year OS between the two groups, with a higher survival rate in the ALND group compared to the SLNB ($P = 0.01$). Furthermore, the multivariate analysis revealed that SLNB was linked to lower survival rates ($P < 0.001$). A different conclusion was reached by Park et al. (69), who conducted a study incorporating data from 14 medical centers in South Korea. The study included 1,103 cases of ALND and 170 cases of SLNB, with all patients receiving RNI. With a median follow-up period of 75.3 months, the study found no statistically significant disparity in DFS ($P = 0.406$) or OS ($P = 0.083$) between two groups, and multivariate analysis indicated SLNB did not compromise oncological outcomes, suggesting that exemption from ALND could be a feasible option for ypN+ patients receiving RNI. The study conducted by Almahariq et al. (68) encountered limitations in data extraction from the NCDB, resulting in the specification of SLNs ranging from 1 to 4. On the other hand, the study conducted by Park et al. (69) did not impose any restrictions on the number of positive lymph nodes either prior to or following NST, but the median number of SLNs in this study was 6. A study conducted by Moo et al. (70) involving 273 patients with positive SLNs undergoing ALND revealed a high incidence of ALND positivity across all molecular subtypes, with no significant difference observed between micrometastases and macrometastases. Therefore, they recommend performing ALND for patients with positive SLNs, regardless of molecular subtype.

Several ongoing trials are exploring these alternatives. Alliance A11202 (64) is an ongoing phase III clinical trial to enroll 2012 cN1 patients with positive SLNs after NST, with one group receiving ALND followed by RNI and the other group receiving RNI alone. TAXIS (65) is a multinational, multicenter phase III clinical trial aimed at assessing the viability and effectiveness of exempting cN1-2 patients with positive SLNs from ALND, which includes both patients who receive NST or not. ADARNAT (71) is a multicenter, randomized, open-label phase 3 trial involving 1,660 patients with 1-2positive SLNs post-NST, across 50 Spanish centers. Patients will be assigned at random to either a group receiving NRT without ALND or a group undergoing ALND. The primary outcome is 5-year axillary recurrence. Table 3 provides detailed information on all the ongoing trials mentioned in this section.

Discussion

In conclusion, the management of LABC remains complex, requiring tailored to individual patient profiles. Challenges still persist in predicting complete responses to NST and omitting surgery seems inappropriate for LABC patients at this time. Existing retrospective studies have demonstrated the safety of BCS in patients who respond well to NST. However, the standard for negative margins after NST needs to be further validated through large-scale randomized controlled trials. For LABC patients with a desire for reconstruction, IR does not compromise tumor safety and does not increase complications. Patients who have large initial tumors should be cautious, and IR at T4 is not recommended. Patients with a desire for IR who still need radiotherapy after surgery, a reverse treatment sequence of NST, preoperative radiotherapy, mastectomy, and IR is feasible. Regarding axillary lymph node management, guidelines emphasize the importance of dual tracer imaging and the identification of three or more SLNs due to the increased FNR following NST. Some of the available retrospective studies had SLNs less than 3, which could potentially contribute to the significant variability in the results. Therefore, it is imperative to include SLN ≥3 as a crucial criterion in the design of clinical trials that explore exemptions from ALND. Based on the findings of retrospective studies, patients who have cN0-1 →ypN0 can potentially be excluded from undergoing ALND. However, it takes extreme caution when treating patients with cN2-3 →ypN0, and ALND is strongly recommended in such cases. As to whether the presence of micrometastases or macrometastases in the SLNs can exempt patients from ALND, the results of the available studies are inconsistent and definitive conclusions will have to await the long-term survival data from the various ongoing clinical trials. We have observed that few clinical studies on axillary lymph node management have considered the impact of different molecular subtypes. As noted by Swarnkar (72), persistent positive lymph nodes after treatment may suggest a more aggressive tumor in HER2-positive and TNBC patients, as these subtypes are generally more responsive to NST compared to luminal subtypes.

TABLE 3 Summary of ongoing large clinical trials.

Trial	Enrollment	Aim and procedures	Follow-up	Outcome measures
AXSAN (57)	cT1-4 N+→ ycN0（SLNB、TAD、ALND）	To evaluate SLNB、 TAD、ALND in cN+ patients treated With NST.	5years	invasive DFS, axillary recurrence rate, health-related quality of life, arm morbidity
Alliance A11202 (64)	cT1-4 N1 →ypN+(ypN0[i+] excluded) (SLNB, SLNs:1-8)	Assess the safety and outcomes of omitting ALND in patients who have ypN+ in the SLNB after NST Arm 1: ALND + NRT Arm 2: NRT + ART	8 years	IBC-RFI, OS, ILR-REC, Arm morbidity, Breast lymphedema
OT1-3-02 (62)	cT1-3 N1→ypN0 (SLNB、ALND)	To determine if NRT can reduce the recurrence of cN1→ypN0 patients. Arm 1: NRT Arm 2: no NRT	7.5 years	IBC-RFI, OS, LRRFI, DRFI, DFS-DCIS
NSABP-B-51 (63)	cT1-3N1→ypN0 (SLNB、ALND)	Evaluating NRT in cN1→ypN0 patients after NST. Arm 1: no NRT Arm 2: NRT	10 years	IBC-RFI, OS, LRRFI, DRFI, DFS-DCIS, Time to SPC
TAXIS (65)	cT1-3 N1-3→ypN+ (tailored axillary surgery, ypN0[i+] included)	Tailored axillary surgery and RT is non-inferior to ALND in terms of DFS of node positive patients at high risk of recurrence. Arm 1: ALND + NRT Arm 2: NRT + ART	20 years	OS, BCSS, STTLR, TTDR, Lymphedema, Shoulder motion
ADARNAT (71)	cT1-4N0-1→ypN+ (SLNB, 1–2 positive nodes)	To evaluate whether NRT is non-inferior to ALND in terms of 5-year axillary recurrence Arm 1: NRT Arm 2: ALND	5 years	Axillary locoregional recurrence, DFS, OS, Quality of life, Lymphedema

BCSS, breast cancer-specific survival; TTLR, time to local recurrence; TTDR, time to distant recurrence; IBC-RFI, invasive breast cancer—recurrence-free interval; DRFI, Distant recurrence-free interval; DFS-DCIS, disease-free survival for ductal carcinoma *in situ*; SPC, second primary cancer; STTLR survival time to local recurrence; ART, axillary radiation therapy.

This observation implies that such cases might necessitate more aggressive surgical approaches, such as ALND. Additional research is required to confirm this hypothesis and to further refine treatment strategies. Overall, the surgical approach following NST for LABC should be tailored based on pre-treatment clinical characteristics, NST efficacy, and the patient's overall condition. A balanced consideration of the benefits and risks, aligned with the patient's preferences, should guide a collaborative decision between the patient and the surgeon.

Author contributions

ZS: Writing – original draft, Conceptualization, Data curation, Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization. KL: Supervision, Visualization, Writing – original draft. YG: Supervision, Validation, Writing – original draft. NJ: Supervision, Validation, Writing – original draft. MY: Writing – review & editing, Conceptualization, Data curation, Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization.

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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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