

Pathological response of breast cancer to neoadjuvant chemotherapy at a single tertiary centre

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Background: Neoadjuvant chemotherapy (NACT) is standard treatment for eligible breast cancer patients. While guidelines recommend combining chemotherapy with trastuzumab for HER2-positive breast cancer, Groote Schuur Hospital is unable to provide trastuzumab due to cost constraints. This study examines the pathological response of breast cancer patients who received NACT, with a particular focus on HER2-positive breast cancer patients who did not receive targeted therapy, trastuzumab, in the neo-adjuvant setting.

Methods: A retrospective audit was conducted on patients who received NACT followed by surgery between January 2017 and December 2018 at a tertiary hospital in Cape Town. Data on baseline tumour size, axillary staging, molecular subtype, and treatment response were analysed.

Results: Out of 160 patients, 97.5% were female ($n = 156$) and 88% underwent mastectomy. Infiltrating ductal carcinoma was the most common histology (94%). Pathological complete response (pCR) was achieved by 21% of patients, and 79% had residual disease. Triple-negative breast cancer showed the best pathological response, with a 31% pCR rate ($p < 0.005$), while ER-positive/HER2-negative patients had a poor pCR rate of 2.4% ($p < 0.005$). ER-negative/HER2-positive patients had a 6.7% pCR rate ($p = 0.147$).

Conclusion: NACT is most effective for triple-negative breast cancer patients, while ER+ve/HER2-ve showed the poorest response. HER2-positive patients, all not receiving trastuzumab, showed a much lower response compared to the international norm when trastuzumab was available. Adding trastuzumab should improve pCR rates for HER2-positive patients.

Keywords: neoadjuvant chemotherapy, breast cancer, trastuzumab, resource constrained setting, pathological complete response

Introduction

According to the 2017 cancer statistics, breast cancer was the most frequently diagnosed cancer in South Africa, underscoring its status as a pressing public health concern.¹ Breast cancer survival rates in South Africa vary significantly between the public and private healthcare sectors. A study by Du Plessis et al.² reported a 64.7% 5-year survival rate for patients with stage 2 and 3 breast cancer in the public sector, a figure notably lower than those observed in developed countries. In contrast, data from Discovery Health indicated a 5-year survival rate of 84% among insured patients, highlighting the disparity in outcomes between the two healthcare systems.³

Traditionally, chemotherapy was used mainly in an adjuvant manner after surgery. However, neoadjuvant chemotherapy (NACT) has gained prominence for patients with unresectable breast cancer, locally advanced breast cancer and inflammatory breast cancer. Over time, indications for NACT expanded to include reducing the size of large tumours to perform breast-conserving surgery.^{4,5} NACT has been utilised to assess patients with aggressive tumours, using pathological complete response (pCR) to

NACT as a prognosticate surrogate.⁴ Moreover, NACT has been instrumental in de-escalating the extent of surgery in the axilla, moving from axillary lymph node dissection to a less invasive sentinel node biopsy.⁶

In patients with triple-negative breast cancer, anthracycline and taxane-based regimes are the standard NACT treatments. The American Association of Clinical Oncology (ASCO) guidelines recommend NACT for all patients with triple negative breast cancer who have T1c or larger, or node-positive disease. HER2-positive patients should be offered trastuzumab and a non-anthracycline regimen or anthracycline and taxane regimen, depending on the availability of trastuzumab.⁷ The response to therapy should be assessed through clinical examination, mammogram and ultrasound.⁷

Several local studies in South Africa have explored NACT's implementation. O'Neil et al.⁸ investigated factors influencing the decision to use NACT in the country, considering resource constraints and found that NACT use was associated with increasing tumour burden and molecular aggressive subtypes. Nietz et al.⁹ focused on pCR in HIV-positive patients relative to viral load, but not much

exploration of other responses to NACT or response in non-HIV patients was conducted. Ruff et al.¹⁰ pointed out the lack of data on pathological response as a major limitation and suggested further research to assess NACT's benefits in the South African context.

This study aimed to evaluate the effects of NACT on pathological responses in various breast cancer molecular subtypes within a South African population. The objective was to analyse NACT responses in relation to patient characteristics and molecular subtypes, with a particular focus on HER2-positive breast cancer.

Methods

Design and participants

A retrospective review of all patients who received NACT followed by surgery at the Cape Town Metro West hospitals after a breast cancer diagnosis was performed between 1 January 2017 and 31 December 2018. All patients with a breast cancer diagnosis who received NACT, followed by surgery at Groote Schuur Hospital during the study period, were included in the study. Patients under 18 years, with incomplete data, who did not complete the intended chemotherapy course and patients who had surgery outside of Groote Schuur Hospital were excluded. Our operation schedule database identified patients who received surgery during the study period. The pharmacy database established which patients received NACT and the treatment used. Data was collected from the pharmacy database, hospital folders, National Health Laboratory Service (NHLS) histology reports and the hospital picture archiving and communication system (PACS). Patient demographics collected were age at presentation. Tumour characteristics recorded included tumour size, nodal status, tumour grade, oestrogen receptor (ER) status, and HER2-neu status. Equivocal HER2-neu receptor status (2+) was recorded as HER2-neu negative due to the absence of routinely available HER2-neu fluorescence in situ hybridisation (FISH) testing. Ki-67 was not included in this study as it was not routinely reported during our study period. Pathological response to NACT, as well as delays to initiation of NACT and surgery were recorded.

Tumour size and axillary staging

Clinical assessment, ultrasound and mammogram were used to assess the tumour size and nodal status. The tumour size, recorded before NACT was the maximal diameter on either a baseline mammogram or ultrasound. The axillary node status recorded before NACT was either node positive if the disease was present on clinical examination or ultrasound and node negative if no disease was suspected. The axillary disease was not confirmed on biopsy but based on clinical and ultrasound criteria.

Tumour subtypes

All patients received a diagnostic core needle biopsy before treatment commenced. Histologic grade, immunohistochemistry (IHC) for oestrogen and HER2-neu expression were assessed on the core needle specimen. Fluorescent in situ hybridisation (FISH) was not done because trastuzumab was not available as a treatment option. IHC analyses were performed on formalin-fixed paraffin-embedded tissue sections. HER2 positive was a score of 3+, and HER2 negative was a score of 1+ and 2+ on IHC.

Positive ER status was defined as at least > 2/8 of tumour cells with nuclear staining.

Currently, breast cancer is classified into distinct molecular subtypes: luminal A, luminal B, HER2 enriched, and triple negative or basal type. Patients in this study could not be divided into these groups because the study site only started doing routine Ki-67 and progesterone receptor (PgR) testing on all patients in 2018. However, an attempt was made to group tumour types. To achieve this, the following four groups were selected: 1. ER+ve/HER2-ve, 2. ER+ve/HER2+ve, 3. ER-ve/HER2+ve and 4. and triple negative.

Oncological regimen

The standard neoadjuvant treatment regimen consisted of doxorubicin, cyclophosphamide and three weekly paclitaxel. A second regimen included the previous regimen with the addition of carboplatin, with or without additional docetaxel. Lastly, a combination of docetaxel and cyclophosphamide was also used. Chemotherapy regimens followed international guidelines.

Response to treatment

It was impossible to assess response to therapy on mammogram or ultrasound at the end of NACT because this was not routinely performed due to a lack of resources. Tumour size post-NACT was measured on the pathology specimen post-excision. The axillary response was assessed on the excision nodal specimen. If no nodal metastases were found, it was recorded as node-negative disease, and if any disease was present, it was recorded as node-positive disease.

The pathological response was assessed on surgical excision specimens. A pCR was defined as having no residual invasive carcinoma in the breast and no tumour in the axillary lymph nodes. Patients with residual ductal carcinoma in situ (DCIS) and no evidence of residual invasive disease were recorded as having achieved a pCR.

Statistical analysis

Data was analysed from an Excel spreadsheet, and simple descriptive stats were used. Non-parametric data was described with median and interquartile range. Data was categorised using numerical variables, and Pearson's chi-square test and Fisher's exact test were used for analysis. A *p*-value of 0.05 was used to show statistical significance, rejecting the null hypothesis.

Results

Over the study period 1 January 2017 to 31 December 2018, 533 patients received surgery for breast cancer at the four Metro West hospitals after an initial diagnosis of breast cancer at Groote Schuur Hospital. From the pharmacy database, it was established that 159 patients with 161 tumours had NACT. Two patients had bilateral tumours. One patient was excluded because of incomplete data. That left 160 tumours operated at Groote Schuur Hospital for analysis. Amongst these cases, 97.5% were females, while the remaining 2.5% represented males. The median age of the patients was 51 (IQR 43–61).

In terms of surgical interventions, 88% of the patients underwent a mastectomy, while 12% opted for breast-conserving surgery. Among the surgical cases, 85% involved axillary clearance, while 13% underwent sentinel lymph

node biopsy; a small minority of 2% did not require any procedure on the axilla.

The chemotherapy regimen administered to 85% of the patients consisted of cyclophosphamide, doxorubicin, and paclitaxel as the foundational treatment.

Table I: Pathological response of tumour to chemotherapy

Clinical response	Frequency	Per cent
pCR	34	21
Residual disease	126	79
Total	160	100

Table II: Response to neoadjuvant chemotherapy and association with different variables

Characteristic/variable	Overall, n = 160	pCR, n = 34	Residual cancer, n = 126	p-Value
Age				*0.214
< 50	79 (49.0%)	20 (25.3%)	59 (74.7%)	
> 50	81 (51.0%)	14 (17.2%)	67 (82.8%)	
ER				*0.07
Positive	76 (48.0%)	11 (14.5%)	65 (85.5%)	
Negative	84 (52.0%)	23 (27.4%)	61 (72.6%)	
PgR				**
Positive	4 (2.5%)	1 (25.0%)	3 (75.0%)	
Negative	78 (49.0%)	22 (28.2%)	56 (71.8%)	
Not recorded	78 (49.0%)	11 (14.1%)	67 (85.9%)	
Her2				*0.805
Positive	49 (30.8%)	11 (22.4%)	38 (77.6%)	
Negative	111 (68.2%)	23 (20.7%)	88 (79.3%)	
Grade				**
1	15 (9.4%)	0 (0.0%)	15 (100%)	
2	60 (37.5%)	1 (1.7%)	59 (98.3%)	
3	50 (31.3%)	1 (2.0%)	49 (98.0%)	
Not recorded	35 (21.8%)	32 (91.4%)	3 (8.6%)	
Type of tumour				*0.426
IDC	151 (94.0%)	33 (21.9%)	118 (79.1%)	
ILC	6 (3.8%)	1 (16.7%)	5 (83.3%)	
Mixed	1 (0.6%)	0 (0.0%)	1 (100%)	
Other	2 (1.3%)	0 (0.0%)	2 (100%)	
ER+ve/Her 2-ve				*< 0.05
Yes	42 (26.3%)	1 (2.4%)	41 (97.6%)	
No	118 (73.8%)	33 (28%)	85 (72%)	
ER-ve/Her 2+ve				*0.147
Yes	15 (9.4%)	1 (6.7%)	14 (93.3%)	
No	145 (90.6%)	33 (22.8%)	112 (77.2%)	
ER+ve/Her2+ve				*0.190
Yes	34 (21.3%)	10 (29.4%)	24 (70.6%)	
No	126 (78.7%)	24 (19%)	102 (81.0%)	
Triple negative				*< 0.05
Yes	67 (41.9%)	21 (31.3%)	46 (68.7%)	
No	93 (58.1%)	13 (14.0%)	80 (86.0%)	
Interval days between dx and Initiation of chemo				*0.244
< 30	20(12.0%)	7(21.0%)	13 (65.0%)	
31–60	85 (53.0%)	19 (22.4%)	66 (77.6%)	
61–90	40 (25.0%)	5 (12.5%)	35 (87.5%)	
> 90	15 (9.4%)	3 (20.0%)	12 (80.0%)	
Interval days between end of chemo and surgery				*0.671
< 30	20(12.0%)	6(30.0%)	14 (70%)	
31–60	98 (61.0%)	21 (21.4%)	77 (78.6%)	
61–90	34 (21.0%)	6 (17.6%)	28 (82.4%)	
> 90	8 (5.0%)	1 (12.5%)	7 (87.5%)	

*Pearson's chi-square test

** Statistical analysis could not be performed due to a high number of unrecorded data

Table III: Evaluation of progression or regression of tumour size with chemotherapy

		Post-chemotherapy tumour size					Total
		T0	T1	T2	T3	T4	
Pre-chemotherapy tumour size	T1	11 48%	10 43%	2 9%	0	0	23 14%
	T2	13 21%	14 23%	25 40%	7 11%	3 5%	62 39%
	T3	3 13%	5 23%	7 32%	7 32%	0	22 14%
	T4	7 13%	7 13%	22 42%	15 28%	2 4%	53 33%
Total		34 21%	36 22%	56 35%	29 19%	5 3%	160

Response to chemotherapy

A comprehensive evaluation of pathological response was conducted among the patients subjected to NACT (Table I).

Complete pathological responders comprised 21% of the cohort, while the remaining 79% had residual disease. Among the patients who responded to chemotherapy, 52% experienced tumour reduction but did not achieve a pCR.

Subtype-specific responses

Tumour subtypes exhibited distinctive response rates. Triple negative tumours showed the highest pCR rate at 31.3%, followed by ER+/HER2+ve tumours at 29.4%. Conversely, ER-ve/HER2+ve tumours exhibited a modest response rate of 6.7%, and ER+ve/HER2-ve tumours demonstrated the lowest response rate at 2.4%. Further statistical analysis found that ER+ve/HER2-ve tumours had a statistically significant ($p < 0.05$) non-response rate favouring residual disease (odds ratio = 0.06), with the triple negative molecular subtype having a statistically significant ($p < 0.05$) response rate favouring pCR (odds ratio = 2.81) (Table II).

Waiting time and response

The waiting time from breast cancer diagnosis to initiation of NACT, as well as the interval from the last dose of NACT to surgery, varied from 30 days to greater than 90 days, with the majority receiving it between 30–60 days. This had no statistical bearing on the response rate (Table II).

Tumour size and response

Significant correlations emerged between the initial tumour size and response rates to NACT. Notably, 48% of patients with T1 tumours achieved pCR, underscoring the favourable outcome associated with lower tumour stages. In contrast, the pCR rates for T2, T3, and T4 tumours were 21%, 13%, and 13%, respectively, indicating a decreasing trend with higher tumour sizes (Table III).

Discussion

The main finding of our study was an observed rate of 52% of patients who responded positively to chemotherapy, with 21% showing a complete pathological response. Comparatively, Sude et al.,¹¹ with a smaller group of 52 patients, reported a complete pathological response of 9.6% and an overall response rate of 84.6%. Taucher et al.¹² demonstrated a pathological complete response rate of 5.9% and an overall response rate of 56.2%. (Table IV).

This study's findings indicated that patients who exhibited a pCR were predominantly in the triple negative and ER+ve/HER2+ve group, representing 32/34 (94%) of patients with a pCR. The triple negative tumours showed the best pCR, 22/69 (32%) of patients, which was statistically significant ($p < 0.05$), followed by ER+ve/HER2+ve, with 10/34 (29%) of patients ($p = 0.146$). Our study findings are similar to a study by Qian et al.¹⁴ in terms of pCR in ER+ve/HER2+ve patients. They found a pCR rate of 28% in a group of patients who were hormone receptor positive/Her 2 +ve. Unfortunately, the limitation of their study, as described by the authors themselves, remained that the chemotherapy regimen used was varied and had not been described. Our pCR in the triple negative group was also similar to a large study by Cortazar et al.¹³ who found a pCR rate in this group of 33%. Both studies showed the best response rate was in the triple negative group, followed by her ER+ve/HER2+ve group, which is similar to our findings.

The added effect of trastuzumab on pCR is not disputed. Cortazar et al.¹³ reported pCR rates of 18.3% for ER+ve/HER2+ve patients and 30.2% for ER-ve/HER2+ve patients not receiving trastuzumab. An increase in pCR was observed from 30.2% to 50.3% for ER-ve/HER2+ve patients and from 18.3% to 30.9% for ER+ve/HER2+ve patients when trastuzumab was administered.¹³ Meta-analyses conducted by Shen et al.¹⁶ and Schettini et al.¹⁵ on HER2+ve tumours demonstrated that targeted therapy to HER2 receptors significantly improved the pCR, especially in HER2-enriched (ER-ve/HER2+ve) tumours. The NOAH trial indicated that adding trastuzumab nearly doubled the pCR from 19% to 38% and improved disease-free survival.¹⁷ Untch et al.¹⁸ showed a response rate of 20% when trastuzumab was not used and 39% when trastuzumab was used. Similarly, Buzdar et al.¹⁹ showed a complete pathological response rate of 25% without trastuzumab use and 66.7% when trastuzumab was used.

This study showed a pCR in patients ER-ve/HER2+ve in only 1/15 (6.7%), which is much lower than expected. Cortazar et al.¹³ showed a response rate of 18% in their pooled analysis, but there was no other study reported on this specific subtype. The reason behind the lower complete response rate among ER-ve/HER2+ve patients in this study is most likely the unresponsiveness of the tumour to our current chemotherapy, either due to a difference in the

Table IV: Studies looking at pathological response rate with chemotherapy

Study	Size of study	Complete pathological response	Overall response
Sude NS (2022) ¹¹	n = 52	9.6%	84.6%
Taucher S (2008) ¹²	n = 203	5.9%	56.2%
O'Neil D (2020) ⁸	n = 505	14.5%	
Cortazar P (2014) ¹³	n = 11 955	18.0%	
This study	n = 160	21.0%	52.0%

molecular biology of these tumours or to our much smaller sample size. Another explanation could be that because FISH testing was not performed, some HER2 2+ IHC results considered HER2-ve in this study were HER2+ve, skewing our results. The tumour size in this group cannot account for the poor response rate, as the median size in this subgroup was 31 mm (IQR 11–100). Similarly, our study shows that the timing of chemotherapy had no impact on tumour size, implying that all responses were most likely due to tumour biology. Introducing trastuzumab into our patients' treatment regimen could have improved our response rates.

Only one patient (2.4%) in the ER+ve/HER2-ve group achieved a pCR. Livingston-Rosanoff et al.²⁰ had a response rate of 9% in this subgroup, while Cortazar et al.¹³ had a response rate of 7.5% in their meta-analysis. The observation suggests that our ER+ve cancers tend to be more resistant to chemotherapy. It is also possible that the tumours in the other studies had a higher Ki-67, even though it was not reported in their respective studies. Unfortunately, during our study, the hospital did not perform Ki-67 testing, so we could not explore the influence of Ki-67 in our analysis. Several studies have highlighted that Ki-67 significantly predicts treatment response.²¹⁻²³

This study found no association between histologic grade and response to NACT. Von Minckwitz et al.'s²⁴ meta-analysis of chemotherapy trials in Germany showed that histological grading was associated with pathological response. Our conflicting result may be attributed to a lower sample size.

In this study, we made noteworthy observations regarding the patients' tumour size and response rates. Notably, 47% of the patients in this study presented with T3 or T4 tumours, a significant deviation from the findings of other studies. For instance, the ABCSG-07 study reported only 8.9% falling into this category, while Diéras et al.²⁵ showed an incidence of 25% in their study.¹² Upon analysing our data, we found that after NACT, 48% of T1, 46% of T2, 68% of T3, and 96% of T4 tumours demonstrated a reduction in tumour size (downsizing). However, the complete pathological response rate for T3-T4 tumours was only 13%. Our findings indicated a clear trend that the higher the T stage, the lower the likelihood of achieving a complete pathological response. This trend is consistent with the results of a comprehensive database study conducted by Livingston-Rosanoff et al.²⁰ which investigated the effect of tumour size on pCR. They proposed that tumour T stage could serve as an independent risk factor for assessing pCR, even after controlling for receptor status. In support of our observations, Goorts et al.²⁶ and Qian et al.¹⁴ have also demonstrated that tumour staging size significantly impacts response rates. Specifically, they found that a smaller tumour size tends to be more responsive to chemotherapy. This aligns with our findings, suggesting that smaller tumour size is more likely to achieve a pCR following NACT.^{14,26}

Our study faced significant limitations that could impact its findings. Firstly, lack of data regarding Ki-67 and PgR status on our histological specimens hindered our ability to comprehensively compare the efficacy of existing treatment regimens on different tumour biology. Secondly, measurement of tumour size, using a combination of radiology and pathology methods, could have introduced potential bias into the study since different modalities were employed to monitor the treatment response from pre-

treatment to post-treatment stages. Thirdly, we classified equivocal HER2-neu (2+) as negative because the majority of these (60%) would be HER2-ve on FISH testing.²⁷ This could influence the study results because some patients included as HER2+ve could be HER2-ve and vice versa. To enhance the robustness of future studies in this area, it is essential to address these limitations by ensuring comprehensive data collection, including Ki-67, progesterone receptor status and HER2-neu FISH testing in histological specimens. Additionally, standardising the method for tumour size measurement using a single modality throughout the study would minimise potential biases. A fourth limitation is the lack of histological correlation in patients classified as node positive disease on clinical and ultrasound assessments. Therefore, it is impossible to comment on nodal response rates to NACT. Lastly, as this study is a single-centre study, the results may not be generalisable to those of other lower-middle-income countries.

Conclusion

Our retrospective study demonstrated that patients with triple negative breast cancers exhibited a statistically favourable response to chemotherapy. Additionally, ER+ve tumours had the worst response to chemotherapy. For HER2 enriched cancers, only one patient achieved a complete pathological response, substantially lower than reported in the literature. Consequently, it is imperative to introduce targeted therapies in HER2-enriched tumours to improve pathological response and ultimately benefit patients.

Conflict of interest

The authors declare no conflict of interest.

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Ethical approval


This study was approved by the University of Cape Town Human Research Ethics Committee HREC Ref no.: 761/2021.

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