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Analysis Of Tumor Response To Preoperative Chemotherapy In Advanced Aggressive Breast Cancer Subtypes

G.A. Khakimov

Prof. MD Head of department of oncology, pediatric oncology and palliative care. Tashkent State Medical University, Tashkent, Uzbekistan

A. Almuradov

PhD, Associate professor of Department of Econometrics. Tashkent State University of Economics, Tashkent, Uzbekistan

D.M. Almuradova

PhD, Associate professor of Department of Oncology, pediatric oncology and palliative care. Tashkent State Medical University, Tashkent, Uzbekistan

G.G. Khakimova

PhD, Associate professor of department of oncology, pediatric oncology and palliative care. Tashkent State Medical University , Tashkent, Uzbekistan

J.Kh. Ismoilov

Assistant of the Department of Oncology, pediatric oncology and palliative care. Tashkent State Medical University, Tashkent, Uzbekistan

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ABSTRACT

Breast cancer is a leading malignancy in women worldwide with aggressive subtypes (triple-negative, HER2-positive, and high-proliferation luminal B) contributing disproportionately to mortality. Neoadjuvant chemotherapy (NACT) has become standard in these subtypes, aiming to downstage tumors and improve survival by achieving pathological complete response (pCR). The Residual Cancer Burden (RCB) index was introduced to standardize post-NACT pathological assessment and refine prognostic stratification.

Purpose: To analyze tumor response to NACT in stage II–III breast cancer with aggressive biological subtypes, using modern evaluation systems of residual pathological stage (ypTN) and RCB.

Materials and Methods: We retrospectively analyzed 172 patients with stage II–III breast cancer (34.3% triple-negative, 28.5% HER2-positive, 37.2% luminal B HER2-negative) treated with NACT and surgery. Median age was 47 years. Most tumors were cT2 (65.1%) and clinically node-positive (69.8%). NACT regimens included anthracycline-taxane combinations for all patients, with platinum added in 77.9% of triple-

negative cases and dual anti-HER2 monoclonal antibody therapy (trastuzumab + pertuzumab) in 87.8% of HER2-positive cases.

Results: A total of 69 patients (40.1%) achieved a pathological complete response (tpCR, ypT0N0, corresponding to RCB-0). Among 103 patients with residual disease, RCB class I (minimal residual) was rare (6.4%), while RCB-II (moderate) and RCB-III (extensive residual burden) were observed in 30.2% and 23.3% of all patients, respectively.

Conclusions: Patients with aggressive breast cancer subtypes demonstrate significantly different NACT response profiles. TNBC and HER2-positive tumors are highly responsive to modern NACT, achieving pCR in about half of cases or more, whereas luminal B/HER2-negative cancers respond poorly

Keywords: Breast cancer, neoadjuvant chemotherapy, pathological complete response, residual cancer, triple-negative, HER2-positive, luminal B, platinum-based chemotherapy, dual anti-HER2 therapy.

INTRODUCTION

Breast cancer (BC) remains a major health concern and the leading cause of cancer-related morbidity and mortality among women worldwide. In the Russian Federation, BC ranks first in cancer incidence and mortality in the female populationfile-kw2zldun64mtra5x565flv. Over the past two decades, advances in tumor biology have revolutionized the classification and treatment of early breast cancer [3]. The identification of key biomarkers – estrogen and progesterone receptors (ER/PR), human epidermal growth factor receptor 2 (HER2), and the Ki-67 proliferation index – has enabled the definition of intrinsic molecular subtypes of BC (e.g. luminal A, luminal B, HER2-enriched, triple-negative). These subtypes differ in prognosis and therapeutic sensitivity, prompting a shift toward subtype-tailored treatment strategies in early-stage disease.

For patients with biologically aggressive subtypes – namely triple-negative breast cancer (TNBC), HER2-positive tumors, and luminal B (high-proliferation, often ER-positive/HER2-negative) – neoadjuvant chemotherapy (NACT) has become a standard component of multidisciplinary carefile. Globally, the use of NACT in stage II–III BC has increased, especially for these subtypes, due to several potential benefits [9]. Administering chemotherapy before surgery can downstage the primary tumor and affected nodes, potentially converting some patients to breast-conserving surgery candidates and reducing the extent of axillary dissection. Furthermore, the response to NACT provides early information on chemosensitivity. Achieving a pathological complete response (pCR) – defined as the absence of invasive cancer in breast and lymph nodes (ypT0N0) – is associated with improved long-term outcomes, particularly in TNBC and HER2-positive disease. Patients who attain pCR after NACT have significantly lower recurrence rates and better survival than those with residual disease, making pCR a key endpoint in clinical trials and a surrogate for treatment efficacy [13,14]. Conversely, the presence of residual invasive disease signals higher risk, guiding the need for additional adjuvant therapies (such as capecitabine for TNBC or T-DM1 for HER2-positive patients) to improve outcomes [2,11].

A critical issue in the neoadjuvant setting is how to accurately quantify and classify the extent of residual disease in patients who do not achieve pCR. Traditional pathological staging after NACT (ypTNM) provides size of the residual tumor (ypT) and residual nodal involvement (ypN). While informative, ypTN staging alone may not fully capture the nuanced burden of residual disease, such as cellularity of the tumor bed or the presence of in situ disease [1,12]. To address this, the Residual Cancer Burden (RCB) scoring system was developed as a standardized quantitative tool integrating multiple parameters of residual tumor: primary tumor size and cellularity, number and size of nodal metastases [10,15]. The RCB index stratifies patients into classes: RCB-0 (pCR), RCB-I (minimal residual disease), RCB-II (moderate residual disease), and RCB-III (extensive residual disease). This system has been validated as an independent prognostic indicator across breast cancer subtypes [4,7]. Patients with RCB-III have significantly worse event-free survival compared to those with RCB-I, even if they share the same ypTN stage [5,9]. Thus, incorporating RCB analysis can improve post-neoadjuvant risk stratification and guide the escalation or de-escalation of

adjuvant treatment. Despite these advances, several questions remain. The concordance between the conventional ypTN staging and the RCB classification in different biological subtypes is not fully understood – for instance, whether certain patterns of residual disease (e.g. small tumor but nodal metastases) align consistently with RCB classes in aggressive subtypes. Moreover, limited data exist on how modern NACT regimens (such as the addition of platinum for TNBC or dual HER2-blockade for HER2-positive tumors) affect not only pCR rates but also the distribution of RCB classes among residual disease cases. Understanding these patterns is important, as differences in residual disease burden could imply different prognostic trajectories and may necessitate subtype-specific post-NACT interventions [6,8]. Here, we present an analysis of the pathological response to neoadjuvant chemotherapy in patients with aggressive breast cancer subtypes (TNBC, HER2-positive, and luminal B HER2-negative) at stage II–III. We evaluate response using both the ypTN system and the RCB index, and we compare the response rates and residual disease characteristics between subtypes. The goal is to elucidate any distinctive response patterns – including rates of pCR and distribution of RCB classes – in these high-risk subtypes, which could have implications for prognostication and tailoring of therapy after NACT.

Purpose

The purpose of this study was to analyze the tumor response to neoadjuvant chemotherapy in patients with stage II–III breast cancer with aggressive biological subtypes, taking into account modern systems for evaluating residual disease: the post-neoadjuvant pathological stage (ypTN) and the Residual Cancer Burden (RCB) index. We aimed to determine pCR rates and residual tumor burden profiles (RCB classes) in each subtype (triple-negative, HER2-positive [luminal and non-luminal], and luminal B HER2-negative), and to assess the concordance between traditional staging and RCB-based assessment of response.

METHODS

This analysis included 172 female patients with stage II–III breast cancer who received comprehensive treatment (NACT followed by surgery) between 2017 and 2021 at two academic centers. All patients had tumors of aggressive biological subtypes, defined as one of the following: triple-negative (ER-negative, PR-negative, HER2-negative), HER2-positive (overexpressing HER2 by immunohistochemistry or amplified by FISH, with any ER/PR status), or luminal B HER2-negative (ER and/or PR positive, HER2-negative, and Ki-67 proliferation index ≥20–30%). Staging was based on AJCC 7th edition criteria. Patients with distant metastases at presentation were excluded. Table 1 summarizes the key clinical and pathological characteristics of the study cohort.

The age of patients ranged from 24 to 81 years (median 47 years). The majority of women (62.2%) were premenopausal (Table 1). At diagnosis, most tumors were relatively large: 65.1% were T2 (2–5 cm) and 21.5% were T4 lesions with chest wall or skin involvement, while only 5.2% were ≤2 cm (T1). Regional lymph node metastases were present in 69.8% of patients (clinically node-positive); specifically, 52.9% had N1 disease (1–3 suspicious nodes), and 16.8% had bulky nodal disease (N2 or N3) on presentation. By clinical staging, 65.1% of cases were stage II (including IIA 30.8% and IIB 34.3%) and 34.9% were stage III (8.7% IIIA, 17.4% IIIB, 8.7% IIIC)file-kw2zldun64mtra5x565flv. Overall, 69.8% of patients had primary operable disease (clinical stage T1–3 with N0–1) and 30.2% had locally advanced disease (T4 and/or N2–3) at diagnosis (tab 1).

All patients underwent pre-treatment core needle biopsy of the primary tumor for diagnosis and biomarker assessment. Histologically, invasive ductal carcinoma of no special type was the dominant tumor histology (83.1%), with invasive lobular carcinoma in 4.7% and other invasive subtypes (medullary, metaplastic, mucinous) in 12.2%. Tumor grade was high in most cases: 62.8% were grade 3 and 37.2% grade 2; no well-differentiated grade 1 tumors were included (consistent with the aggressive biology inclusion criteria).

Table 1. Clinical and Pathological Characteristics of Patients (N = 172)

Characteristic	Number of patients	%
Age (years)		
Median (range)	47 (24–81)	–
< 40	49	28.5%
40–50	52	30.2%

50–60	34	19.8%
> 60	37	21.5%
Menopausal status		
Premenopausal	107	62.2%
Postmenopausal	65	37.8%
Clinical tumor size (cT)		
T1 (≤2 cm)	9	5.2%
T2 (>2–5 cm)	112	65.1%
T3 (>5 cm)	14	8.1%
T4 (any size, chest wall or skin involvement)	37	21.5%
Clinical nodal status (cN)		
N0	52	30.2%
N1 (1–3 lymph nodes)	91	52.9%
N2 (4–9 lymph nodes)	14	8.1%
N3 (≥10 lymph nodes or supraclavicular)	15	8.7%
Clinical stage (before NACT)		
IIA	53	30.8%
IIB	59	34.3%
IIIA	15	8.7%
IIIB	30	17.4%
IIIC	15	8.7%
Operability		
Primary operable (T1–3 N0–1)	120	69.8%
Locally advanced (T4 and/or N2–3)	52	30.2%
Tumor grade		
Grade 2 (moderately differentiated)	64	37.2%
Grade 3 (poorly differentiated)	108	62.8%
Ki-67 proliferation index		
Median (range)	53% (10–98%)	–
Ki-67 < 30%	16	9.3%
Ki-67 ≥ 30%	156	90.7%
Biological subtype of tumor		
Luminal B, HER2-negative (HR+ HER2–)	64	37.2%
HER2-positive, HR-positive (Luminal HER2+)	22	12.8%
HER2-positive, HR-negative (Non-luminal HER2+)	27	15.7%
Triple-negative (TNBC)	59	34.3%
Tumor-infiltrating lymphocytes (TILs)‡		
Median (range)	10% (0–90%)	–
Low TILs (<10%)	75	48.4%
Intermediate (10–20%)	19	12.3%

High (>20%)	61	39.4%

The proliferation index Ki-67 ranged from 10% to 98%, with a median of 53%. The vast majority of tumors (90.7%) had high proliferative activity (Ki-67 ≥30%), whereas only 9.3% had Ki-67 <30%. Tumor-infiltrating lymphocytes (TILs) were evaluated on pre-treatment biopsy specimens for 155 patients: the median stromal TIL level was 10%, with 48.4% of cases showing low TIL infiltration (<10%), 12.3% intermediate (10–20%), and 39.4% exhibiting >20% TILs in the tumor stroma. As expected by design, the cohort's subtype distribution was 34.3% triple-negative, 28.5% HER2-positive, and 37.2% HR-positive/HER2-negative (luminal B). Among HER2-positive patients (n=49), 22 (12.8% of total) were ER-positive (HER2+/HR+, often termed luminal B HER2-positive) and 27 (15.7%) were ER-negative (HER2-enriched subtype). BRCA1/2 and CHEK2 germline mutation testing was performed in 128 patients with available data; pathogenic mutations were identified in 23 cases (18% of those tested), predominantly BRCA1 mutations (78% of detected mutations) BRCA1 mutations were most frequent in the triple-negative subgroup, as expected, although detailed correlation with response was beyond this study's scope.

All patients underwent neoadjuvant systemic therapy tailored to tumor subtype and clinical factors, following current protocols. The majority (91.9%) received an anthracycline-taxane-based chemotherapy regimen. Specific regimens included: (1) four cycles of doxorubicin 60 mg/m^2 and cyclophosphamide 600 mg/m^2 (AC) every 3 weeks, followed by four cycles of a taxane (either docetaxel 75 mg/m^2 or paclitaxel 175 mg/m^2 every 3 weeks), administered to 47 patients (27.3%); (2) four cycles of AC followed by 12 weekly doses of paclitaxel 80 mg/m^2, given to 57 patients (33.1%); (3) four cycles of AC followed by a taxane combined with carboplatin (AUC 5–6), received by 33 patients (19.2%); and (4) a non-anthracycline regimen of docetaxel 75 mg/m^2 plus carboplatin AUC 6 for six cycles, administered to 35 patients (20.3%). Additionally, 14 patients (8.1%) received dose-dense chemotherapy scheduling (every 2 weeks with growth factor support) for part or all of their treatment.

The use of platinum agents and HER2-targeted therapy was guided by tumor subtype. Notably, 77.9% of patients with triple-negative breast cancer received a platinum-containing regimen as part of NACT (generally regimen 3 or 4). For HER2-positive tumors (n=49), all patients received anti-HER2 therapy alongside chemotherapy in the neoadjuvant phase. Dual HER2 blockade with trastuzumab and pertuzumab was administered in 43 of 49 HER2+ patients (87.8%), reflecting current standards for HER2-positive, node-positive or high-risk disease. The remaining 6 HER2+ patients (12.2%) received trastuzumab alone (in cases treated earlier or with contraindications to dual therapy). Trastuzumab was given intravenously at a loading dose of 8 mg/kg followed by 6 mg/kg every 3 weeks; pertuzumab was given at 840 mg loading then 420 mg every 3 weeks, in accordance with standard dosing. Hormonal therapy was not administered in the neoadjuvant setting even for ER-positive tumors, as the intent was to assess chemosensitivity; endocrine therapy was planned for the adjuvant setting in those cases.

After completion of NACT (typically 6–8 cycles over ~18–24 weeks), all patients underwent definitive surgery. Surgical management was decided based on tumor response and patient preference. A total of 124 patients (72.1%) underwent mastectomy (either simple or modified radical), of which 58 (33.7% of the entire cohort) also received immediate breast reconstruction. Breast-conserving surgery (lumpectomy or segmental resection) was performed in 48 patients (27.9%). Axillary surgical management was individualized: patients with initial node positivity generally had axillary lymph node dissection (ALND) unless they converted to node-negative and were eligible for sentinel lymph node biopsy (SLNB) after NACT. Overall, 57.9% of patients underwent mastectomy with ALND, 14.0% mastectomy with SLNB only, 14.6% breast-conserving surgery with ALND, and 13.5% breast-conserving with SLNB (Table 1). Thus, 27.5% of node-positive patients were able to be managed with SLNB alone post-NACT, reflecting cases with nodal downstaging.

All resection specimens (breast and axillary contents) were evaluated by dedicated breast pathologists. The pathological assessment included measurement of residual invasive tumor size in the breast (largest dimension of residual cancer, or if multiple foci, an aggregate span) and the number and size of metastatic tumor foci in lymph nodes. Tumor cellularity (percentage of tumor bed area with invasive cancer vs therapy-

induced fibrosis or necrosis) was estimated. The presence of ductal carcinoma in situ (DCIS) and lymphovascular invasion in the specimen was also noted. Pathologic staging after NACT was assigned according to the AJCC ypTNM system (8th edition, consistent with 7th for these purposes). A pathological complete response (pCR) was defined as no residual invasive carcinoma in both the breast and sampled lymph nodes (ypT0/Tis ypN0). We specifically distinguished total pCR (tpCR) as the absence of invasive tumor in breast and nodes, allowing for residual in situ disease; this corresponds to Miller-Payne grade 5 or "complete response" in some classification systems.

In addition to traditional staging, we calculated the Residual Cancer Burden (RCB) for each patient using the MD Anderson Cancer Center online calculator (MDACC RCB calculator, version 3.0). The RCB calculation incorporates: (a) primary tumor bed area (two-dimensional diameter and percent cellularity of invasive carcinoma, factoring in DCIS), and (b) nodal metastasis burden (number of positive nodes and size of largest nodal metastasis). Based on the RCB index, patients were categorized into RCB classes: RCB-0 (no residual invasive cancer, i.e. pCR), RCB-I (minimal residual disease), RCB-II (moderate residual disease), or RCB-III (extensive residual disease). For example, a patient with a 1.5 cm residual tumor of moderate cellularity and no nodal metastasis might fall into RCB-I, whereas a patient with a 4 cm residual tumor and multiple positive nodes would be RCB-III. We performed statistical analysis using SPSS software (Version 22.0, IBM Corp). The distribution of clinicopathologic factors and response outcomes was summarized with descriptive statistics. Associations between categorical variables (such as subtype and pCR rate, or subtype and RCB class distribution) were analyzed using the χ^2 test or Fisher's exact test, as appropriate. A p-value < 0.05 was considered statistically significant. In particular, we evaluated the difference in pCR rates across the four subtype groups and the association between subtype and RCB categories among those with residual disease. We also examined the concordance between ypTN staging and RCB class (e.g. which ypT/ypN combinations corresponded to RCB-I vs II vs III) using cross-tabulation. No multivariate analyses were planned, as the study focused on descriptive outcomes of NACT response.

RESULTS

After neoadjuvant chemotherapy, 69 out of 172 patients achieved a total pathological complete response (tpCR), defined as ypT0N0 with no invasive cancer in the breast or lymph nodes. This corresponds to a tpCR rate of 40.1% in the overall study population (Table 2). All patients with tpCR are by definition in RCB-0 class. Conversely, 103 patients (59.9%) had residual invasive disease in the breast and/or lymph nodes after NACT (non-pCR). Among these cases with residual disease, the extent of residual tumor varied widely.

According to RCB index assessment, only 11 patients (6.4% of the total cohort) were classed as RCB-I (indicating minimal residual cancer burden). RCB-I represents patients with very small residual tumors (generally ≤1 cm with low cellularity) and no or minimal nodal involvement. In contrast, 52 patients (30.2%) fell into RCB-II (moderate residual disease) and 40 patients (23.3%) were RCB-III (extensive residual disease) (Table 2). Thus, the majority of those with residual disease had a moderate-to-high burden of tumor remaining, whereas relatively few had only minimal residual tumor. In the entire cohort (including those with pCR as RCB-0), the distribution of RCB classes was: 40.1% RCB-0, 6.4% RCB-I, 30.2% RCB-II, and 23.3% RCB-III.

When considering conventional pathological staging, we found that 74 patients (43.0%) had no residual invasive tumor in the breast (ypT0). This number includes the 69 tpCR patients (ypT0N0) plus a few patients (n=5) who had ypT0 in the breast but residual nodal metastasis (ypT0N1, i.e. "breast-only pCR"). Among those with residual breast tumor, the majority had relatively small remnants: 56 patients (32.6%) were ypT1 (tumor ≤2 cm) and 32 patients (18.6%) were ypT2 (tumor 2–5 cm). Only 5 patients (2.9%) had residual tumors classified as ypT3 (>5 cm), and 5 patients (2.9%) were ypT4 (due to diffuse chest wall/skin involvement despite shrinkage) (Table 2).

In terms of nodal status after therapy, 112 patients (65.5%) had no histopathological evidence of lymph node metastases (ypN0) at surgery (including all pCR cases and some with only breast residual) (Tab 2). Nodal clearance was achieved in many patients who were node-positive initially. Among those with remaining nodal disease, 38 patients (22.1%) were ypN1 (1–3 positive nodes), 18 (10.5%) were ypN2 (4–9 positive nodes), and only 3 patients (1.8%) remained ypN3 (≥10 positive nodes). The relatively low fraction of ypN3 indicates that very extensive nodal disease was eradicated by NACT in most cases, though a small

number of patients still had a high nodal tumor burden post-therapy.

Table 2. Summary of Pathological Response to Neoadjuvant Chemotherapy (N = 172)

Response category	Patients (n)	%
Pathological complete response (tpCR*)	69	40.1%
Residual invasive disease (non-pCR)	103	59.9%
Residual Cancer Burden (RCB) class		
RCB-0 (pCR)	69	40.1%
RCB-I (minimal residual)	11	6.4%
RCB-II (moderate residual)	52	30.2%
RCB-III (extensive residual)	40	23.3%
Post-NACT tumor size (breast, ypT)		
ypT0 (no invasive tumor)	74	43.0%
ypT1 (≤2 cm)	56	32.6%
ypT2 (>2–5 cm)	32	18.6%
ypT3 (>5 cm)	5	2.9%
ypT4 (any size + local extension)	5	2.9%
Post-NACT nodal status (ypN)		
ypN0 (0 positive nodes)	112	65.5%
ypN1 (1–3 positive nodes)	38	22.1%
ypN2 (4–9 positive nodes)	18	10.5%
ypN3 (≥10 positive nodes)	3	1.8%

The combined post-NACT pathological stage (ypT and ypN) varied widely across patients, reflecting the heterogeneous response. The most common residual pathologic stage patterns observed were: ypT1a–bN0 in 7.6% of patients, ypT1cN0 in 10.5%, ypT1cN1 in 8.1%, and ypT2N2 in 8.1% (each of these represents 13–18 patients). Notably, 4 patients (2.3%) had no tumor in breast but small volume nodal disease (ypT0N1), and 5 patients (2.9%) had small breast tumors with limited nodal spread (ypT1a–bN1). These detailed patterns underline that even among those not achieving pCR, many had significant partial responses resulting in minimal residual disease in one or both anatomical locations.

We assessed the concordance between the RCB classification and the conventional ypTN staging in our data. Overall, there was a strong association between RCB class and the extent of residual disease by ypTN (χ^2 $p<0.0001$). As expected, RCB-0 corresponds exactly to ypT0N0 (by definition, pCR). Importantly, we found that RCB-I (minimal residual disease) cases almost exclusively had very limited residual tumor by traditional staging. Specifically, 81.8% of RCB-I patients had a tiny residual tumor confined to the breast (≤0.5 cm, ypT1a-b) and node-negative status (ypT1a–bN0). The remaining RCB-I cases had either slightly larger tumors or a single involved node, but none had multi-node disease. In fact, none of the RCB-I

patients had any nodal metastasis – all were ypN0, except one case of a single microscopic node (ypT0N1) that still fell under RCB-I due to minimal overall tumor cellularity. Meanwhile, RCB-II (moderate residual) encompassed a broad range of post-treatment stages. RCB-II cases typically had residual tumors not exceeding 5 cm (often ypT1 or ypT2) with either node-negative or limited nodal involvement (ypN1 in many cases, some ypN2). RCB-III (high residual burden) was strongly associated with more extensive disease: these patients either had large residual tumors (ypT3–T4) or significant nodal involvement (ypN2–N3), or both. For example, most patients with post-NACT stage ypT3–T4 or with ≥4 positive nodes ended up classified as RCB-III.

Interestingly, one particular residual pattern – ypT2N0 (a 2–5 cm tumor with no nodal metastases) – occurred across all RCB categories. In our cohort, a ypT2N0 status was observed in a few patients who were RCB-I (9.1% of RCB-I cases), some who were RCB-II (13.5% of RCB-II cases), and even in a couple of RCB-III patients (5% of RCB-III). This implies that tumor size ~3–5 cm without nodal involvement can correspond to different levels of tumor cellularity or burden: an extensively necrotic 3 cm tumor might be RCB-I, whereas a highly cellular 3 cm tumor could be RCB-III. This finding underscores how RCB provides additional granularity beyond simple size criteria, by accounting for cancer cellularity and dispersion.

In summary, our overall results show that 40% of patients achieved pCR (tpCR) with NACT, and among those with residual disease, there was a wide distribution of how much tumor remained (from minimal to extensive). The RCB system correlates with, but adds depth to, the traditional ypTN staging, helping distinguish truly minimal residual disease from more threatening residual disease even when tumor dimensions overlap.

A primary objective of our study was to compare NACT responses across the different biological subtypes of breast cancer. The pCR rate differed significantly among subtypes (χ^2 test, $p<0.0001$), highlighting substantial variability in chemosensitivity (Table 3). Patients with HER2-positive breast cancer had the highest likelihood of achieving tpCR, especially those with non-luminal (ER-negative) HER2-positive tumors. In the HER2-positive, hormone receptor-negative subgroup (sometimes called HER2-enriched, 27 patients), the tpCR rate was 63.0%. Similarly, in HER2-positive, hormone receptor-positive tumors (luminal B HER2-positive, 22 patients), the tpCR rate was 59.1%. Combining these, the overall tpCR for all HER2-positive cases was 61.2% (30 of 49). By contrast, the triple-negative breast cancer (TNBC) subgroup (59 patients) had a tpCR rate of 50.8%, which is high and comparable to HER2-positive outcomes, but slightly lower. The luminal B, HER2-negative cancers (64 patients) were the least responsive, with tpCR achieved in only 15.6%. In other words, fewer than 1 in 6 of the HR-positive/HER2-negative high-grade tumors had complete eradication of invasive tumor with chemotherapy.

These differences underline that HER2-driven and triple-negative tumors are highly chemosensitive to contemporary regimens, whereas ER-positive/HER2-negative tumors are relatively chemoresistant. The inclusion of targeted therapies likely contributed to the high pCR in HER2-positive disease (dual HER2 blockade) and TNBC (platinum). Indeed, our TNBC pCR of ~51% is consistent with rates reported in clinical trials using carboplatin in the neoadjuvant setting, and the ~60% pCR in HER2-positive mirrors results from trials of trastuzumab+pertuzumab with chemo.

Beyond pCR, we also compared the distribution of residual cancer burden (RCB classes) among the subtypes for those patients who did not achieve pCR. Interestingly, we found that not only the frequency of pCR, but the nature of residual disease in non-pCR cases, differed markedly by subtype ($p<0.0001$ for association between subtype and RCB class distribution). Table 3 presents the breakdown of response outcomes by subtype.

In triple-negative disease, if a patient did not attain pCR, they were more likely to have significant residual tumor burden. Specifically, RCB-I (minimal residual) was exceedingly rare in TNBC – only ~1.7% of all TNBC patients (essentially 1 out of 59) ended up in RCB-I (Table 3). The majority of non-pCR TNBC cases were moderate or extensive: 25.4% of TNBC patients were RCB-II and 23.7% were RCB-III. In practical terms, among TNBC patients who did not achieve pCR, most had either multiple foci or sizable residual tumor, often with nodal involvement (consistent with the earlier observation that TNBC residual disease tends to be high burden).

For HER2-positive cancers, the picture was more favorable in terms of residual disease. A substantial subset of HER2+ patients who did not

have pCR still had only minimal residual disease. In HER2-positive, HR-negative cases, RCB-I was observed in ~11% of all patients (meaning about one-sixth of those who did not reach pCR, since 63% achieved pCR, the remainder 37% is the non-pCR group; of that remainder, 11% of total corresponds to ~30% of non-pCR group). In HER2-positive, HR-positive cases, RCB-I comprised ~9.1% of all (roughly one-quarter of non-pCR patients). Combining luminal and non-luminal HER2+, roughly 10% of HER2+ patients overall ended up RCB-I. Meanwhile, RCB-II (moderate residual) occurred in approximately 25% of HER2+ patients – "one in four," consistent across both luminal and non-luminal variants. Strikingly, RCB-III was nearly absent in HER2-positive/HR-negative tumors – none of the non-luminal HER2+ patients had extensive residual disease (0% RCB-III). In the HR-positive HER2+ subgroup, a small fraction (around 9%) had RCB-III residuals.Therefore, among HER2-positive patients who did not achieve pCR, most had either minimal or moderate residual tumor, and large extensive residuals were uncommon, especially in the ER-negative (HER2-enriched) group.

Finally, the luminal B/HER2-negative subtype not only had the lowest pCR rate, but also tended to have substantial residual disease. Only ~7.8% of these patients were RCB-I (very few minimal residual cases). In contrast, 39.1% of luminal B patients were RCB-II and 37.5% were RCB-III (Table 3). In other words, the vast majority of luminal B cancers had moderate to extensive residual tumor after NACT, reflecting their relative chemoresistance. This finding is clinically consistent with the knowledge that ER-positive tumors often shrink less with chemo and rely more on subsequent endocrine therapy to control microscopic disease.

Table 3. Neoadjuvant Chemotherapy Response by Breast Cancer Subtype

Subtype	n	tpCR (RCB-0)	RCB-I	RCB-II	RCB-III
HER2-positive, HR– (non-luminal HER2+)	27	63.0%	11.1%	25.9%	0.0%
HER2-positive, HR+ (luminal HER2+)	22	59.1%	9.1%	22.7%	9.1%
Triple-negative (TNBC)	59	50.8%	1.7%	25.4%	23.7%
Luminal B, HER2-negative	64	15.6%	7.8%	39.1%	37.5%

The above results demonstrate notable subtype-specific response patterns. In summary, HER2-positive tumors (treated with chemo and HER2 blockade) and triple-negative tumors (treated with chemo ± platinum) both had high pCR rates around 50–60%. However, in the event of an incomplete response, TNBC patients more often had a high residual burden (often multiple nodes or larger masses remaining), whereas HER2-positive patients more often had only minimal or moderate residual disease. Luminal B/HER2-negative cancers showed poor response, with low pCR and often sizeable residual disease. Statistical analysis confirmed that both the likelihood of pCR and the profile of residual disease (RCB class) were significantly associated with subtype ($p<0.0001$ for each).

These findings have potential prognostic implications. Achieving a pCR is associated with favorable prognosis in all subtypes, but it is

particularly critical in TNBC and HER2-positive disease where pCR correlates with significantly improved survival. Our data indicate that over half of patients in those subgroups reach that favorable category. On the other hand, patients with residual disease after NACT, especially those with TNBC or luminal B subtypes, form a high-risk group. Notably, our TNBC patients with residuals were often RCB-III (extensive burden), which prior studies have shown corresponds to poor outcomes if managed with standard therapy alone. Similarly, luminal B patients with large residual tumor remain at high risk of recurrence despite endocrine therapy, suggesting a need for additional systemic treatments (e.g. CDK4/6 inhibitors in the adjuvant setting, as supported by recent trials). For HER2-positive patients, even those with residual disease might have a relatively better outcome if the residual is minimal (RCB-I/II); nonetheless, current guidelines recommend adjuvant T-DM1 for any residual invasive disease to improve outcomes in HER2+ (based on the KATHERINE trial, not explicitly part of our data).

Overall, the differential response patterns we observed reinforce a tailored approach: TNBC patients who do not achieve pCR should be considered for aggressive adjuvant therapy (like capecitabine or clinical trials), whereas HER2-positive residual disease can be addressed with targeted agents (T-DM1). For luminal tumors, the indication for neoadjuvant chemo may need to be weighed against alternatives (neoadjuvant endocrine therapy) in borderline cases, given the low pCR yield.

Neoadjuvant chemotherapy was delivered as per protocol in the majority of patients, with some requiring dose adjustments or supportive measures. Overall, the treatment was tolerable and safe, with toxicity profiles consistent with the known effects of the chemotherapy agents and targeted therapies used (Tab 4) summarizes the incidence of the main Grade 3–4 treatment-related adverse events in our cohort.

As expected, myelosuppression was the most common serious toxicity. Grade ≥3 neutropenia occurred in 78 patients (45.3%), reflecting the myelotoxicity of anthracyclines, taxanes, and especially carboplatin. Granulocyte colony-stimulating factor (G-CSF) support was used in patients receiving dose-dense regimens and some standard regimens at physician discretion, which likely mitigated the incidence of febrile neutropenia. Febrile neutropenia (neutropenia with fever/infection) was observed in 9 patients (5.2%). All cases of febrile neutropenia were managed with antibiotics and G-CSF, and there were no neutropenia-related septic deaths. Anemia (Grade 3–4) was noted in 18 patients (10.5%), some of whom required blood transfusions. Thrombocytopenia (Grade 3–4) occurred in 14 patients (8.1%), largely attributable to carboplatin in TNBC patients; none of these cases led to major bleeding, and platelet counts recovered with treatment pauses or dose reductions.

Non-hematologic toxicities were generally less frequent and mostly low-grade. However, some notable Grade ≥3 events included peripheral neuropathy and diarrhea. Peripheral neuropathy (Grade 3) developed in 9 patients (5.2%), predominantly in those receiving extended paclitaxel or higher doses of docetaxel. Neurotoxicity was cumulative and led to early cessation of the taxane in a few cases; symptoms partially improved with time in most patients after stopping therapy. Severe diarrhea (Grade 3) was reported in 4 patients (2.3%), all of whom were in the dual HER2 blockade group (pertuzumab-related diarrhea is a known adverse effect). These cases were managed with loperamide and supportive care, and none required hospitalization. Severe nausea/vomiting despite prophylactic antiemetics occurred in 5 patients (2.9%), typically during AC chemotherapy; no patient had uncontrolled emesis with newer antiemetic protocols. Mucositis (stomatitis) Grade 3 was seen in 4 patients (2.3%), mostly with dense-dose therapy, managed with topical analgesics and mouthwashes.

Importantly, cardiac toxicity was minimal: no patients developed clinical congestive heart failure during neoadjuvant therapy. Two patients (1.2%) experienced an asymptomatic decrease in left ventricular ejection fraction >10% (to below 50%) during or after anthracycline + trastuzumab treatment; these cases led to holding HER2 therapy temporarily, with subsequent recovery of ejection fraction and completion of planned trastuzumab/pertuzumab therapy. There were no treatment-related deaths in this cohort. Approximately 90% of patients were able to complete the planned course of NACT; the remaining had early discontinuation or regimen modifications due to toxicity or insufficient tumor response (progression on chemo was rare, seen in <5% of patients, predominantly in chemo-

refractory luminal B cases).

Overall, the safety profile observed aligns with prior reports on similar regimens. The addition of carboplatin in TNBC, while improving pCR rates, is known to increase hematologic toxicity. Our data reflects this, as TNBC patients contributed to many of the Grade 3–4 neutropenia and thrombocytopenia events. The use of dual HER2-targeted antibodies was associated with some increased risk of diarrhea and dermatologic side effects (not severe in our series) but did not notably increase neutropenia when combined with chemotherapy. Dose delays were occasionally necessary (in ~20% of patients) but did not compromise the overall delivery of therapy. These findings indicate that intensive NACT regimens including platinum and dual HER2 blockade are feasible in a tertiary care setting with appropriate supportive care, and the toxicities, while non-trivial, are manageable and acceptable given the potential benefit in tumor response.

Table 4. Main grade 3–4 treatment-related toxicities during neoadjuvant chemotherapy

Adverse Event (Grade ≥3)	Patients (N = 172)
Neutropenia (low neutrophils)	78 (45.3%)
Febrile neutropenia	9 (5.2%)
Anemia (low hemoglobin)	18 (10.5%)
Thrombocytopenia (low platelets)	14 (8.1%)
Peripheral neuropathy	9 (5.2%)
Diarrhea	4 (2.3%)
Nausea/vomiting	5 (2.9%)
Mucositis (stomatitis)	4 (2.3%)

DISCUSSION

In this study, we evaluated the response to neoadjuvant chemotherapy in 172 patients with stage II–III breast cancer of aggressive subtypes (TNBC, HER2-positive, and luminal B/HER2-negative) using both traditional pathological staging and the Residual Cancer Burden (RCB) system. Our findings provide insight into how modern NACT regimens are performing in real-world practice for these subtypes, and highlight important differences in outcomes between them.

High pCR rates in TNBC and HER2-positive disease with modern NACT: We observed tpCR rates of ~50% in TNBC and ~60% in HER2-positive cancers, which are remarkably high and consistent with recent clinical trial data. In TNBC, the incorporation of platinum agents in the neoadjuvant setting has been associated with significantly increased pCR rates. Meta-analyses and randomized trials report that adding carboplatin to anthracycline-taxane NACT raises pCR in TNBC from ~30% to ~50%. Our TNBC patients had a 50.8% pCR, aligning well with these findings and reflecting that 78% of them received a platinum-inclusive regimen. Achieving pCR in TNBC is particularly meaningful, as it is strongly linked to long-term survival benefits. Bonnefoi et al. demonstrated that pCR was an independent predictor of improved event-free survival in all intrinsic subtypes of BC, including basal/TNBC. Conversely, residual disease after NACT in TNBC confers a high risk of early relapse.

For HER2-positive breast cancer, our combined pCR rate of 61% is in line with results from pivotal trials of dual HER2 blockade. In the NeoSphere trial, the addition of pertuzumab to trastuzumab plus docetaxel yielded a pCR rate of ~45% in HER2+ tumors, and subsequent studies (TryPHAENA, PEONУ, etc.) reported pCR around 55–60% with dual antibodies. Our slightly higher pCR in the ER-negative HER2+ subset (63%) is likely due to the known effect of hormone receptors: HER2+ tumors that are ER-negative (non-luminal) are more sensitive to chemo + anti-HER2 therapy than ER-positive (luminal HER2+) tumors. We indeed saw 63.0% pCR in HER2+/HR– vs 59.1% in HER2+/HR+ (though this difference is not large, possibly due to limited sample). The use

of trastuzumab and pertuzumab in 88% of our HER2+ patients reflects current standards and has clearly translated into excellent response rates. Pathologic complete response in HER2-positive disease has also been linked to better survival, although HER2-targeted therapy even without pCR can still yield good outcomes. The landmark CTNeoBC pooled analysis found that pCR was prognostic across subtypes, but the association was strongest in TNBC and HER2-positive (especially ER-negative) cancers. Our data reinforce that achieving pCR is a realistic goal in the majority of HER2+ patients with the therapies now available.

Luminal B/HER2-negative tumors: low pCR and need for better approaches: In contrast, the luminal B/HER2-negative subgroup in our study had a disappointingly low pCR rate of 15.6%. This is consistent with historical data: ER-positive/HER2-negative breast cancers – even high-grade luminal B – respond less frequently to chemotherapy. Hormone-driven tumors are intrinsically less chemosensitive; instead, their outcomes are more influenced by endocrine therapy. In the CTNeoBC analysis, hormone receptor-positive/HER2-negative tumors had much lower odds of pCR compared to other subtypes, and importantly, pCR in those tumors did not correlate with survival as strongly as in others. This does not necessarily mean NACT has no benefit in luminal B cases – it can still downstage tumors and indicate tumor biology – but it highlights a gap in effective neoadjuvant treatment for this group. Emerging approaches such as neoadjuvant endocrine therapy or adding targeted agents (e.g. CDK4/6 inhibitors) might be considered for luminal B patients, especially if chemotherapy alone is unlikely to eradicate the tumor. The recent positive results of adjuvant abemaciclib in high-risk ER+ breast cancer (post-NAC residual disease or high nodal burden) support the notion of augmenting therapy beyond chemo/endocrine in these cases. While our study did not explore such interventions, our finding that 85% of luminal B patients had residual invasive disease (often large volume) underscores that they remain at significant risk and could be candidates for additional adjuvant trials or therapies.

Differences in residual disease patterns between subtypes: A novel aspect of our analysis is the observation that the quality of residual disease (as captured by RCB classes) varies by subtype, not just the binary pCR vs non-pCR outcome. We found that TNBC, despite its high pCR rate, showed a propensity for heavy residual disease when pCR was not achieved. Essentially, TNBC appears to be "all or nothing" – either the tumor is completely eradicated by chemo, or if some cells survive, they often proliferate or persist in significant amount (RCB-II/III). This dichotomous behavior might relate to intra-tumor heterogeneity in TNBC: a fraction of chemo-resistant clones can repopulate aggressively. Clinically, this is critical because TNBC patients with any residual disease (especially if substantial) have poor prognosis, with reported 3-year relapse-free survival under 50% for RCB-III cases. Our data reinforce the importance of post-neoadjuvant capecitabine in TNBC with residual disease, which has been shown to improve outcomes. Ongoing trials are evaluating other agents (e.g. immunotherapy, PARP inhibitors for BRCA-mutants) in the adjuvant setting for such patients.

In HER2-positive cancers, we observed a more favorable residual pattern: even when pCR was not achieved, a good proportion had minimal residual disease (small tumor or few cells, RCB-I). Particularly in HER2-enriched (HR–) tumors, we saw zero cases of extensive residual (RCB-III) – an intriguing finding. It suggests that dual HER2 blockade was so effective that if it didn't completely eliminate the tumor, it at least greatly reduced it in most cases. For luminal HER2+ tumors, a few had RCB-III, possibly because ER-positive/HER2+ disease can sometimes be less responsive to chemo (the ER pathway conferring some resistance). Nonetheless, even those luminal HER2+ RCB-III cases will likely benefit from the standard practice of giving adjuvant T-DM1, which in the KATHERINE trial cut recurrence risk by ~50% compared to continuing trastuzumab in patients with residual disease. Although our study concluded in 2021 and likely preceded widespread T-DM1 use in all residuals, current management would address that.

The luminal B group had not only low pCR but also some of the highest residual burdens (37.5% RCB-III). These tumors, being ER-positive, will all receive endocrine therapy, but one must consider whether that is sufficient. The prognosis of patients with extensive residual luminal disease (e.g. large tumor left, many nodes positive) can be quite guarded, even though ER-positivity confers a more indolent relapse pattern. The addition of ovarian suppression in premenopausal and extended hormonal therapy are measures often

used. As noted, adjuvant CDK4/6 inhibition (e.g. abemaciclib) for 2 years has shown improved invasive disease-free survival in high-risk ER+ patients (like those with ≥4 positive nodes or residual disease after NACT). This subtype might also benefit from neoadjuvant endocrine therapy in carefully selected cases (to avoid chemo toxicity and still attempt downstaging), but trials show chemotherapy is still standard if the goal is maximum tumor shrinkage in stage II–III ER+ disease with high Ki-67.

We acknowledge that this study is retrospective and observational. The treatment regimens were not uniform for all patients (though they followed general subtype-based protocols), and there is inherent selection bias in regimen choice (e.g. some TNBC did not get carboplatin perhaps due to comorbidity or physician choice). Our sample size within subgroups (especially HER2+/HR+ and HER2+/HR− separately) is moderate, which may limit the power to detect differences between those subgroups (though trends were evident). We focused on pathological response endpoints; survival follow-up is limited at the time of analysis, so we cannot directly correlate RCB or pCR with long-term outcomes in this cohort yet. However, the prognostic implications are drawn from established literature. Another limitation is that we did not collect detailed data on genomic features (beyond BRCA status) that might influence response, nor on post-neoadjuvant therapies given (some patients, especially more recent ones, may have received capecitabine or T-DM1 based on residual disease, which could affect outcomes). Despite these limitations, the strength of our study is the comprehensive pathological evaluation (including RCB) and the real-world insight into how new components (platinum, dual HER2 block) are impacting response in routine practice.

In summary, our study reaffirms that achieving a pathological complete response is a critical milestone in the treatment of aggressive breast cancer subtypes, as it is associated with an excellent prognosis. We demonstrated that with current NACT approaches, pCR can be achieved in a substantial proportion of TNBC and HER2-positive patients. For those who do not reach pCR, assessing the degree of residual disease with tools like RCB is very informative. Patients with minimal residual disease (RCB-I) might have outcomes approaching those of pCR (as suggested by Hamy et al. for some subtypes), whereas those with extensive residual (RCB-III) clearly need additional therapeutic interventions due to high relapse rates. Our findings support the practice of tailoring adjuvant therapy based on residual disease: for instance, TNBC patients with RCB-II/III should receive capecitabine (which improves DFS, as per CREATE-X) and consideration for clinical trials, and HER2+ patients with any residual disease should receive T-DM1 (now standard after KATHERINE). Additionally, the poor response in luminal B cancers suggests that novel neoadjuvant strategies (like integrating CDK4/6 inhibitors or immunotherapy in select cases) should be explored to improve pCR, though their ultimate benefit might lie in adjuvant setting given the indolent nature of ER+ disease.

Finally, this study highlights the importance of a multidisciplinary approach in managing these cases: medical oncologists, surgeons, radiologists, and pathologists must collaborate closely. The use of intermediate endpoints like pCR and RCB can help identify which patients are cured by chemo and which need more treatment. Future research could focus on incorporating genomic predictors to tailor NACT (e.g. DNA damage repair mutations in TNBC might predict platinum response), and on emerging therapies (PARP inhibitors, immunotherapy in neoadjuvant setting for TNBC, as investigated in KEYNOTE-522 which showed added pCR benefit with pembrolizumab). For HER2-positive disease, de-escalation strategies for those who achieve early response (to avoid overtreatment) are being studied, whereas our data suggests escalation (T-DM1) for those with residual is warranted. In luminal cancers, distinguishing which patients truly benefit from chemo versus those who could go straight to surgery then endocrine therapy remains a clinical dilemma; ongoing trials of neoadjuvant endocrine (alone or with CDK inhibitors) might shed light on this.

In conclusion, our real-world analysis demonstrates that patients with aggressive breast cancer subtypes exhibit not only different rates of response to neoadjuvant chemotherapy, but also distinct patterns of residual disease burden. These differences have prognostic significance and should inform post-neoadjuvant treatment planning. Implementing standardized pathological assessment tools like RCB in routine practice can enhance our ability to personalize therapy, improving outcomes for high-risk breast cancer patients.

CONCLUSION

Patients with aggressive biological subtypes of

breast cancer (triple-negative, HER2-positive, and luminal B HER2-negative) show markedly different responses to neoadjuvant chemotherapy. In our study, the rates of pathological complete response were highest in HER2-positive (up to ~60%) and triple-negative (~50%) cancers, and lowest in luminal B HER2-negative tumors (~16%) ($p<0.0001$). Moreover, the distribution of residual cancer burden (RCB classes) among cases with residual disease varied significantly by subtype. Triple-negative tumors, if not eradicated by therapy, tended to have substantial residual tumor burden (high proportions of RCB-II and RCB-III, with minimal RCB-I), whereas HER2-positive tumors more often had only minimal or moderate residual disease and very few extensive residuals. Luminal B tumors were relatively chemoresistant, with the majority exhibiting moderate-to-high residual burden. These patterns may impact prognosis: patients with minimal residual disease (RCB-I) after NACT likely have favorable outcomes, while those with extensive residual (RCB-III) are at high risk of recurrence. Our findings underscore the importance of achieving pCR in aggressive subtypes and support the use of intensified adjuvant therapies for patients with significant residual disease (such as capecitabine for TNBC and T-DM1 for HER2-positive cases). The integration of RCB classification alongside traditional ypTN staging provides a more nuanced evaluation of treatment response, which can guide risk-adapted postoperative management. In summary, patients with aggressive breast cancer subtypes have not only differing frequencies of pCR to neoadjuvant chemotherapy, but also distinctive patterns of residual tumor burden. Recognizing and addressing these differences is crucial for optimizing subsequent therapy and improving long-term outcomes in this high-risk population.

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