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Neoadjuvant Chemotherapy in Breast Cancer: Toxicity Profile, Response Rates, and Surgical-Pathological Outcomes from a Single-Center Cohort

F. Al-Marzooqi[1*], M. Saeed[1], A. Khan[1]

[1]Department of Clinical Oncology, School of Medicine, University of Sharjah, Sharjah, UAE.

***E-mail** ✉ sharjah.clinonc.42@protonmail.com

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ABSTRACT

This research aimed to examine the neoadjuvant chemotherapy (NACTx) pathway in breast cancer (BC) patients, highlighting major therapy-related adverse effects (trAEs), tumor response profiles, operative and histopathologic outcomes, and determining the predictors of cavity shaving and axillary lymph node dissection (ALND) after sentinel lymph node biopsy (SLNB). A retrospective single-institution analysis was performed on individuals who received NACTx for BC between 2015 and 2021. Records from 242 cases were analyzed. Roughly 21.5% experienced grade ≥3 trAEs, and 3.3% discontinued therapy. Anthracycline-related cardiotoxicity occurred in 2.2%, including one fatality (mortality rate 0.4%). Surgical and pathological assessments were feasible for 229 participants. Clinical progression was reported in 3.9% (notably 14% among triple-negative BC; $p = 0.004$). Breast-conserving surgery (BCS) was achieved in 55% of patients. Surgical type (BCS vs. mastectomy) showed no meaningful relation with histologic classification, tumor size, molecular subtype, or pathological response level. Among BCS cases (n = 134), 20% needed cavity shaving because of invasive carcinoma at the surgical margin (SM). Both tumor histology (ductal vs. lobular; OR: 4.962, 95% CI 1.007–24.441, $p = 0.049$) and SUVMax score (OR: 0.866, 95% CI 0.755–0.993, $p = 0.039$) were independent determinants of SM involvement. SLNB was initially used in 75%, yet nearly half later required ALND. ALND incidence was higher in luminal A and LB-HER2(−) phenotypes (87% vs. 69%) compared with HER2(+) and triple-negative (43–50%) subgroups ($p = 0.001$). Every luminal A case and all invasive lobular tumors needed ALND after SLNB, whereas none in the HER2-enriched group did. Elevated ER and PR expressions increased the probability of requiring ALND, whereas HER2 positivity and higher lymph node SUVMax were inversely correlated. Overall, 27% reached complete pathological remission (pCR), though none occurred in luminal A patients. Owing to the risks of toxicity and disease advancement, the NACTx process requires vigilant clinical oversight. Treatment planning should be made by experienced multidisciplinary tumor boards that account for tumor biology and predicted therapeutic outcomes.

Keywords: Breast carcinoma, NACTx, Molecular classification, Therapy-induced toxicity, Clinical course, Operative results, Cavity re-excision, Histopathologic findings

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Introduction

Breast cancer (BC) represents the most frequently diagnosed malignancy and a primary contributor to cancer mortality among women globally [1, 2]. While surgery remains the foundation of treatment for non-metastatic BC, neoadjuvant chemotherapy (NACTx) is widely employed to render inoperable tumors operable, facilitate breast preservation, limit axillary dissection (AD), evaluate in vivo chemosensitivity, and eliminate micrometastatic disease. NACTx has become standard care for locally advanced disease and is increasingly offered in earlier but biologically aggressive forms [2-5].

The NACTx course, typically lasting 3–6 months, poses substantial clinical challenges, with some patients developing severe or irreversible treatment-related adverse effects (trAEs). Tumor progression during

chemotherapy (CTx) can result in loss of eligibility for breast-conserving surgery (BCS) or even necessitate mastectomy, in addition to elevating metastatic risk [6-9]. After NACTx completion, imaging reassessment is performed to determine tumor and lymph node (LN) response and to decide whether BCS and SLNB are feasible. Positive surgical margins (SM) following BCS or residual nodal disease after SLNB may require reoperation, lengthening anesthesia and procedure times [10, 11].

Selection of candidates for NACTx should be made by an integrated multidisciplinary tumor board composed of a breast surgeon, oncologist, pathologist, radiologist, and radiation specialist, ensuring that therapeutic goals and potential complications are clearly defined [12-14].

Breast cancer is biologically diverse and encompasses several molecular entities that shape both response to therapy and patient prognosis. Literature reviews highlight inconsistencies in defining these molecular subtypes, leading to broad categorizations (e.g., hormone receptor [HR]-positive or HER2-positive) that fail to capture underlying heterogeneity. Tumors expressing high levels of estrogen receptor (ER) and progesterone receptor (PR), coupled with low proliferation and low grade, tend to respond poorly to chemotherapy, while those with reduced HR expression and greater proliferative activity often exhibit higher sensitivity. Similarly, within HER2(+) BC, subsets such as HER2-enriched and HR(+)/HER2(+) show distinct chemosensitivity patterns [15, 16]. Thus, studies that employ rigorously defined molecular classification yield more reproducible, clinically relevant evidence, which is vital for refining personalized therapeutic strategies.

This investigation was designed to review and interpret NACTx treatment patterns and surgical–pathological results in BC patients evaluated by our multidisciplinary team. The main research questions were:

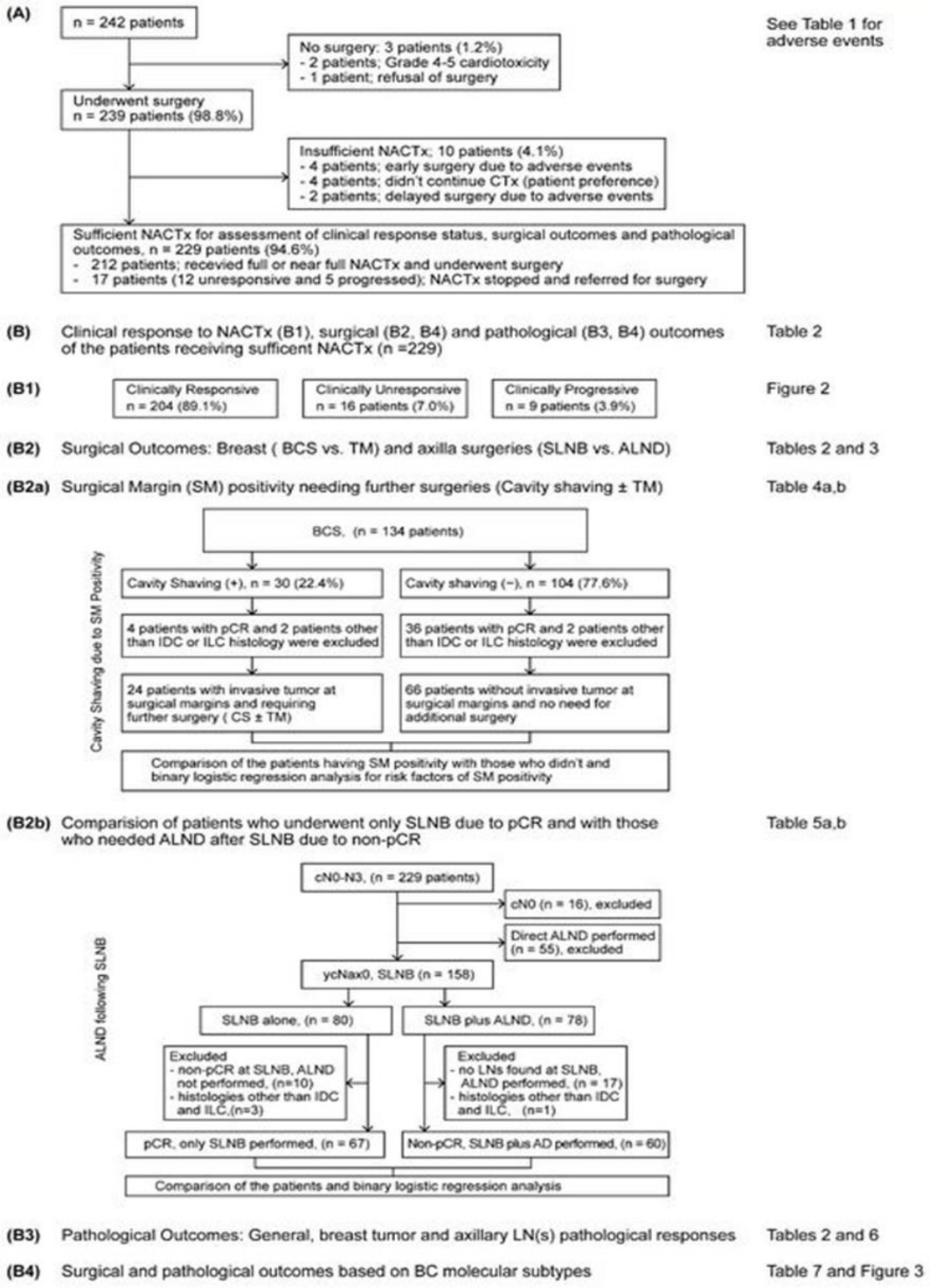
- What proportion of patients completed NACTx and proceeded to surgery?
- What was the frequency of grade ≥3 trAEs?
- How often did tumors respond or progress during NACTx, and which cases were at higher risk?
- What were the distribution and types of surgical interventions for breast and axilla?
- Which variables predicted additional surgery among patients undergoing BCS or SLNB?
- What were the pathological response rates across clearly defined molecular BC subtypes?

Materials and Methods

A retrospective analysis was carried out on breast cancer (BC) patients who received neoadjuvant chemotherapy (NACTx) between January 2015 and January 2021 at Bozyaka Education and Research Hospital, a tertiary care institution in Izmir, Turkey. Data were retrieved from hospital archives, encompassing demographic information, baseline tumor features (tumor diameter, multifocality, histological type, molecular subtype, clinical stage, and—when available—the results of axillary lymph node [LN] biopsy), chemotherapy regimens, treatment-related adverse effects (trAEs), clinical treatment responses, surgical interventions, and corresponding pathological findings.

Diagnosis of BC prior to treatment initiation was confirmed through core (tru-cut) biopsy of the primary lesion(s). Clinical staging was based on physical examination combined with imaging results. Each patient underwent bilateral mammography and ultrasound imaging of the breasts and axillae; most were also assessed using magnetic resonance imaging (MRI) and positron emission tomography (PET) for staging purposes.

All individuals starting NACTx were examined for completion status, causes of early discontinuation, occurrence of grade ≥ 3 trAEs, and whether surgical management followed chemotherapy. Only participants completing at least 90% of their scheduled cycles and proceeding to surgery were evaluated for tumor response and postoperative pathological outcomes **(Figure 1)**. Patients who either failed to complete chemotherapy, missed surgery, or had surgery postponed were not included in these analyses. Adverse events were graded in accordance with the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE), version 5.0.



Abbreviations: NACTx: Neoadjuvant chemotherapy, BCS: Breast-conserving surgery, TM: Total mastectomy, SLNB: Sentinel lymph node biopsy, ALND: Axillary lymph node dissection, SM: Surgical margin, CS: Cavity shaving, pCR: Pathological complete response, IDC: Invasive ductal carcinoma, ILC: Invasive lobular carcinoma, cN: Clinical lymph node, ycNax0: Clinical complete response in axillary lymph nodes

Figure 1. Study flow outline: (a) Overall treatment course for patients undergoing NACTx; (b1) response classification; (b2–b4) corresponding surgical and pathological outcome assessments.

Evaluation of clinical response

Imaging data, primarily ultrasonography during therapy and ultrasonography/MRI following chemotherapy, were used to categorize tumors into responsive, non-responsive, or progressive groups.

- A ≥30% shrinkage in measurable tumor dimension was considered a positive response.
- A ≥20% increase in tumor size defined progression.
- Enlargement or appearance of pathologic axillary LNs was also classified as disease progression.

Clinical course and tumor behavior were examined within each molecular subtype. Complete disappearance of previously pathologic LNs on imaging was interpreted as a clinical complete nodal response (cCR; ycNax0).

Surgical evaluation

The operative management of patients who received adequate chemotherapy was reviewed. Among those treated with breast-conserving surgery (BCS), the requirement for cavity shaving (CS) or conversion to total mastectomy (TM) was noted. For axillary procedures, the need for axillary lymph node dissection (ALND) after sentinel lymph node biopsy (SLNB) was also analyzed.

Reasons for performing ALND following SLNB—either incomplete pathological response or absence of retrieved sentinel nodes—were documented.

BCS cases with negative surgical margins (SM−) were compared to those with positive margins (SM+) who required additional resection. Likewise, patients who achieved pCR after SLNB were contrasted with those who underwent ALND due to persistent nodal disease.

Pathological assessment

Tumors were categorized into five molecular phenotypes based on the 2013 St. Gallen consensus:

- Luminal A (LA): ER ≥70%, PR ≥20%, HER2−, Ki-67 <14%;
- Luminal B–HER2−: other HER2-negative luminal cancers;
- Luminal B–HER2(+);
- HER2-enriched;
- Triple-negative (TN) [17].

Hormone receptor (HR) positivity was defined as ER or PR ≥1%. A pathologic complete response (pCR) was established when no invasive carcinoma was detected in the surgical specimen, regardless of ductal carcinoma in situ (DCIS).

Residual disease was graded as:

1. Minimal residual disease (MRD): <10% invasive component;
2. Partial response: ≥30% reduction in tumor size or cellularity relative to baseline;
3. No response: lack of histologic regression.

Pathological slides were re-evaluated if the response category was ambiguous. SM positivity was defined as “ink on tumor, ” which warranted re-excision (CS and/or TM).

Statistical analysis

Data distribution was assessed using Kolmogorov–Smirnov and Shapiro–Wilk tests. Continuous variables with normal distribution were analyzed via independent-sample t-tests, whereas nonparametric data employed the Mann–Whitney U test. Categorical variables were compared using Pearson’s chi-square (χ^2) or Fisher’s exact test when χ^2 conditions were unmet.

The impact of selected factors on the likelihood of CS after BCS and ALND after SLNB was examined through univariate and multivariate logistic regression models. All statistical tests were two-sided, with $p < 0.05$ considered significant. Analyses were performed using IBM SPSS Statistics v28.0 (Armonk, NY, USA).

Results and Discussion

NACTx course and treatment-related adverse events (n = 242)

A total of 242 breast cancer cases receiving NACTx during the study period were included. Chemotherapy-related toxicity caused treatment interruption in 8 patients (3.3%), which led to four early surgeries, two delayed surgeries, and two patients not operated on. An additional four individuals declined further chemotherapy, and one patient refused surgery entirely **(Figure 1a)**.

The remaining 229 participants (94.6%) successfully completed ≥90% of the prescribed regimen and subsequently underwent surgery, thus forming the evaluable group for clinical, surgical, and pathological analyses **(Figure 1b)**.

Overall, 52 grade ≥3 trAEs (21.5%) were recorded in 46 patients (19%) **(Table 1)**. The most common severe reaction was docetaxel-associated hand–foot syndrome, affecting 13.7% of docetaxel users (3.7% of the total cohort). Neutropenic fever requiring hospitalization occurred in six patients (2.5%). Anthracycline-induced cardiac toxicity (grade ≥3) developed in five of 225 patients (2.2%), resulting in one fatality (0.4%); two of these patients did not proceed to surgery. Diabetes-related complications caused surgical delays in two additional cases.

Table 1. Summary of grade ≥3 treatment-related adverse events (n = 242).

Adverse Event	n	Overall	Actual *
Allergic taxane reactions (n = 225)	5	2.1%	2.2%
Anthracycline cardiotoxicity (n = 225)	5	2.1%	2.2%
Docetaxel induced hand-foot syndrome (n = 68)	9	3.7%	13.2%
Acute renal failure	3	1.2%	
Acute gastroenteritis	4	1.7%	
Paclitaxel induced hepatotoxicity (n = 154)	4	1.7%	2.6%
Neutrophenic fever	6	2.5%	
Nail toxicity	3	1.2%	
Transfusion required anemia	5	2.1%	
Peripheric neuropathy	6	2.5%	
Diabetic complications	2	0.8%	
****Total adverse events in 46 patients ****	52	21.5%	

Notes: (*) Percentages refer to the number of patients receiving the specific chemotherapeutic drug. (**) Multiple adverse events could occur in the same patient during therapy.

Clinical outcomes of NACTx and surgical–pathologic findings (n = 229)

Patient profile and tumor attributes

Among the cohort, 229 individuals met inclusion criteria for evaluation of surgical, pathological, and treatment response outcomes. The average age was 51 years (ranging from 27 to 75 years), and approximately 85% were older than 40.

Histologically, invasive ductal carcinoma (IDC) dominated (89%), while an invasive lobular component (ILC) was present in 6.5% of patients.

Distribution across molecular subtypes revealed 10% Luminal A (LA), 45% Luminal B HER2-negative (LB–HER2−), 20.5% Luminal B HER2-positive (LB–HER2+), 8.7% HER2-enriched, and 15.7% triple-negative (TN).

The most prevalent tumor size category at diagnosis was T2, representing 63% of all cases. Clinically positive axillary lymph nodes (cNax1–3) were recorded in 93%. Of the 179 who underwent axillary biopsy, 129 had confirmed malignancy (pNax+).

Roughly 45% were early-stage (cT1–2/N0–1), another 45% fell into the locally advanced group (cT3–4 or N2–3), while the rest exhibited inflammatory or oligometastatic presentations. An overview of tumor data, chemotherapy regimens, and operative–pathologic findings is shown in **Table 2**.

Table 2. Clinicopathologic characteristics, NACTx regimens, and surgical–pathologic outcomes (n = 229).

Category	**Subgroup**	**n**	**%**
Age (years)	Mean ± SD (range)	51 ± 10	(27–75)
	18–30	4	1.7
	31–40	30	13.1
	41–50	84	36.7
	51–60	66	28.8
	61–70	41	17.9
	>70	4	1.7
Menopausal status	Pre-menopausal	97	42.4
	Peri-menopausal	24	10.5
	Post-menopausal	108	47.2

Molecular subtype	Luminal A	23	10.0
	LB-HER2(−)	103	45.0
	LB-HER2(+)	47	20.5
	HER2 enriched	20	8.7
	Triple-negative	36	15.7
Clinical stage	Local (early) *	104	45.4
	Locally advanced **	104	45.4
	Inflammatory	8	3.5
	Oligo-metastatic	13	5.7
Histology	Invasive ductal	203	88.6
	Invasive lobular	12	5.2
	Mixed	3	1.3
	Other	11	4.8
Tumor distribution	Solitary	116	50.7
	Multifocal	86	37.6
	Multicentric	27	11.8
Tumor size (mm)	Mean ± SD (range)	32 ± 14	(5–85)
cT	T1	32	14.0
	T2	144	62.9
	T3	21	9.2
	T4	32	14.0
cNaxilla	N0	16	7.0
	N1	125	54.6
	N2	73	31.9
	N3	15	6.6
ER status	Positive	167	72.9
	Negative	62	27.1
ER expression, %	Mean ± SD (range)	55 ± 40	(0–100)
ER score	0	62	27.1
	I	11	4.8
	II	21	9.2
	III	135	59.0
PR status	Positive	155	67.7
	Negative	74	32.3
PR expression, %	Mean ± SD (range)	41 ± 39	(0–100)
PR score	0	74	32.3
	I	21	9.2
	II	19	8.3
	III	115	50.2
HER2 status	Positive	67	29.3
	(FISH positive)	(15)	(6.6)
	Negative	162	70.7
Tumor grade	I	13	5.7
	II	125	54.6
	III	91	39.7
Ki-67, %	Mean ± SD (range)	35 ± 21	(5–90)
	<14	31	13.5
	14–20	45	19.7
	>20	153	66.8
Axillary LN biopsy	Yes	179	78.2
	No	50	21.8
Axillary LN biopsy result (n = 179)	Malign	129	72.1
	Benign	23	12.8
	Non-diagnostic	23	12.8
	Suspicious	4	2.2
Neoadjuvant Chemotherapy			

Cytotoxic chemotherapy regimen	DD AC (q14d)-wPtx	92	40.2
	EC (q21d)-wPtx	47	20.5
	DD AC (q14d)-Dtx (q21d)	44	19.2
	Only taxane (T) based	15	6.6
	Only anthracycline (A) based	12	5.2
	Other regimens (contains A plus T)	19	8.3
Chemotherapeutic agent	Epirubicin	56	24.5
	Doxorubicin	158	69.0
	Cyclophosphamide	217	94.8
	5-Fluorouracil	4	1.7
	Docetaxel	64	27.9
	Paclitaxel	153	66.8
	Carboplatin	11	4.8
Anti-HER2 drug(s) for HER2(+) disease (n = 67)	Trastuzumab	27	40.3
	LB-HER2(+)	(20)	
	HER2 enriched	(7)	
	Trastuzumab + Pertuzumab	39	58.2
	LB-HER2(+)	(27)	
	HER2 enriched	(12)	
	Not received	1 ***	1.5
Surgery			
Breast surgery	BCS	126	55.0
	Mastectomy	103	45.0
Axilla surgery	SLNB	92	40.2
	ALND	137	59.8
Overall Surgery	PM + SLNB	64	27.9
	TM + SLNB	28	12.2
	PM + AD	62	27.1
	TM + AD	75	32.8
Further surgery after BCS (n = 134)	BCS (no further surgery)	104	77.6
	BCS with cavity shaving	22	16.4
	BCS → Mastectomy	8	6.0
SLNB ± AD (n = 171)	SLNB only, no AD	92	40.2
	SLNB, malign LN → AD	62	27.1
	SLNB, no LN(s) → AD	17	7.4
	Directly AD	58	25.3
Pathologic Response			
Breast tumor (n = 229)	pCR	65	28.4%
	Near-pCR (MRD)	21	9.2%
	Partial response	103	45.0%
	Unresponsive	40	17.5%
Axillary LN(s); (cN0-N3), (n = 229)	pCR	88	38.4%
	Non-pCR	141	61.6%
Axillary LN(s); (cN1-N3), (n = 213)	pCR	88	41.3%
	Non-pCR	125	58.7%
Axillary LN(s) biopsy; malignant, pN+, (n = 129)	pCR	48	37.2%
	Non-pCR	81	62.8%
Overall PR (n = 229)	pCR	61	26.6%
	Partial	128	55.9%
	Unresponsive	40	17.5%

Notes: *cT1–2/N0–1; **cT3–4/N2–3; **patient with progression under anthracycline-based regimen.

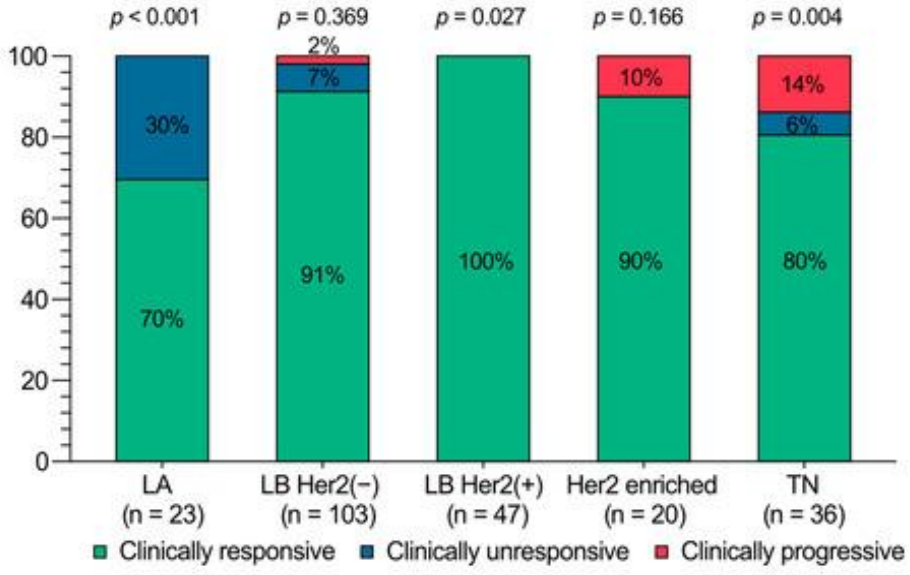
Abbreviations: SD – standard deviation; LN – lymph node; LB – luminal B; cT – clinical tumor stage; cN – clinical lymph node stage; ER – estrogen receptor; PR – progesterone receptor; EC – epirubicin + cyclophosphamide; DD – dose-dense; AC – doxorubicin + cyclophosphamide; wPtx – weekly paclitaxel; Dtx – docetaxel; q14d – every 14 days; q21d – every 21 days; BCS – breast-conserving surgery; PM – partial mastectomy; TM – total mastectomy; SLNB – sentinel lymph node biopsy; ALND (AD) – axillary lymph node dissection; pCR – pathologic complete response; MRD – minimal residual disease.

Neoadjuvant chemotherapy (NACTx)

A majority (88%) received sequential anthracycline–taxane chemotherapy (AT-sCTx), whereas 12% were treated exclusively with anthracycline (Ab-CTx) or taxane (Tb-CTx) agents.
The most frequent combinations were dose-dense AC (adriamycin + cyclophosphamide, q14d) followed by weekly paclitaxel (40%), EC (epirubicin + cyclophosphamide, q21d) followed by weekly paclitaxel (20%), and dose-dense AC (q14d) followed by docetaxel (q21d).
Among 67 HER2-positive individuals, 40% received trastuzumab alone, while 58% underwent dual HER2 blockade. Further details are listed in **Table 2**.

Clinical response evaluation

Following NACTx, 89% of participants displayed a favorable reduction in tumor burden, whereas 16 (7%) showed no measurable improvement. Nine patients (3.9%) experienced disease progression during therapy.
Within the triple-negative group, five deteriorated under anthracycline-based treatment. Four worsened despite transitioning to weekly paclitaxel, subsequently developed metastatic disease, and died within two years. The fifth proceeded to surgery but developed metastases 26 months later.
Two HER2-enriched tumors also progressed under anthracycline therapy—one underwent surgery, and the other later improved after taxane plus dual HER2-targeted therapy.
Additionally, two LB–HER2(−) cases worsened: one under taxane monotherapy, the other due to tumor necrosis with hemorrhage, representing pseudoprogression.
Progression was most frequent in the TN subtype (14%, $p = 0.004$), while LA tumors most often showed nonresponsiveness (30%, $p < 0.001$) **(Figure 2)**.
Eight of the progressing tumors were IDC, and one was metaplastic. Compared to the rest, these cases had higher Ki-67 indices (mean 59 ± 21 vs. 34 ± 20; median 65 vs. 30, $p = 0.003$) and a larger proportion of grade 3 lesions (78% vs. 38%, $p = 0.031$).



Note. The *p*-value (chi-square test) above the column of each molecular subtype represents the comparison of that molecular subtype with the other four molecular subtypes.

Figure 2. Clinical response to NACTx by molecular subtype (n = 229).

Surgical assessments

Breast surgery

Initial surgical management consisted of breast-conserving surgery (BCS) in 134 cases (59%). Cavity shaving (CS) was performed in 30 (22%), with 26 (19%) harboring residual invasive tumor at the surgical margin (SM). Subsequently, eight patients (6%) required total mastectomy (TM). In the end, 55% completed treatment with BCS, and 45% underwent TM **(Table 2)**.

Axillary surgery

Owing to clinical nodal remission (ycNax0), 171 patients (75%) initially underwent sentinel lymph node biopsy (SLNB). Nevertheless, 79 (46%) required axillary lymph node dissection (ALND)—62 due to residual malignancy, and 17 because no nodes were retrieved. Altogether, 40% had SLNB alone, whereas 60% underwent ALND, either immediately (25%) or following SLNB (35%) **(Table 2)**.

The rate of ALND was considerably higher among LA (87%) and LB–HER2(−) (69%) cancers but substantially lower in HER2-positive and TN variants (43–50%, p = 0.001). It was also more common in ILC compared with IDC (93% vs. 57%, p = 0.006).

Patients initially cNax0 achieved higher SLNB rates than those cNax+ (75% vs. 37.6%, p = 0.032). Among cN1, cN2, and cN3 stages, SLNB frequencies were comparable (38%, 37%, and 33%, respectively). Those with unresponsive, progressive, inflammatory, or oligometastatic disease showed very high ALND requirements (87–100%) **(Table 3)**.

Table 3. Breast (BCS vs. TM) and axillary (SLNB vs. ALND) surgical approaches.

Category	Subgroup	Breast Surgery: BCS	Breast Surgery: TM	p	Axilla Surgery: SLNB	Axilla Surgery: ALND	p
Overall		55% (n = 126)	45% (n = 103)		40% (n = 92)	60% (n = 137)	
Molecular subtypes	Luminal A	48% (11)	52% (12)	0.891	13% (3)	87% (20)	0.010
	LB-Her2(−)	57% (59)	43% (44)		31% (32)	69% (71)	0.011
	LB-Her2(+)	53% (25)	47% (22)		57% (27)	43% (20)	0.011
	Her2 enriched	50% (10)	50% (10)	0.484	50% (10)	50% (10)	
	Triple-negative	58% (21)	42% (15)	0.062	56% (20)	44% (16)	
Histology	IDC	56% (115)	44% (89)	0.218 *	43% (87)	57% (117)	0.006 *
	ILC	40% (6)	60% (9)		7% (1)	93% (14)	
	Other	50% (5)	50% (5)		40% (4)	60% (6)	
Tumor size, mm	Median (range)	29 (5–65)	30 (8–85)	0.288	32 (7–65)	28 (5–85)	0.307 m
Focality/centricity	Solitary	74% (86)	26% (30)	<0.001	45% (52)	55% (64)	0.281
	Multifocal	43% (37)	57% (49)		41% (11)	59% (16)	
	Multicentric	11% (3)	89% (24)		34% (29)	66% (57)	
cT	cT1	59% (19)	41% (13)	0.002	44% (14)	56% (18)	0.030
	cT2	63% (90)	37% (54)		42% (60)	58% (84)	
	cT3	38% (8)	62% (13)		57% (12)	43% (9)	
	cT4	28% (9)	72% (23)		19% (6)	81% (26)	
cN	cN0	50% (8)	50% (8)	0.054	75% (12)	25% (4)	0.032
	cN1	63% (79)	37% (46)		38% (48)	62% (77)	
	cN2	44% (32)	56% (41)		37% (27)	63% (46)	
	cN3	47% (7)	53% (8)		33% (5)	67% (10)	
Clinical stage	Early	68% (71)	32% (33)	<0.001	42% (44)	58% (60)	0.006
	Locally advanced	49% (51)	51% (53)		45% (47)	55% (57)	
	Inflammatory	0% (0)	100% (8)		13% (1)	87% (7)	
	Oligo-metastatic	31% (4)	69% (9)		0% (0)	100% (13)	
NACTx	Sequential CTx	56% (114)	44% (89)	0.434	42% (86)	58% (117)	0.077
	Only A	36% (4)	64% (7)		9% (1)	91% (10)	
	Only T	53% (8)	47% (7)		33% (5)	67% (10)	
Clinical response	Responsive	57% (117)	43% (87)	0.075	44% (89)	56% (115)	0.010
	Unresponsive	44% (7)	56% (9)		13% (2)	87% (14)	
	Progressive	22% (2)	78% (7)		11% (1)	89% (8)	
Tumor pR	pCR	62% (40)	38% (25)	0.551	80% (52)	20% (13)	<0.001
	MRD	52% (11)	48% (10)		52% (11)	48% (10)	
	Partial response	54% (56)	46% (47)		28% (29)	72% (74)	
	Unresponsive	48% (19)	52% (21)		0% (0)	100% (40)	
Axillary pR	pCR	67% (59)	33% (29)	0.004	80% (70)	20% (18)	<0.001

Non-pCR	48% (67)	52% (74)	16% (22)	84% (119)	

Note: p-values calculated between IDC and ILC (other subtypes excluded). m – Mann–Whitney U Test. Abbreviations: BCS – breast-conserving surgery; TM – total mastectomy; SLNB – sentinel lymph node biopsy; ALND – axillary lymph node dissection; IDC – invasive ductal carcinoma; ILC – invasive lobular carcinoma; LB – luminal B; cT – clinical tumor stage; cN – axillary lymph node stage; NACTx – neoadjuvant chemotherapy; CTx – chemotherapy; A – anthracycline; T – taxane; pR – pathological response; pCR – pathological complete response; MRD – minimal residual disease.

Risk factors for SM positivity during BCS

A comparison was made between 66 patients with clear surgical margins (SM) and 24 patients who had positive SM, requiring additional surgery (**(Figure 1, B2a)** for patient selection). Patients with positive SM had significantly lower tumor SUVmax values than those with clear margins (Mdn 9.4 vs. 6.2, p = 0.005). In terms of tumor type, invasive lobular carcinoma (ILC) had a notably higher rate of positive SM compared to invasive ductal carcinoma (IDC) (62.5% vs. 23.2%, p = 0.029). Among the eight ILC patients, five required cavity shaving (CS) **(Table 4)**. Multivariate logistic regression analysis identified tumor histology (IDC vs. ILC; OR: 4.962, 95% CI 1.007–24.441, p = 0.049) and tumor SUVmax value (OR: 0.866, 95% CI 0.755–0.993, p = 0.039) as significant predictors of positive SM **(Table 4)**.

Table 4. (a) Comparison of BCS patients with and without further surgery (cavity shaving ± mastectomy) based on the presence of invasive tumor at surgical margins. (b) Binary logistic regression analysis for cavity revision due to invasive tumor at surgical margins.

(a)

Category	**Subgroups/Unit**	**Cavity Shaving ± Mastectomy**									
		No (SM Negative, n = 66)				**Yes (SM Positive, n = 24)**					
		M ± SD (Range)/n-%			**Mdn**	**M ± SD (Range)/n-%**			**Mdn**	**p**	
Patient age	(years)	52	±10	(27–74)	50	50	±9	(32–66)	50	0.465	t
Molecular subtypes	Luminal A	7		58.3%		5		41.7%		0.544	X2
	LB-HER2(−)	39		76.5%		12		23.5%			
	LB-HER2(+)	11		84.6%		2		15.4%			
	HER2 enriched	2		66.7%		1		33.3%			
	Triple negative	7		63.6%		4		36.4%			
Histology	Invasive ductal	63		76.8%		19		23.2%		0.029	**f**
	Invasive lobular	3		37.5%		5		62.5%			
Clinical Stage	Early *	37		68.5%		17		31.5%		0.307	X2-cc
	Advanced **	29		80.6%		7		19.4%			
No of tumors	Solitary	40		70.2%		17		29.8%		0.520	X2-cc
	Multiple	26		78.8%		7		21.2%			
cT	cT1	9		64.3%		5		35.7%		0.695	X2
	cT2	49		75.4%		16		24.6%			
	cT3 and cT4	8		72.7%		3		27.3%			
Tumor size	(mm)	29	±11	(5–60)	29	30	±14	(8–65)	27	0.639	t
ER	Positive	55		74.3%		19		25.7%		0.756	**f**
	Negative	11		68.8%		5		31.3%			
PR	Positive	54		76.1%		17		23.9%		0.402	X2-cc
	Negative	12		63.2%		7		36.8%			
HER2	Positive	13		81.3%		3		18.8%		0.544	**f**
	Negative	53		71.6%		21		28.4%			
ER expression	(%)	66	±35	(0–100)	80	64	±37	(0–100)	80	0.889	m
PR expression	(%)	48	±38	(0–100)	50	50	±40	(0–100)	60	0.945	m
Ki-67 index	(%)	30	±16	(7–75)	25	29	±20	(7–80)	23	0.458	m
Tumor grade	Low-intermediate	41		71.9%		16		28.1%		0.882	X2-cc

	High	25		75.8%		8		24.2%			
Tumor SuvMax		10.1	±4.4	(2–27)	9.4	7.6	±4.7	(0–20)	6.2	0.005	m

(b)

Cavity Revision Required	**Univariate Model**					**Multivariate Model**				
	OR	**95% CI**			**p**	**OR**	**95% CI**			**p**
Patient age	0.982	0.937	-	1.030	0.461					
Clinical stage (Early vs. advanced)	0.525	0.192	-	1.436	0.210					
Solitary vs. Multiple tumor	0.633	0.231	-	1.738	0.375					
Tumor size (mm)	1.010	0.970	-	1.051	0.635					
IDC vs. ILC	5.526	1.208	-	25.280	0.028	4.962	1.007	-	24.441	0.049
ER status (positive vs. negative)	1.316	0.405	-	4.277	0.648					
ER expression (%)	0.998	0.985	-	1.012	0.812					
ER score (0–1 vs. 2–3)	0.844	0.263		2.712	0.776					
PR status (positive vs. negative)	1.853	0.629	-	5.455	0.263					
PR expression (%)	1.002	0.990	-	1.014	0.789					
PR score (0–1 vs. 2–3)	0.625	0.233		1.679	0.351					
HER2 status (negative vs. positive)	0.582	0.150	-	2.254	0.434					
Ki-67 index	0.997	0.970	-	1.025	0.814					
Tumor grade (1–2 vs. 3)	0.820	0.307	-	2.193	0.693					
Tumor SuvMax value	0.857	0.747	-	0.982	0.026	0.866	0.755	-	0.993	0.039

(a) Comparison of patients who underwent breast-conserving surgery (BCS) with or without further surgery (cavity shaving ± mastectomy) based on invasive tumor at surgical margins.

(b) Binary logistic regression for cavity revision due to invasive tumor at surgical margins.

Note: (a) t: t-test for independent samples, X^2: chi-square test, f: Fisher's exact test, X^2-cc: chi-square test—continuity correction, m: Mann–Whitney U Test. (b) Logistic regression (forward LR). Abbreviations: BCS: breast-conserving surgery, M: mean, SD: standard deviation, Mdn: median, ER: estrogen receptor, PR: progesterone receptor, cT: clinical tumor stage, * cT1–2 and N0–1 and M0, ** cT3–4 or N2–3 or M1, IDC: invasive ductal carcinoma, ILC: invasive lobular carcinoma.

Factors predicting ALND after SLNB

A total of 127 patients who had an initial sentinel lymph node biopsy (SLNB) due to cCR in the axilla (ycNax0) were analyzed (**(Figure 1, B2b)** for patient selection). Of these, 67 patients achieved axillary pathological complete response (pCR) and did not need axillary lymph node dissection (ALND), while 60 required ALND due to non-pCR. Significant differences were found between molecular subtypes ($p < 0.001$). All patients in the LA subtype who underwent SLNB required ALND, whereas none in the HER2-enriched subtype did. Additionally, ILC patients required ALND in all cases (IDC vs. ILC; 42% vs. 100%, $p < 0.001$) **(Table 5)**. Multivariate analysis identified several factors affecting ALND need: ER and HER2 status, PR expression, and SUVmax of axillary LN(s). Specifically, ER-positive tumors had a 19-fold increased likelihood of requiring ALND compared to ER-negative tumors. For each 10-unit increase in PR expression, the probability of needing ALND increased by 17%. On the other hand, HER2-positive tumors had a 90% reduced likelihood of requiring ALND. Furthermore, every 1-unit increase in SUVmax value of the axillary LN(s) led to a 9% decrease in the likelihood of ALND **(Table 5)**.

Table 5. (a) Axillary Surgery: Clinicopathological Characteristics

Category	**Subgroup / Unit**	**SLNB Only (pCR, n = 67)**		**SLNB + ALND (Non-pCR, n = 60)**		**p**	**Test**
		Mean ± SD (Range) / n–%	**Median**	**Mean ± SD (Range) / n–%**	**Median**		
Patient age (years)		49 ± 10 (27–70)	50	51 ± 9 (36–75)	50	0.303	t
Molecular subtype	Luminal A	0 (0%)	—	13 (100%)	—	<0.001	χ^2
	LB–HER2(–)	20 (34%)	—	39 (66%)	—		
	LB–HER2(+)	21 (78%)	—	6 (22%)	—		

	HER2-enriched	10 (100%)	—	0 (0%)	—		
	Triple-negative	16 (89%)	—	2 (11%)	—		
Histology	IDC	67 (58%)	—	49 (42%)	—	<0.001	χ^2-cc
	ILC	0 (0%)	—	11 (100%)	—		
Clinical stage	Early	26 (42%)	—	36 (58%)	—	0.017	χ^2
	Advanced	41 (63%)	—	24 (37%)	—		
Number of tumors	Single	36 (55%)	—	30 (45%)	—	0.674	χ^2
	Multiple	31 (51%)	—	30 (49%)	—		
cT category	T1	10 (43%)	—	13 (57%)	—	0.425	χ^2
	T2	42 (53%)	—	38 (48%)	—		
	T3–T4	15 (63%)	—	9 (38%)	—		
Tumor size (mm)		34 ± 14 (7–65)	32	27 ± 13 (5–75)	25	0.004	m
cN status	N1	40 (47%)	—	46 (53%)	—	0.064	χ^2-cc
	N2–N3	27 (66%)	—	14 (34%)	—		
ER status	Positive	35 (38%)	—	58 (62%)	—	<0.001	χ^2-cc
	Negative	32 (94%)	—	2 (6%)	—		
PR status	Positive	37 (40%)	—	55 (60%)	—	<0.001	χ^2-cc
	Negative	30 (86%)	—	5 (14%)	—		
HER2 status	Positive	31 (84%)	—	6 (16%)	—	<0.001	χ^2-cc
	Negative	36 (40%)	—	54 (60%)	—		
ER expression (%)		37 ± 41 (0–100)	10	77 ± 25 (0–100)	85	<0.001	m
PR expression (%)		27 ± 33 (0–100)	5	67 ± 34 (0–100)	80	<0.001	m
Ki-67 index (%)		42 ± 22 (8–90)	40	25 ± 15 (7–80)	20	<0.001	m
Tumor grade	Grade 1–2	32 (41%)	—	46 (59%)	—	0.002	χ^2-cc
	Grade 3	35 (71%)	—	14 (29%)	—		
Tumor SUVmax		14 ± 7 (3–48)	13	9 ± 4 (0–23)	9	<0.001	m
Axillary LN SUVmax		9 ± 6 (0–28)	8	6 ± 4 (0–21)	6	0.016	m

(b) Predictors of ALND Requirement (Univariate and Multivariate Regression)

Variable	Univariate OR	95% CI	p	Multivariate OR	95% CI	p
Patient age (years)	1.019	0.983–1.057	0.301	—	—	—
Clinical stage (early vs. advanced)	0.423	0.207–0.862	0.018	—	—	—
Solitary vs. multiple tumor	1.161	0.578–2.333	0.674	—	—	—
Tumor size (mm)	0.961	0.934–0.989	0.007	—	—	—
cN (N1 vs. N2–N3)	0.451	0.208–0.976	0.043	—	—	—
ER status (negative vs. positive)	26.514	5.982–117.515	<0.001	19.137	3.377–108.451	<0.001

ER expression (%)	1.031	1.019–1.043	<0.001	—	—	—
ER score (0–1 vs. 2–3)	10.676	3.799–30.002	<0.001	—	—	—
PR status (negative vs. positive)	8.919	3.170–25.093	<0.001	—	—	—
PR expression (%)	1.032	1.020–1.043	<0.001	1.017	1.002–1.032	0.029
PR score (0–1 vs. 2–3)	8.017	3.304–19.454	<0.001	—	—	—
HER2 status (negative vs. positive)	0.129	0.049–0.341	<0.001	0.110	0.035–0.341	<0.001
Ki-67 index (%)	0.950	0.927–0.973	<0.001	—	—	—
Tumor grade (1–2 vs. 3)	0.278	0.129–0.599	0.001	—	—	—
Tumor SUVmax	0.850	0.784–0.922	<0.001	—	—	—
Axillary LN SUVmax	0.908	0.846–0.975	0.008	0.909	0.835–0.990	0.029

(a) Comparison of clinicopathological characteristics of patients who underwent SLNB alone versus those requiring SLNB plus ALND.
(b) Binary logistic regression for ALND after SLNB due to non-pCR.
Note: (a) t: t-test for independent samples, X^2: chi-square test, X^2-cc: chi-square test—continuity correction, m: Mann–Whitney U test. (b) Logistic regression (forward LR). Abbreviations: SLNB: sentinel lymph node biopsy, ALND: axillary lymph node dissection, LN: lymph node, LB: luminal B, IDC: invasive ductal carcinoma, ILC: invasive lobular carcinoma, cT: clinical tumor stage, cN: clinical lymph node stage, ER: estrogen receptor, PR: progesterone receptor, HER2: human epidermal growth factor receptor-2, pCR: pathologic complete response.

Pathological outcomes

General pathologic response (breast and axillary LNs)

Of the 227 patients, 61 (27%) achieved pCR in both the breast and axilla. Significant differences were noted in pathologic response status (pCR vs. non-pCR) across molecular subtypes ($p < 0.001$). The LA subtype showed no pCR, while 15% of LB-HER2(−) patients, 45% of LB-HER2(+) patients, 65% of HER2-enriched patients, and 33% of TN patients achieved pCR. **Table 6** shows response rates by subtype and axillary lymph node involvement. In HER2(+) BC patients, a 30% pCR was achieved with trastuzumab and CTx, while dual anti-HER2 blockade and CTx led to a 67% pCR ($p = 0.007$).

Table 6. (a) Overall Cohort (cNax 0–3; n = 229) (b) Clinically Axillary LN Positive (cNax 1–3; n = 213) (c) Axillary LN Biopsy Positive (pNax+; n = 129)

Comparison of pCR vs. Non-pCR Across Groups

Category	(a) pCR	(a) Non-pCR	p*	(b) pCR	(b) Non-pCR	p*	(c) pCR	(c) Non-pCR	p*
General PR	27% (61)	73% (168)	<0.001	26% (55)	74% (158)	<0.001	26% (33)	74%	<0.001
Luminal A	0%	100%	0.005 cc	0%	100%	0.006 cc	0%	100%	0.012 f
LB-HER2(–)	15%	85%	<0.001	13%	87%	<0.001	9%	91%	<0.001 cc
LB-HER2(+)	45%	55%	0.003 cc	44%	56%	0.006 cc	39%	61%	0.092
HER2-enriched	65%	35%	<0.001 cc	65%	35%	<0.001 cc	71%	29%	<0.001 cc
Triple-negative	33%	67%	0.433 cc	34%	66%	0.327 cc	46%	54%	0.094 f
Breast Tumor PR	28% (65)	72% (164)	<0.001	27% (58)	73% (155)	<0.001	27%	73% (94)	<0.001

Luminal A	0%	100%	0.003 cc	0%	100%	0.004 cc	0%	100%	0.011 f
LB-HER2(–)	16%	84%	<0.001	14%	86%	<0.001	9%	91%	<0.001 cc
LB-HER2(+)	51%	49%	<0.001 cc	49%	51%	<0.001 cc	45%	55%	0.018 cc
HER2-enriched	65%	35%	<0.001 cc	65%	35%	<0.001 cc	71%	29%	<0.001 f
Triple-negative	33%	67%	0.606 cc	34%	66%	0.442 cc	46%	54%	0.113 f
Axillary LN PR	38% (88)	62% (141)	<0.001	41% (88)	59% (125)	<0.001	37% (48)	63% (81)	<0.001
Luminal A	0%	100%	<0.001 cc	0%	100%	<0.001 cc	0%	100%	0.004 cc
LB-HER2(–)	25%	75%	<0.001	27%	73%	<0.001	18%	82%	<0.001 cc
LB-HER2(+)	55%	45%	0.012 cc	63%	37%	0.003 cc	55%	45%	0.034 cc
HER2-enriched	95%	5%	<0.001 cc	95%	5%	<0.001 cc	100%	0%	<0.001 cc
Triple-negative	47%	53%	0.320 cc	53%	47%	0.202 cc	54%	46%	0.231 [f]

General (breast and axilla), breast tumor, and axillary LN(s) pathologic responses. Note: *: Chi-square test, f: Fisher's exact test, cc: continuity correction. Abbreviations: Bx: biopsy, cNax: clinical axillary lymph node stage, pNax: histopathologically malignant axillary lymph node, pCR: pathological complete response, PR: pathologic response, LN: lymph node.

Primary breast tumor pathologic response

Sixty-five patients (28%) achieved pCR in the breast. There were significant differences across molecular subtypes ($p < 0.001$), with no pCR in the LA subtype. Among other subtypes, 15% of LB-HER2(−), 51% of LB-HER2(+) patients, 65% of HER2-enriched, and 33% of TN patients achieved pCR **(Table 6)**.

Axillary LN(s) pathologic response

Eighty-eight patients (38%) achieved pCR in the axilla (ypNax0). No patients from the LA subtype showed axillary pCR. However, 25% of LB-HER2(−), 50% of LB-HER2(+) and TN patients, and almost all HER2-enriched patients did ($p < 0.001$). Similar trends were observed in analyses of cNax+ ($n = 213$) and pNax+ ($n = 129$) patients **(Table 6)**. Among the 16 cNax0 cases, none demonstrated axillary pCR despite being cN0.

Surgical and pathological outcomes by molecular subtypes

Table 7 and **Figure 3** provide a detailed breakdown of tumor characteristics, NACTx regimens, clinical response status, and surgical and pathological outcomes by molecular subtype of BC.

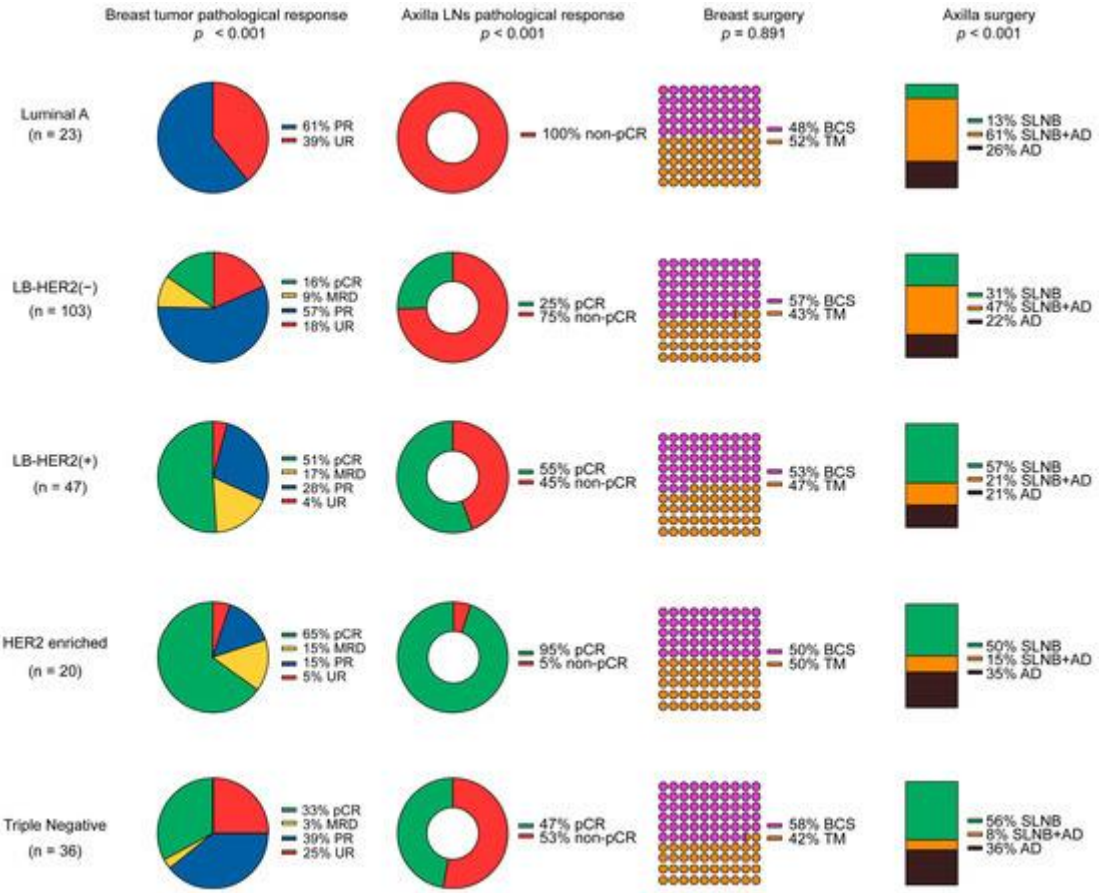


Figure 3. Surgical and pathological outcomes categorized by molecular subtypes of breast cancer.

Table 7. Overview of tumor traits and surgical-pathological results based on molecular subtypes.

Categories	Subgroups/Units	Molecular Subtype										
		Luminal A (n = 23)		LB-HER2(−) (n = 103)		LB-HER2(+) (n = 47)		HER2 Enriched (n = 20)		Triple Negative (n = 36)		
		n	%	n	%	n	%	n	%	n	%	p
Age, years	mean ± SD	54	±10	51	±10	53	±9	49	±10	48	±11	0.028 a*
Tumor size, mm	median (range)	25	(13–50)	27	(5–75)	30	(16–85)	31	(14–60)	33	(12–80)	0.097 kw
Histology	IDC	19	83%	88	85%	44	94%	19	95%	34	94%	0.166 X2
	ILC	4	17%	9	9%	2	4%	0	0%	0	0%	
	Other	0	0%	6	6%	1	2%	1	5%	2	6%	
Clinical stage	Early	12	52%	54	52%	18	38%	4	20%	16	44%	0.070 X2
	Advanced	11	48%	49	48%	29	62%	16	80%	20	56%	
cT	cT1–T2	20	87%	77	75%	38	81%	14	70%	27	75%	0.628 X2
	cT3–T4	3	13%	26	25%	9	19%	6	30%	9	25%	
cN	cN0–N1	18	78%	69	67%	27	58%	6	30%	21	58%	0.012 X2
	cN2–N3	5	22%	34	33%	20	43%	14	70%	15	42%	
Number of tumors	Solitary	13	57%	61	59%	17	36%	5	25%	20	56%	0.012 X2
	Multiple	10	43%	42	41%	30	64%	15	75%	16	44%	
Chemotherapy	Sequential CTx	17	74%	98	95%	38	81%	17	85%	33	92%	
	Only A	3	13%	4	4%	0	0%	1	5%	3	8%	
	Only T	3	13%	1	1%	9	19%	2	10%	0	0%	
	Trastuzumab	-	-	-	-	20	43%	7	37%	-	-	
	Dual Anti-Her2	-	-	-	-	27	57%	12	63%	-	-	
	Responsive	16	70%	94	91%	47	100%	19	95%	29	81%	

Clinical response	Unresponsive	7	30%	7	7%	0	0%	0	0%	2	6%	<0.001 X^2
	Progressive	0	0%	2	2%	0	0%	1	5%	5	14%	
Breast surgery	BCS	11	48%	59	57%	25	53%	10	50%	21	58%	0.891 X^2
	TM	12	52%	44	43%	22	47%	10	50%	15	42%	
Cavity shaving	No	7	58%	50	78%	23	88%	8	80%	16	73%	0.323 X^2
	Yes	5	42%	14	22%	3	12%	2	20%	6	27%	
Breast PR	non-pCR	23	100%	87	84%	23	49%	7	35%	24	67%	<0.001 X^2
	pCR	0	0%	16	16%	24	51%	13	65%	12	33%	
Breast surgery for cT1-T2, (n = 176)	BCS	10	50%	50	65%	23	60%	8	57%	18	67%	0.749 X^2
	TM	10	50%	27	35%	15	40%	6	43%	9	33%	
cT3-T4, (n = 53)	BCS	1	33%	9	35%	2	22%	2	33%	3	33%	0.974 X^2
	TM	2	67%	17	65%	7	78%	4	67%	6	67%	
Axilla surgery −1	SLNB	3	13%	32	31%	27	57%	10	50%	20	56%	<0.001 X^2
	AD	20	87%	71	69%	20	43%	10	50%	16	44%	
Axilla surgery - 2	SLNB only	3	13%	32	31%	27	57%	10	50%	20	56%	<0.001 X^2
	SLNB plus AD	14	61%	48	47%	10	21%	3	15%	3	8%	
	Direct AD	6	26%	23	22%	10	21%	7	35%	13	36%	
Axillary LN(s) PR	non-pCR	23	100%	77	75%	21	45%	1	5%	19	53%	<0.001 X^2
	pCR	0	0%	26	25%	26	55%	19	95%	17	47%	
Axilla surgery for cN0-N1, (n = 141)	SLNB	1	6%	25	36%	16	59%	4	67%	14	67%	<0.001 X^2
	AD	17	94%	44	64%	11	41%	2	33%	7	33%	
cN2-N3, (n = 88)	SLNB	2	40%	7	21%	11	55%	6	43%	6	40%	0.134 X^2
	AD	3	60%	27	79%	9	45%	8	57%	9	60%	
General pCR (breast and axilla)		0	0%	15	15%	21	45%	13	65%	12	33%	<0.001 X^2

Note: X^2: Chi-square test, a: one-way ANOVA, * no significant pairwise differences after Bonferroni correction, kw: Kruskal–Wallis test. Abbreviations: SD: standard deviation, IDC: invasive ductal carcinoma, ILC: invasive lobular carcinoma, cT: clinical tumor stage, cN: clinical axillary lymph node stage, LN: lymph node, BCS: breast-conserving surgery, TM: total mastectomy, PR: pathological response, pCR: pathological complete response, SLNB: sentinel lymph node biopsy, AD: axillary dissection.

Luminal A (n = 23)

Approximately 75% of these patients underwent AT-sCTx, and no clinical progression was observed. However, 30% showed no therapeutic response. Breast-conserving surgery (BCS) was performed in 48% of patients, with sentinel lymph node biopsy (SLNB) used in 13% and axillary lymph node dissection (ALND) in 87%. Cavity shaving (CS) was performed in 42% of patients. Of those who had SLNB, all 17 required ALND (showing non-pCR in the axilla). No patients reached pCR in either breast or axilla **(Table 7)**. MRD was absent in all cases, and 39% were pathologically unresponsive.

LB-HER2(−) (n = 103)

The majority (95%) received AT-sCTx. Only 2% experienced disease progression. Surgical procedures included BCS (57%), SLNB (31%), and ALND (69%). CS was required in 22%, and 60% (48 out of 80) of patients who underwent SLNB later required ALND. The breast pCR rate was 16%, axillary pCR was 25%, and overall pCR was 15% **(Table 7)**.

LB-HER2(+) (n = 47)

Most patients (81%) underwent AT-sCTx, while 19% had Tb-CTx. All patients showed positive responses to NACTx. BCS was done in 53%, SLNB in 57%, and ALND in 43%. CS was needed by 12%, with 27% requiring ALND after SLNB. pCR rates were 51% in the breast, 55% in the axilla, and 45% overall **(Table 7)**.

HER2 enriched (n = 20)

The majority (85%) of patients had AT-sCTx, 10% received Tb-CTx, and 5% (one patient) underwent only Ab-CTx. Progression was observed in 10% of patients treated with Ab-CTx, one of whom was referred for surgery, while the other switched to Tb-CTx with HER2-targeting drugs. BCS was performed in 50%, SLNB in 50%, and ALND in 50% of cases. CS was required by 20%, and ALND after SLNB was needed in 23%. pCR in the breast was 65%, 95% in the axilla, and 65% overall **(Table 7)**.

Triple-negative (n = 36)

A large majority (92%) of patients received AT-sCTx, while 8% received only Ab-CTx. Fourteen percent experienced clinical progression during Ab-CTx. Surgical procedures included BCS (58%), SLNB (56%), and ALND (44%). CS was performed in 27%, and 13% of SLNB patients required ALND. pCR in the breast was 33%, in the axilla 47%, and overall 33% **(Table 7)**.

While NACTx provides significant improvements, particularly in surgical outcomes, it is not without its risks. Monitoring is essential due to the severe side effects associated with chemotherapy and the potential for disease progression. In this study, 3.3% of participants were unable to complete their prescribed NACTx due to treatment-related adverse events (trAEs). This led to 1.6% undergoing surgery prematurely, 0.8% experiencing delays, and 0.8% being deemed ineligible for surgery.

Clinical progression

Studies on clinical progression during NACTx for BC typically report rates between 3% and 4% [9, 18, 19]. Caudle *et al*. noted a 3% progression rate (59 out of 1928 patients, 1994–2007), with some patients developing distant metastases, others needing mastectomies instead of BCS, and a few becoming inoperable [9]. Similarly, Nozawa *et al*. documented a 4% progression rate (24 out of 595 patients, 2001–2018). Patients with progression had significantly worse disease-free and overall survival rates compared to non-progressed patients [17]. Our research found a clinical progression rate of 4%, which aligns with these previous findings. However, progression rates varied by BC molecular subtype. Notably, the highest progression rate (14%) was found in the TN subtype, whereas the LA subtype had no progression. These differences underscore the importance of monitoring disease progression in the context of molecular subtypes, as illustrated in **Figure 2**.

Progressing tumors often displayed aggressive features, such as higher Ki-67 indices and greater tumor grades, which supports the findings of Caudle *et al*. [9]. In our study, five TN patients progressed despite Ab-CTx, with four continuing to progress after a chemotherapy switch. All of these patients eventually developed metastases and passed away. In contrast, two HER2(+) patients who progressed under Ab-CTx had one referred for surgery and the other switched to a taxane regimen with HER2-targeted therapy, which yielded positive results. A retrospective analysis of TNBC patients treated with NACTx found 10.3% (26 out of 252) showed radiologic progression [20]. Given the poorer survival outcomes for patients who progress under NACTx, progression in aggressive subtypes like TNBC remains a significant clinical challenge. The best treatment for these patients when progression occurs is still debated, but options like chemotherapy switches (e.g., platinum-based therapies or taxane ± immunotherapy) or surgery may be considered. Based on our findings and current literature, we recommend close monitoring of TNBC patients during NACTx, with immediate surgical referral if progression occurs [18]. For HER2(+) patients experiencing progression under Ab-CTx, switching to HER2-targeted regimens or Tb-CTx-based therapy should be considered [21-23].

Use of anthracyclines

Anthracyclines are a staple in neoadjuvant chemotherapy (NACTx) for breast cancer (BC), yet they are linked to serious side effects such as cardiotoxicity (e.g., heart failure, arrhythmias) and secondary blood cancers [24-30]. In a meta-analysis of 18 studies with 22, 815 cancer patients receiving anthracyclines, 6.3% developed overt cardiotoxicity, 17.8% showed subclinical signs, and 0.4% died from cardiac-related issues. The risk of cardiotoxicity increased with extended follow-up periods, averaging 9 years [31]. In our cohort, 2.2% of patients receiving anthracyclines developed overt cardiotoxicity during or immediately after treatment, and one patient (0.4%) died. The incidence of cardiotoxicity is likely to rise with longer follow-up. Due to the severe potential side effects, it's advised to minimize the use of anthracyclines when possible. Alternatives such as docetaxel-cyclophosphamide for early HR(+) BC and TNBC, as well as Tb-CTx combined with dual HER2-targeting therapies for HER2(+) BC, are preferred [32-35]. In cases where anthracyclines are necessary, epirubicin may be a better option than doxorubicin, as it allows for higher cumulative doses [36].

Luminal A (LA) disease

In this study, no LA breast cancer (BC) patients achieved a pathological complete response (pCR). With the majority having cT1-T2 tumors, BCS could have been an option without NACTx, though only half chose this route. Despite 74% of patients achieving a clinical complete response (cCR) in the axilla, none showed pCR in SLNB, and all required axillary lymph node dissection (ALND). Other studies have documented pCR in LA patients after NACTx, though their definitions of LA differ from generally accepted criteria. Collins *et al*. reported an 8% pCR in 114 patients, but their criteria did not align with the established definition for LA [37]. A meta-analysis of 156 LA cases reported an axillary pCR of 13%, but four of the studies did not meet the LA criteria [38]. In contrast, only one study using the 2013 St. Gallen consensus for LA definition reported a 0% pCR [17, 39]. Our study, which used precise LA criteria (ER $\geq$ 70, PR $\geq$ 20, Ki-67 < 14, and HER2-negative), indicates that achieving pCR in LA patients is unlikely. NACTx in early-stage LA BC could result in overtreatment and excessive exposure to anthracyclines. The ACOSOG Z0011 trial suggests that ALND may be avoided in patients with 1-2 pathologic sentinel lymph nodes who do not receive NACTx [40]. However, in those receiving NACTx, unnecessary ALND is almost inevitable due to lack of pCR. Alternative strategies, such as surgery or non-anthracycline chemotherapy regimens, might be more appropriate for this patient group.

HER2(+) disease

The addition of trastuzumab to NACTx has been shown to improve pCR rates in HER2-positive BC [41]. The NEOSPHERE trial demonstrated that pCR rates rose from 29% to 46% with dual HER2-targeted therapy [42]. Our study also found that dual HER2 therapy significantly improved pCR (67% vs. 30%, p = 0.007). A meta-analysis highlighted that HER2-enriched BC patients tend to have much higher pCR rates than LB-HER2(+) patients [43]. We saw a similar trend in our data, with HER2-enriched patients showing higher pCR rates (65% vs. 45%, p = 0.128). In the LB-HER2(+) group, breast and axilla pCR rates were consistent with BCS and SLNB success rates (51% vs. 55%, 53% vs. 57%). However, for HER2-enriched patients, the pCR rates were significantly higher in both the breast (65%) and axilla (95%) compared to LB-HER2(+), though BCS and SLNB rates were lower (50% vs. 50%). A higher incidence of multifocal or multicentric disease in HER2(+) cases (LB-HER2(+): 64% vs. HER2-enriched: 75%) may partly explain the need for total mastectomy (TM), though it seems that TM is often performed unnecessarily. Among the 19 HER2-enriched patients receiving optimal treatment, all achieved pCR in the axilla, yet half still underwent ALND. Factors influencing this decision could include concerns about SLNB effectiveness after NACTx, lack of clear protocols for SLNB after chemotherapy, or reliance on pre-treatment nodal status. Despite persistent clinical axillary node positivity, patients with high pCR rates should still be considered for SLNB.

Triple-negative (TN) disease

In TNBC, pCR rates of 30-40% are achievable with AT-sCTx. Adding carboplatin increases the pCR rate to 52% [44]. Our study, using AT-sCTx without carboplatin, achieved a pCR rate of 33%, which aligns with existing findings. NACTx is often the treatment of choice for TNBC due to its significant chemosensitivity [44, 45]. However, TNBC is a heterogeneous disease with distinct molecular subtypes, such as basal-like 1 (BL-1), basal-like 2 (BL-2), mesenchymal (M), and luminal androgen receptor (LAR), each having different levels of chemosensitivity. The BL-1 subtype, the most prevalent, shows the highest response to chemotherapy, with a pCR rate of 41%. On the other hand, BL-2 and LAR subtypes have much lower pCR rates (18% and 29%, respectively) [46]. In our cohort, about 25% of cases had no pathological response, and 14% showed clinical progression, emphasizing the heightened risk of progression in this subtype. This data supports previous research indicating poor outcomes for patients with progression during NACTx [8, 19].

Cavity shaving

The incidence of positive surgical margins (SM) that necessitate additional interventions after neoadjuvant chemotherapy (NACTx) ranges from 5% to 40% [47]. In our study, 22% of patients required cavity shaving (CS) and/or total mastectomy (TM) due to positive margins following breast-conserving surgery (BCS). Analyzing those who had CS due to positive margins versus those who didn't provides important insights into surgical approaches. Notably, patients who needed CS tended to have tumors with lower SUVmax values, implying that tumors with lower metabolic activity may spread more widely, making it harder to obtain clear SM during surgery. Moreover, a significantly higher percentage of patients with invasive lobular carcinoma (ILC) required CS

compared to those with invasive ductal carcinoma (IDC) (62.5% vs. 23.2%). This indicates the challenges associated with ILC, which tends to spread more diffusely and lacks well-defined borders, complicating the ability to achieve a clear surgical margin. Multivariate regression analysis further confirmed that both tumor type and SUVmax values play a critical role in determining the need for CS. ILC patients needed CS five times more often than IDC patients, and tumors with higher metabolic activity had a lower likelihood of requiring CS. Studies have shown that adding intraoperative circumferential CS can help reduce positive margin rates and the need for re-excision in patients at high risk for positive SM [48, 49].

ALND after SLNB

The integration of neoadjuvant chemotherapy (NACTx) and sentinel lymph node biopsy (SLNB) has resulted in a significant reduction in the need for axillary lymph node dissection (ALND) in breast cancer patients. Research by Tinterri *et al*. showed that patients with cNax+ disease who became ycNax0 after NACTx and underwent SLNB alone had significantly better long-term survival outcomes compared to those who underwent ALND either directly or following SLNB [50]. This supports the idea that minimizing axillary surgery can be beneficial for long-term cancer control. In our study, around 75% of patients achieved a ycN0 status in the axilla and underwent SLNB. However, half of these patients still required ALND, either because no lymph nodes were found (22%) or because of non-pCR in the SLNB (78%). When analyzing the factors that influenced the need for ALND after SLNB, we found that ER positivity, elevated PR expression, HER2 negativity, and low SUVmax retention in axillary lymph nodes were all associated with an increased need for ALND. These factors should be considered when planning axillary surgery for patients who show clinical complete response (cCR) in the axilla after NACTx. If ALND is deemed likely, performing a frozen section analysis of sentinel lymph nodes can prevent the need for additional surgeries. The analysis of patients needing ALND due to lack of pCR in the axilla showed that ILC patients required ALND far more often than IDC patients (100% vs. 42%, $p < 0.001$). As for molecular subtypes, 11% of triple-negative (TN), 22% of LB-HER2(+), and 66% of LB-HER2(−) patients required ALND after SLNB. Every patient in the LA subtype needed ALND, whereas none in the HER2-enriched subtype did. These findings suggest that the axillary clinical response after NACTx may not be as reliable for ILC or LA subtypes but is more predictive for HER2-enriched and TNBC subtypes.

Pathological response

In clinical breast cancer trials, pathological complete response (pCR) is commonly used as an indicator of the effectiveness of NACTx. Studies have consistently shown that achieving pCR correlates with improved long-term survival rates, including better disease-free survival and overall survival. This correlation is particularly strong in aggressive molecular subtypes such as TNBC and HER2-positive BC [51-53]. Since achieving pCR is associated with reduced recurrence and improved survival, various treatments are being tested or employed to improve pCR rates in different molecular subtypes. Adding carboplatin or immunotherapy to the treatment regimen for TNBC has been shown to improve pCR rates [54-56]. In our study, since no immunotherapy was administered and only limited carboplatin was used, only about one-third of TNBC patients achieved pCR, highlighting the need for more effective therapies. However, adjuvant therapies like capecitabine for TNBC and trastuzumab emtansine for HER2-positive BC have been shown to improve survival in patients with residual disease [57, 58]. Achieving pCR is much less common in HR-positive HER2-negative BC, as seen in our study, where only 15% of LB-HER2(−) BC patients and none of the LA BC patients achieved pCR. Although the pCR rates in these groups were low, NACTx or neoadjuvant endocrine therapy may still help in reducing tumor size, facilitating breast surgery, and minimizing the need for extensive axillary surgery, especially in patients with smaller breasts or significant axillary nodal involvement.

Study limitations

One key limitation of this research is that it is a single-center, retrospective study, which could restrict the broader application of the findings. Retrospective designs are inherently prone to biases, such as selection bias, incomplete data, and lack of randomization, all of which could undermine the consistency and generalizability of the results. Since treatment choices in retrospective studies often reflect individual physician judgment and patient preferences, the lack of a standardized approach may lead to varied treatment protocols. Additionally, conducting the study at a single institution limits the external applicability of the results. Differences in treatment protocols, patient demographics, and available resources across different hospitals or regions could result in different

treatment outcomes. For example, the generic form of docetaxel used in our facility may differ from that used in other centers, possibly leading to differences in side effects, such as allergic reactions or hand-foot syndrome [59]. This study only examined immediate or short-term adverse events related to NACTx. However, potential long-term complications, such as cardiotoxicity, hematological issues, or neuropathy, were not considered but could emerge as the treatment progresses. Another limitation stems from the variability in radiological and pathological evaluations, as these were performed by multiple clinicians, introducing observer bias. Furthermore, treatment regimens varied across patients, and the lack of a uniform chemotherapy protocol, such as the use of either single-agent or dual-agent HER2 therapy, may have impacted both clinical responses and subsequent outcomes. While the goal of the study was to capture real-world treatment patterns and outcomes, standardizing the therapeutic approaches would likely result in more consistent findings.

The small sample size, especially for subgroups like HER2-enriched and LA patients, may further limit the ability to generalize the findings. Additionally, the study's lack of long-term follow-up data—such as disease-free survival (DFS) and overall survival (OS)—is a notable shortcoming. Further research that includes long-term outcome data, particularly in patients who experienced clinical progression or severe treatment-related adverse events, would enhance the robustness of the findings. Multicenter, prospective studies with larger patient populations are needed to confirm the results and expand the applicability of these findings.

Conclusion

The management of newly diagnosed non-metastatic breast cancer (BC) should involve a multidisciplinary team of experienced professionals. When considering neoadjuvant chemotherapy (NACTx), it is crucial to take into account the tumor's specific characteristics and molecular subtype to guide treatment decisions. Close monitoring is required throughout treatment, as serious adverse events (AEs) and disease progression can occur. The use of anthracyclines, in particular, requires careful consideration due to their potential cardiotoxic effects. Triple-negative breast cancer (TNBC) poses the highest risk for progression during treatment.

It is important to classify patients based on their precise molecular subtypes rather than relying on broad categories like HR-positive or HER2-positive. Specifically, the definition of locally advanced (LA) breast cancer needs to be clear, as chemotherapy has limited benefit in this group, even when the disease is locally advanced. For tumors with invasive lobular carcinoma (ILC) histology and those with low SUVmax values, the risk of positive surgical margins is higher, so more precise surgical planning is necessary. Additionally, while clinical complete response (cCR) in the axilla may not always be reliable in LA BC and ILC, HER2-enriched BC patients are more likely to achieve axillary pCR, even if the axilla does not show complete response to NACTx. In such cases, performing sentinel lymph node biopsy (SLNB) should still be considered.

This study, although limited to a single center, provided comprehensive data on the treatment approaches, significant side effects, clinical responses, and surgical outcomes of patients undergoing NACTx for BC. Moving forward, multicenter studies or meta-analyses with larger cohorts would provide more generalizable results and help validate these findings.

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