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Results of Neoadjuvant Chemotherapy in ER-Positive HER2/neu-Negative Breast Cancer After 2–8 Courses

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ABSTRACT

Background: Neoadjuvant chemotherapy (NCT) is an optimal treatment for estrogen receptor (ER)-positive/human epidermal growth factor receptor 2 (HER2/neu)-negative breast cancer. We evaluated the results after 2, 4, 6, and 8 courses.

Methods: We conducted a retrospective analysis of the effectiveness of 2 to 8 courses of NCT in 121 patients. NCT consisted of doxorubicin, endoxan, and docetaxel. After NCT, all patients received surgery, radiation, and endocrine therapy.

Results: In Group 2, treatment showed no effect in 1 case (4%), while partial response was observed in 6 cases (23%) and stabilization in 19 cases (73%). In the 4-course group, there was no treatment effect in 2 cases (6.5%), partial response in 15 cases (48.4%), and stabilization in 13 cases (41.9%). Additionally, 1 case (3.1%) achieved a pathologic complete response (pCR). In the 6-course group, 1 case (3.1%) showed no treatment effect, 18 cases (56.3%) had a partial response, and 8 cases (25%) exhibited stabilization. A pCR was achieved in 5 cases (15.6%). In the final group (8 courses), 1 case (3.1%) had no treatment response, 18 cases (56.3%) demonstrated partial response, and 4 cases (12.5%) showed stabilization, with 9 cases (28.1%) achieving pCR.

The 5-year cancer-specific survival rate ranged from 88.1±6.4% to 96.8±3.2%.

Conclusion: Two courses of NCT were ineffective. Tumor progression occurred in 3% to 6% of cases, while the Ki-67 index increased by 9.4% to 22.6%. A pCR was achieved in 3.2% to 15.6% of patients after 4 to 6 courses. Intermediate tumor biopsy can identify cases of treatment resistance or high chemosensitivity.

INTRODUCTION

Neoadjuvant (preoperative) chemotherapy (NCT) is the preferred treatment approach for patients with stage II-III estrogen receptor (ER)-positive/human epidermal growth factor receptor 2 (HER2)-negative breast cancer who desire breast conservation.[1,2] According to international guidelines, the optimal regimen consists of 8 courses: 4 cycles of AC (doxorubicin + cyclophosphamide) followed by 4 cycles of docetaxel (D) or paclitaxel (P), administered at 21-day intervals. This treatment protocol enables tumor and lymph node metastasis regression, facilitates downstaging, and increases the likelihood of successful breast-conserving surgery. Furthermore, achieving a complete pathological response (pCR) with this regimen is associated with improved long-term recurrence-free survival.[2] It is clear that chemotherapy can induce complications, such as cardiopathy, neutropenia, and neuropathy. In

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some cases, when luminal breast cancer is resistant to chemotherapy, treatment can be changed to preoperative (neoadjuvant) endocrine therapy (NET). Recent evidence suggests neoadjuvant endocrine therapy (NET) has emerged as a viable alternative and potentially the primary preoperative treatment approach for stage II-III ER-positive/HER2-negative breast cancer.[1,5] The best methods for assessing tumor regression are magnetic resonance imaging (MRI), ultrasound, mammography and assessment of tumor cellularity after NCT, along with changes in Ki-67[6,7], At the same time, a decreased Ki-67 value correlates with the residual tumor mass (i.e., residual cancer burden) and cellularity[8-11] or pathomorphosis.

Multiple classification systems exist for evaluating response to neoadjuvant therapy, including the Chevallier, Bonadonna, and Smith criteria. While these systems differ slightly in their specifics, they all categorize responses along a spectrum ranging from complete pathological response to no tumor response. This raises a critical clinical question: can treatment be safely discontinued before completing all 8 courses when either (1) complete pathological response is achieved early, or (2) when chemotherapy proves ineffective, necessitating either regimen modification or transition to endocrine therapy? The key challenge lies in accurately identifying these scenarios during treatment. During NCT, with an interval of every 2 courses, an examination of the tumor and metastases in the lymph nodes (mammography, ultrasound, MRI) is carried out. But these techniques do not guarantee full compliance of radiological changes with morphological ones. Thus, it is imperative to conduct an intermediate (repeated or intercourse) biopsy of the tumor, which will provide accurate information about morphological changes in response to treatment.

METHODS

We evaluated the results of 2, 4, 6, and 8 courses of NCT, from 2018 to 2019, in the Kyiv Clinical Oncology Center. In our clinical practice, the full 8-course NCT regimen was not routinely administered prior to surgery due to various constraints, including patient or surgeon preference and limited chemotherapy coverage under government healthcare programs. However, all patients ultimately received a total of 8 chemotherapy courses through a combination of neoadjuvant and adjuvant treatment. Following surgery, patients completed their therapy with either 6, 4, or 2 additional adjuvant chemotherapy courses as needed to maintain the standardized total treatment duration (Figure 1).

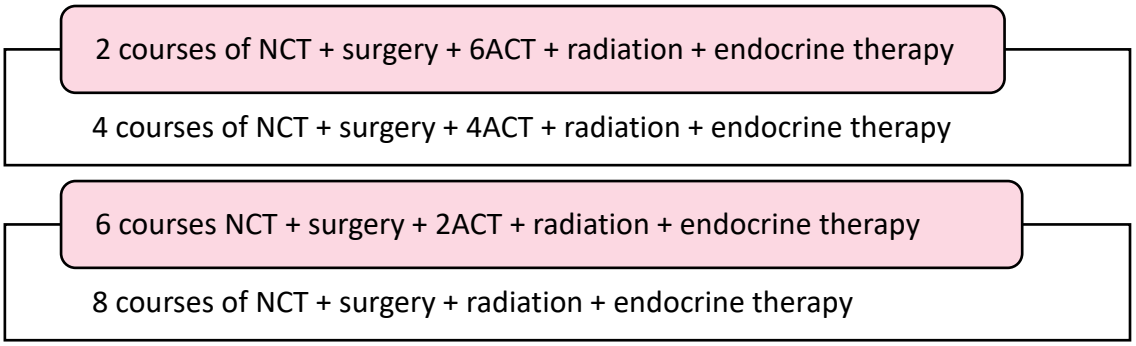

Figure 1. Blockchain Schema of Treatment Patients in Different Groups

In the present study, all patients received a standard treatment, which allowed us to analyze the effectiveness of 2,4,6, and 8 preoperative courses. This study was designed to evaluate tumor response dynamics throughout the complete NCT course. By performing serial tumor biopsies at regular intervals (after every 2 chemotherapy cycles during the 8-course regimen), we hypothesized that we could: (1) characterize the temporal patterns of pathological and molecular changes during treatment, and (2) identify critical transition points where early treatment modification might be warranted based on individual tumor response characteristics. This retrospective cohort study analyzed data from patients with breast cancer treated at the Kyiv City Clinical Oncology Center between January 2019 and December 2024. Using simple random sampling, we selected patients who initiated NCT in 2019 and evaluated their 5-year cancer-specific survival outcomes in 2024. The study protocol was approved by the institutional review board, and all data were anonymized prior to analysis.

The study included adult female patients aged 18 to 75 years with pathologically confirmed stage II or III breast cancer, an Eastern Cooperative Oncology Group (ECOG) performance status of ≤1, and ER-positive tumors. Eligible participants had received 2, 4, or 6 (but no more than 8) courses of preoperative chemotherapy, and their clinical data were accessible through the hospital information system.

Patients were excluded if they presented with: (1) secondary malignancies (except basal cell carcinoma); (2) inoperable breast cancer following

NCT; (3) inflammatory breast carcinoma; (4) active HIV infection (confirmed by positive testing), chronic hepatitis B or C (without requiring screening); (5) triple-negative or HER2-positive tumor status; (6) evidence of distant metastases; or (7) significant comorbidities affecting cardiac, pulmonary, or hepatic function that would contraindicate treatment.

NCT consisted of anthracycline-taxane regimens: doxorubicin 60 mg/m^2 plus cyclophosphamide 600 mg/m^2 every 21 days × 4 cycles and docetaxel at 100 mg/m^2 every 21 days × 4 cycles. In Group 2, there were only 2 cycles of doxorubicin with cyclophosphamide, but in Group 4, there were 4 cycles of doxorubicin with cyclophosphamide. In Goup 6, chemotherapy consisted of 4 cycles of doxorubicin with cyclophosphamide, followed by 2 more cycles of docetaxel. In Group 8, chemotherapy consisted of 4 cycles of doxorubicin with cyclophosphamide, followed by 4 cycles of docetaxel. Informed consent was obtained from all patients. We conducted this study on the effectiveness of 2 courses (26 patients), 4 (31 patients), 6 (32 patients), and 8 (32 patients) courses of NCT in 121 patients.

Tumor diameter, side, lymph node involvement, and distant metastasis status were obtained by the use of mammography, ultrasound, and computed tomography (CT). Tumor diameter was assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 during NCT.[12] A core biopsy was performed prior to neoadjuvant therapy in order to determine the histopathological diagnosis, molecular subtype, receptor status, and Ki-67 proliferation index. Biopsy of axillary lymphatic nodes was not conducted. The determination of ER and progesterone receptor (PR) status was conducted in accordance with standard immunohistochemical methods. The evaluation of ER expression was conducted in accordance with the updated guidelines set forth by the American Society of Clinical Oncology (ASCO)/College of American Pathologists (CAP).[13] We used the 2019 European Society of Medical Oncology guideline for Ki-67 determination as a reference point, with values exceeding 30% classified as elevated.[14]

Statistical analysis

Statistical analyses were performed using MedCalc Statistical Software version 23.0.9 (MedCalc Software Ltd, Ostend, Belgium; 2024). For quantitative variables, normality of distribution was assessed using the Shapiro-Wilk test. Normally distributed variables are presented as mean±standard deviation (SD), while non-normally distributed variables are expressed as median (interquartile range [IQR], Q1–Q3). Categorical variables are reported as frequencies (percentages). Five-year cancer-specific survival rates are presented as percentages±standard error (SE).

When comparing quantitative variables in more than two groups, the Kruskal-Wallis test was used. Posterior comparisons were performed using Dunn's test. The chi-square test was used to compare qualitative variables. Patient survival was analyzed using Kaplan-Meier survival curves, and the logrank test was used for comparison purposes. The level of significance was set at 0.05.

RESULTS

The median age across treatment groups was as follows: Group 2 (2 courses), 56 years; Group 4 (4 courses), 56 years; Group 6 (6 courses), 58.5 years; and Group 8 (8 courses), 55.5 years (Table 1). Stage distribution was comparable among groups receiving 4, 6, or 8 courses of preoperative chemotherapy (P>0.05). However, Group 2 showed a significant imbalance in stage distribution, with proportionally more stage II (P=0.020) and fewer stage III patients compared to other groups, which maintained approximately equal proportions of stage II and III cases. This difference was not observed in the higher-course-number groups, where stage distribution remained statistically similar.

The tumor characteristics across the groups were as follows: in Group 2 (2 courses): 7.7% (2/26) invasive lobular and 92.3% (24/26) ductal carcinomas, with 7.7% (2/26) G3 and 92.3% (24/26) G2 tumors, including 73% (19/26) ER$^+$PR$^+$HER2$^-$ and 27% (7/26) ER$^+$PR$^+$HER2^{low} cases; Group 4 (4 courses): 3.2% (1/31) lobular and 96.8% (30/31) ductal carcinomas, 3.2% (1/31) G3 and 96.8% (30/31) G2 tumors, comprising 58% (18/31) ER$^+$PR$^+$HER2$^-$, 35.5% (11/31) ER$^+$PR$^-$HER2$^-$, and 6.5% (2/31) ER$^+$PR$^+$HER2^{low} cases; Group 6 (6 courses): 3.1% (1/32) lobular and 96.9% (31/32) ductal carcinomas, 3.1% (1/32) G3 and 96.9% (31/32) G2 tumors, with 65.6% (21/32) ER$^+$PR$^+$HER2$^-$, 18.8% (6/32) ER$^+$PR$^-$HER2$^-$, and 15.6% (5/32) ER+PR+HER2-low cases; and Group 8 (8 courses): 12.5% (4/32) lobular and 87.5% (28/32) ductal carcinomas, 9.4% (3/32) G3 and 90.6% (29/32) G2 tumors, including 71.9% (23/32) ER$^+$PR$^+$HER2$^-$, 25% (8/32) ER$^+$PR$^-$HER2$^-$, and 3.1% (1/32) ER$^+$PR$^+$HER2^{low} cases, with no statistically significant differences between groups (P=0.37).

Tumors were stratified by Ki-67 proliferation index into 2 groups: Low Level (≤30%) and Elevated Level (>30%), as detailed in Table 1. A statistically significant difference in tumor Ki-67 proliferation index was observed between patients receiving 2

courses (median, X%; IQR, X–X) and 8 courses (median, X%; IQR, X–X) of NCT (P=0.XX). In Group 2, there were 7 patients (26.9%) with a Ki-67 value of up to 30% and 19 patients (73.1%) with a Ki-67 value higher than 30%. In Group 4, there were 12 patients (38.7%) with a Ki-67 value up to 30% and 19 patients (61.3%) with a Ki-67 value more than 30%. In Group 6, there were 10 patients (31.25%) with a Ki-67 value up to 30% and 22 patients (68.75%) with a Ki-67 value higher than 30%, and in Group 8, there were 15 patients (46.9%) with a Ki-67 value up to 30% and 17 patients (53.1%) with a Ki-67 value more than 30% (Table 1).

Table 1. Distribution and Characteristics of Patients

Indicator		Group T2 (n=26)	Group 4 (n=31)	Group 6 (n=32)	Group 8 (n=32)	P value
Age		56 (46–64.5)	56 (46–62)	58.5 (39.5–66.5)	55.5 (46–63.5)	0.981
T	1	3 (11.5)	2 (6.5)	1 (3.1)	6 (18.8)	0.020
	2	21 (80.8)	22 (71)	18 (56.3)	17 (53.1)	
	3	2 (7.7)	2 (6.5)	3 (9.4)	6 (18.8)	
	4	0 (0)	5 (16.1)	10 (31.3)	3 (9.4)	
N	0	8 (30.8)	3 (9.7)	6 (18.8)	4 (12.5)	0.060
	1	12 (46.2)	17 (54.8)	11 (34.4)	18 (56.3)	
	2	2 (7.7)	10 (32.3)	9 (28.1)	9 (28.1)	
	3	4 (15.4)	1 (3.2)	6 (18.8)	1 (3.1)	
Morphological structure	1	22 (84.6)	29 (93.5)	30 (93.8)	25 (78.1)	0.370
	2	1 (3.8)	1 (3.2)	1 (3.1)	4 (12.5)	
	3	3 (11.5)	1 (3.2)	1 (3.1)	3 (9.4)	
Ki-67 before NCT	1	7 (26.9)	12 (38.7)	10 (31.3)	15 (46.9)	0.400
	2	19 (73.1)	19 (61.3)	22 (68.8)	17 (53.1)	

For quantitative variables, the table presents the median and the interquartile range. Comparisons were made using the Kruskal-Wallis test. For qualitative variables, the comparison was carried out using the 2-test. Morphological structure: 1, invasive ductal carcinoma; 2, invasive lobular carcinoma; 3, G3 histological grade. NCT, neoadjuvant chemotherapy.

In Group 2, after the second course of NCT, the tumor was evaluated according to RECIST 1.1. In 1 case (4%), there was no effect of treatment (tumor and Ki-67 value growth), in 6 (23%) cases, there was a partial response of the tumor, and in 19 (73%) cases, there was stabilization (Figure 2). The mean diameter of the tumor in the breast decreased from 31 mm to 25.8 mm (by 17%). Breast-conserving surgery (BCS) was performed in 9 (34.6%), subcutaneous mastectomy with implant reconstruction in 2 (7.7%), and mastectomy in 15 (57.7%) cases. Post-NCT Ki-67 value in 18 (69.2%) cases decreased, in 5 (19.2%) patients it was not changed, and in 3 (11.5%) cases it increased. An increase in Ki-67 value in 3 cases may indicate ineffectiveness, and possibly primary resistance to NCT, and in such cases, there may be a better effect from endocrine therapy [9]. Grade 1 pathological tumor response was in 18 (69.2%) cases, grade 2 in 3 (11.5%), and grade 3 was in 5 (19.2%) samples. There were no samples with grade 4 pathological tumor response in Group 2. In 2 (7.7%) cases, the effect of chemotherapy was not visible at all; there was no pathological tumor response. 5-year cancer-specific survival in group 2 was 88.1±6.4%.

In Group 4, after the second and fourth courses of NCT, the tumor was evaluated. In 2 cases (6.5%), there was no effect of treatment (tumor diameter growth), in 15 (48.4%) cases, there was a partial response of the tumor, and in 13 (41.9%) cases, there was no change (Figure 2). One case (3.1%) demonstrated pCR despite imaging findings suggestive of partial response, with persistent tumor shadow on mammography and ultrasound. The mean tumor diameter decreased by 31.2% (from 33 mm to 22.8 mm).

Surgical interventions included BCS in 38.7% (12/31) and mastectomy in 61.3% (19/31) of patients. Postoperative analysis revealed Ki-67 reduction in 61.3% (19/31) of cases, no change in 16.1% (5/31), and an increase in 22.6% (7/31). Pathological responses were graded as: grade 1 (29%, 9/31), grade 2 (64.5%, 20/31), grade 3 (3.1%, 1/31), and grade 4 (3.1%, 1/31).

The group demonstrated excellent 5-year cancer-specific survival of 96.8%±3.2%. In Group 6, after the second, fourth, and sixth courses of NCT, the tumor was evaluated. In 1 case (3.1%), there was no effect of treatment (tumor diameter growth), in 18 (56.3%) cases, there was a partial response, and in 8 (25%) cases, no change was observed (Figure 2).

Five cases (15.6%) achieved pCR despite demonstrating imaging characteristics consistent with partial response, with residual tumor shadows persisting on mammography and ultrasound.

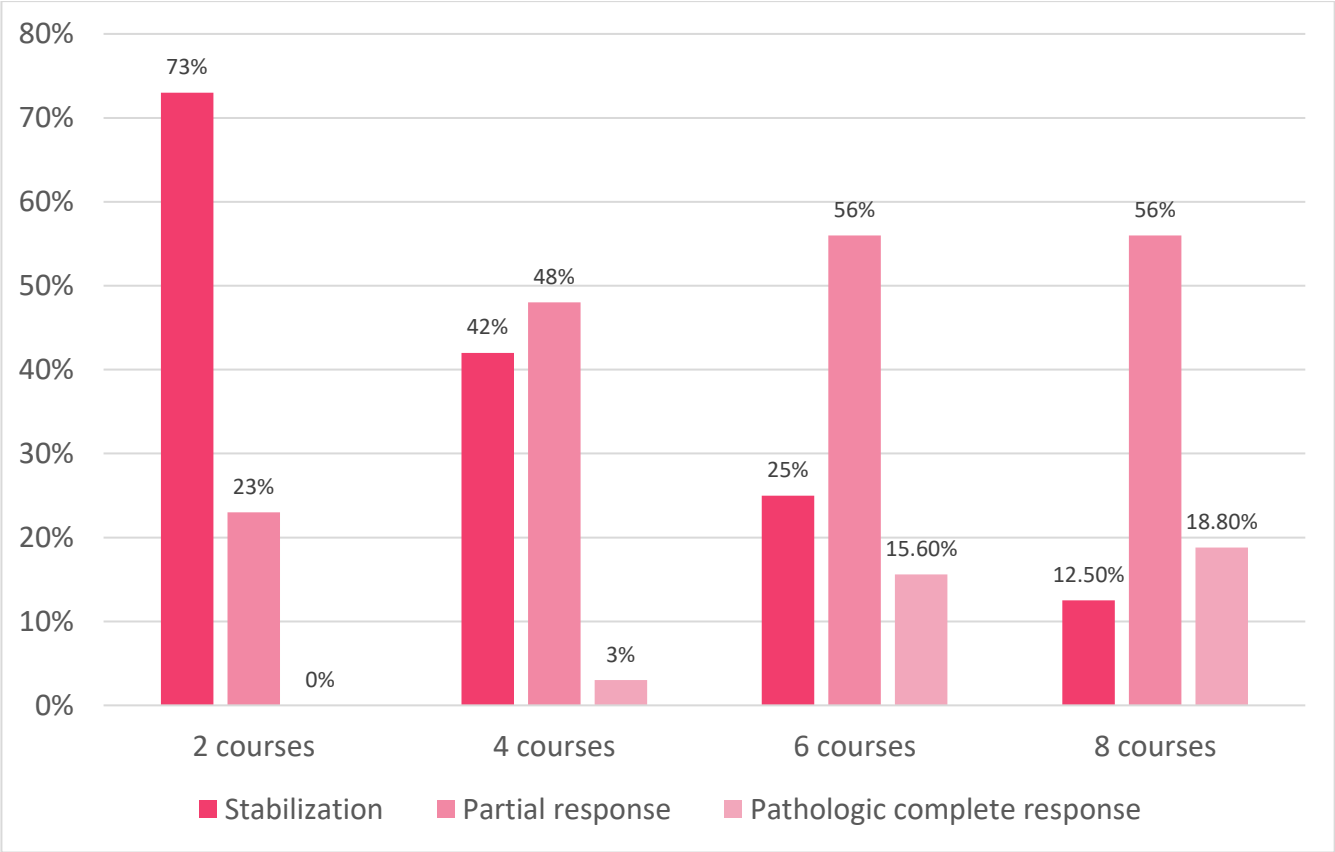

Figure 2. Dynamics of Tumor Response After Neoadjuvant Chemotherapy

The mean diameter of the tumor in the breast decreased from 38.4 mm to 25.8 mm (by 32.2%). BCS was performed in 9 (28.1%) patients, mastectomy in 20 (62.5%) patients, and subcutaneous mastectomy with autologous flaps reconstruction in 3 (9.3%) patients. Following NCT, Ki-67 proliferation index decreased in 84.4% of cases (27/32), remained stable in 3.1% (1/32), and increased in 12.5% (4/32). Grade 1 pathological tumor response was observed in 6 (18.8%) cases, Grade 2 in 13 (40.6%), Grade 3 in 7 (21.9%) cases, and Grade 4 in 5 cases (15.6%). The 5-year cancer-specific survival rate was 90.6±5.2%.

In the final treatment group, tumor response was assessed following each 2-course interval of NCT. Treatment outcomes included: no response in 3.1% of cases (1/32), partial response in 56.3% (18/32), disease stabilization in 12.5% (4/32), and pCR in 28.1% (9/32) (Figure 2). The mean tumor diameter demonstrated significant reduction from 36.3±17.4 mm to 14.6±12.9 mm (60% decrease), with maximal tumor regression observed after completion of all 8 NCT courses (Figure 3).

BCS was performed in 15 (46.9%), mastectomy in 11 (34.4%) patients, and subcutaneous mastectomy with implant or autologous flaps reconstruction in 6 (18.7%) cases. Ki-67 value decreased in 27 (84.4%) cases, did not change in 2 (6.2%) patients, and increased in 3 (9.4%) cases. Grade 1 pathological tumor response was observed in 5 (15.6%) cases, Grade 2 in 12 (37.5%), Grade 3 in 9 (28.2%) cases, and Grade 4 in 6 cases (18.7%). The 5-year cancer-specific survival in group 8 was 96.4±3.5%. The results of the above statistical analyses are shown in Table 2.

For qualitative variables, we performed comparisons using the chi-square test followed by post hoc multiple comparisons, which revealed statistically significant differences ($P<0.05$) between: (1) Group 2 versus other groups, (2) Group 4 versus other groups, (3) Group 6 versus other groups, and (4) Group 8 versus other groups. The 5-year cancer-specific survival results showed that the survival rates in the groups did not differ statistically, and ranged from 88.1±6.4% to 96.8±3.2%, $P=0.525$ (Figure 4).

DISCUSSION

Our findings demonstrate that the proportion of chemotherapy-resistant tumors remains relatively stable (10–20%) regardless of the number of NCT courses administered, consistent with reports in the literature. Notably, these treatment-resistant cases were characterized by (1) elevated post-NCT Ki-67 levels, (2) absence of pathological response (grade 0), and (3) radiological evidence of disease stabilization (by mammography/ultrasound).

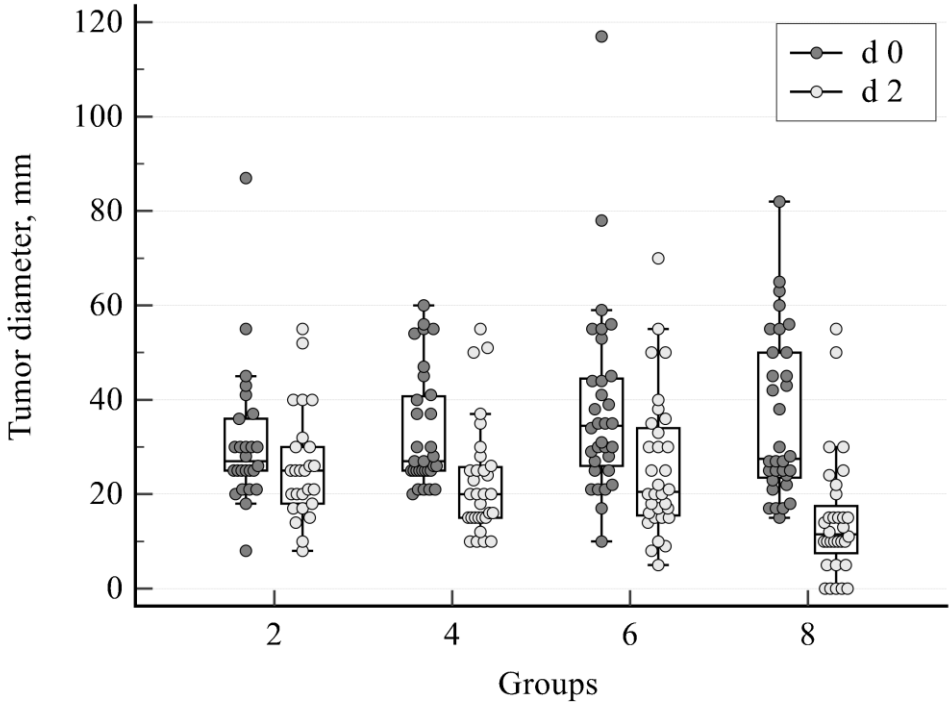

Figure 3. Dynamics of Tumor Diameter Reduction Before Treatment (d 0) and After NCT (d 2).

Table 2. Response to Treatment, Pathological Tumor Response, Ki-67 Changes, and Type of Surgery

Indicator		Group 2 (n=26)	Group 4 (n=31)	Group 6 (n=32)	Group 8 (n=32)	P value
Response to treatment	0	1 (3.8)[3,4]	2 (6.5)[4]	1 (3.1)[1]	1 (3.1)[1,2]	<0.001
	1	19 (73.1)	13 (41.9)	8 (25)	4 (12.5)	
	2	6 (23.1)	15 (48.4)	18 (56.3)	18 (56.3)	
	3	0 (0)	1 (3.2)	5 (15.6)	9 (28.1)	
Pathological tumor response	0	2 (7.7)[3,4]	0 (0)[4]	1 (3.1)[1]	0 (0)[1,2]	0.002
	1	13 (50)	9 (29)	6 (18.8)	5 (15.6)	
	2	9 (34.6)	20 (64.5)	13 (40.6)	12 (37.5)	
	3	2 (7.7)	1 (3.2)	7 (21.9)	9 (28.1)	
	4	0 (0)	1 (3.2)	5 (15.6)	6 (18.8)	
Ki-67 post-NCT	1	18 (69.2)	19 (61.3)	27 (84.4)	27 (84.4)	0.184
	2	3 (11.5)	7 (22.6)	4 (12.5)	3 (9.4)	
	3	5 (19.2)	5 (16.1)	1 (3.1)	2 (6.3)	
Type of surgery	1	15 (57.7)	19 (61.3)	20 (62.5)	11 (34.4)	0.094
	2	2 (7.7)	0 (0)	3 (9.4)	6 (18.8)	
	3	9 (34.6)	12 (38.7)	9 (28.1)	15 (46.9)	

Treatment response was categorized as: 0 (no response/progression), 1 (stabilization/<30% reduction), 2 (partial response/≥30% reduction), or 3 (complete pathological response [pCR]); pathological tumor regression was graded 0 (no response) through 4 (complete response); post-NCT Ki-67 changes were classified as 1 (decreased/≥10% reduction), 2 (increased/≥10% elevation), or 3 (stable/<10% change); surgical approaches included 1 (total mastectomy), 2 (subcutaneous mastectomy with reconstruction), or 3 (breast-conserving surgery [BCS]).

Importantly, a subset of patients experienced significant pathological responses (grade 3-4) despite showing only minimal clinical or radiological regression. These resistant cases are of particular concern as patients derive no therapeutic benefit while being exposed to cumulative treatment-related toxicities. It is clear that the tumor on X-ray images or ultrasound images may persist for some time, even though it is decreasing, and morphologically, there may be complete morphological regression. In such cases, the only reliable analysis of the response of the tumor to chemotherapy is the morphological changes. For this purpose, the so-called repeated biopsy during treatment between 4 and 6 courses can be useful. Tumor biopsy itself is a safe procedure and will not stimulate the progression of the disease, as evidenced by the literature. In addition, this method is implemented to determine the sensitivity and resistance of the tumor during neoadjuvant endocrine therapy (ET).[15-17] Multiple clinical trials have

demonstrated the prognostic value of monitoring Ki-67 index, tumor-infiltrating lymphocytes (TILs), and tumor differentiation grade through serial biopsies during NCT.[18-20] These biomarkers effectively identify patient subgroups with intrinsic resistance to preoperative chemotherapy (CHT) and endocrine therapy (ET).

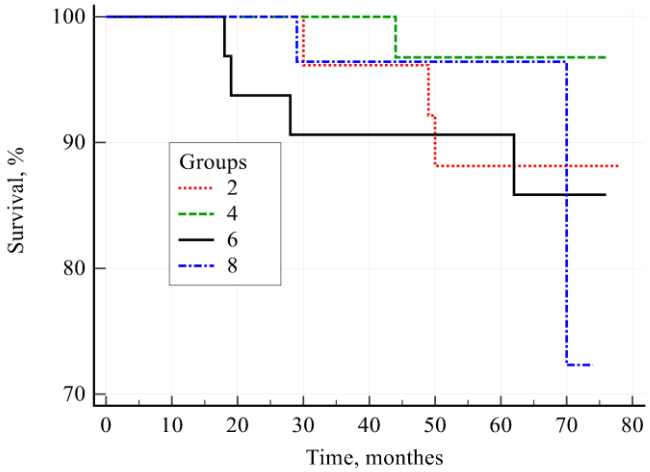

Figure 4. Five-Year Cancer-Specific Survival Results in All Groups

The predictive utility of Ki-67 is particularly well-established, with higher baseline levels (>25% cutoff) consistently associated with reduced likelihood of pCR, especially in ER-negative and HER2-positive subtypes.[21] However, approximately 10-15% of tumors demonstrate paradoxical Ki-67 elevation during treatment, highlighting the complex and heterogeneous nature of tumor biology that may underlie treatment resistance.[22] These findings highlight the importance of reassessing Ki-67 thresholds in luminal B breast cancer and refining predictive models to tailor chemotherapy strategies more effectively.[23,24] This highlights the need for more precise predictive models, integrating additional biomarkers and genomic profiling to improve treatment personalization. Morphological type (ductal or lobular infiltrative carcinoma) may be different in prognosis and response to therapy, and in the case of lobular carcinoma, the prognosis is worse in the case of metastases in the lymph nodes.[25] Given the small content of lobular carcinomas in the groups, we did not note the effect of the histological type on the prognosis and response to NCT in our trial. In contrast to the study in 26, which reviewed the results of research on the value of Her-2/neu low status in the tumor, we did not note its prognostic value, since there were not many such tumors before treatment. We have found a larger number of tumors with Her-2/neu low type after treatment, as a result of the transformation of the receptor status of the tumor in response to NCT. Axillary lymph nodes I-II levels were removed upon surgery, since most cases showed metastasis in the lymph nodes.

Our treatment approach maintained therapeutic adequacy by adhering to current evidence-based standards. The omission of lymphadenectomy in patients with clinically and sonographically negative lymph nodes, as validated by the INSEMA (1) and SOUND (2) trials, does not constitute undertreatment, but rather reflects contemporary practice paradigms for axillary management.[27-29] This approach aligns with modern de-escalation strategies while maintaining oncological safety.

CONCLUSION

Results showed that conducting 2 courses of NCT does not have the required result, and that the effectiveness of such treatment is low. In all groups, tumor progression during chemotherapy was noted in 3% to 6% of the patients. The growth of the Ki-67 value was in the range of 9.4% to 22.6% of cases, and complete morphological regression was maximally observed after 8 courses, but appeared in 3.2% to 15.6% of cases after 4 to 6 courses of NCT. Serial tumor biopsies during neoadjuvant therapy enable early identification of (1) primary resistant tumors and (2) highly chemosensitive tumors. This approach facilitates timely treatment modification–either intensification for resistant cases or early discontinuation (after 2 courses) for exceptional responders–while maintaining oncological efficacy. These findings highlight the importance of balancing chemotherapy intensity with individual patient characteristics to maximize treatment efficacy while minimizing unnecessary exposure to additional cycles.

ETHICAL CONSIDERATIONS

This study was conducted in full compliance with international ethical guidelines, including the principles of the 1964 Helsinki Declaration and its subsequent revisions. The protocol received approval from the appropriate institutional and national research ethics committees, the Ethical Commission of the Bogomolets National Medical University (reference number 183, April 25, 2024). Prior to participation, all subjects provided written informed consent following detailed explanations of the study procedures.

DATA AVAILABILITY

All experimental data included in this study can be obtained by contacting the first author if needed.

CONFLICT OF INTERESTS

The authors confirm they have no competing interests to disclose.

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