Pathological response of Breast cancer to neo-adjuvant chemotherapy at a single tertiary centre with no access to Trastuzumab

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DECLARATION

I, Dr Arvin Khamajeet, hereby declare that the work on which this dissertation/thesis is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or anyother university. I empower the university to reproduce for the purpose of research either the whole or any portion of the contents in any manner whatsoever.

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Abstract: Pathological response of breast cancer to neoadjuvant chemotherapy at a single tertiary centre with no access to trastuzumab

Introduction

Neoadjuvant chemotherapy (NACT) has firmly solidified its status as the gold standard in the treatment of breast cancer for eligible patients. While prevailing guidelines advocate for a combined approach involving chemotherapy and Trastuzumab for individuals with HER2-positive breast cancer, Groote Schuur Hospital faces constraints in administering Trastuzumab due to cost-related considerations. This study delves into the impact of neoadjuvant chemotherapy on breast cancer patients, specifically focusing on the response of local patients who are HER2-positive and do not receive Trastuzumab.

Methods

A retrospective audit was conducted on all patients who underwent NACT followed by surgical intervention, to assess response, between 1 January 2017 and 31 December 2018 within the Cape Town, Metro West surgical platform. Comprehensive data were gathered about tumour dimensions, axillary staging, tumour subtype, and treatment response.

Results

Data from 160 tumours were included. Predominantly, the cohort comprised women (97.5%, n=156), with a smaller representation of men (2.5%, n=4). In terms of surgical approach, a majority of patients underwent mastectomy (88%,n=141), while a minority opted for breast-conserving surgery (12%, n=19). The most common histology was infiltrating ductal carcinoma (94%, n=151), followed by infiltrating lobular carcinoma (3.8%, n=6). The analysis of NACT responses revealed a spectrum of outcomes: overall, 21% of patients achieved a pathological complete response (pCR), 31% demonstrated a partial response, 31% exhibited stable disease, and 17% experienced disease progression. Notably, triple-negative breast cancer displayed the most favourable response, with a pCR rate of 32% ($p<0.005$). In contrast, patients with ER-positive/HER2-negative tumours exhibited

the least favourable response, with 2.9% achieving pCR ($p<0.05$). ER-negative/HER2-positive patients demonstrated a pCR rate of only 6.7% ($p=0.215$)

Conclusion

Neoadjuvant chemotherapy appears particularly beneficial for patients with triple-negative breast cancer. This study reveals a significantly lower pCR rate in ER-negative/HER2-positive patients, even when compared to studies where Trastuzumab was not administered. For HER2-positive patients, the addition of Trastuzumab is advocated to augment the likelihood of achieving pCR and thereby improve overall survival rates.

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Abbreviations

USA	United States Of America
ER	Estrogen receptor
PgR	Progesterone receptor
HER2	Human epidermal growth receptor 2
NACT	Neo-adjuvant chemotherapy
pCR	Complete pathological response
CR	Complete response
PR	Partial response
NR	No response
PD	Progressive disease
RESIST	Response Evaluation Criteria in Solid Tumours
NHLS	National Health Laboratory Service
PACS	Hospital Picture Archiving and Communication System

Introduction

In 2020, breast cancer accounted for 15.7% of all newly diagnosed cancers in the USA, affecting 15% of women. Its impact on cancer mortality was significant, contributing to 7% of all cancer deaths [1]. Similarly, South Africa's 2017 cancer statistics placed breast cancer as the most frequently diagnosed cancer in the country, underscoring its status as a pressing public health concern[2].

The treatment of breast cancer is multifaceted, with chemotherapy playing a crucial role due to the systemic nature of the disease. Traditionally, chemotherapy has been 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 first to include reducing the size of large tumours to perform breast-conserving surgery[3,4]. Recently, NACT has been utilised to assess patients with aggressive tumours, using pathological complete response (pCR) to NACT to prognosticate patients[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[5].

For 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-neu-positive patients should be offered Trastuzumab and a non-anthracycline regimen or anthracycline and taxane regimen, depending on the availability of Trastuzumab[6]. The

response to therapy should be assessed through clinical examination, mammogram and ultrasound [6].

Several local studies in South Africa have explored NACT's implementation. O'Neil et al. investigated factors influencing the decision to use NACT in the country, considering resource constraints[7]. Nietz et al. 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[8]. Ruff et al. 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 [9]. Surprisingly, no study has examined NACT's impact on axillary staging or actual tumour size reduction in a South African setting. Of note, Trastuzumab is not widely available in the public health care system, particularly in the Western Cape, depriving patients of this life-saving medication.

To bridge these gaps in knowledge, this study aimed to evaluate the effects of NACT on clinical and pathological responses in various breast cancer subtypes within a South African population. The objective was to compare patient characteristics, receptor status, and molecular subtypes of breast carcinoma with their responses to NACT. By conducting this research, valuable insights were gained into the effect of NACT on our patient population.

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 who received NACT, followed by surgery at Groote Schuur hospital after a diagnosis of breast cancer was made during the study period, were included in the study. Patients under 18, patients with incomplete data and patients who did not complete the intended chemotherapy course because of side effects 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 stage, nodal stage, tumour grade, estrogen 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 FISH testing.

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 surgery, was the maximal diameter on either a mammogram or ultrasound. The axillary node status recorded before NACT was either N1 if the disease was present on clinical examination or ultrasound and N0 if no disease was suspected. Axillary disease was not confirmed on biopsy but based on clinical and ultrasound criteria. N1 was termed as being node positive, and N0 as being node negative.

Tumour subtypes

All patients received a diagnostic core needle biopsy before treatment commenced. Histologic grade, immunohistochemistry (IHC) for estrogen and HER2-neu expression via IHC were assessed on the core needle specimen. Fluorescent in situ hybridization (FISH) was not performed 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 an Allred score of more than 2/8 of tumour cells with nuclear staining.

Currently, breast cancer is divided into distinct molecular subtypes. The subtypes are 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 Ki67 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 4) triple negative.

Oncological regimen

The standard neoadjuvant treatment regimen consisted of doxorubicin, cyclophosphamide and 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.

Response to treatment

Response to treatment was assessed and reported, as represented in (Table 1). The system used was based on the Response Evaluation Criteria in Solid Tumours (RESIST) [10].

Table 1: Response to treatment	
Complete Response (CR):	Disappearance of all invasive cancer in resected specimen
Partial Response (PR):	At least a 30% decrease the LD of the initial radiological measurement compared to resected specimen
Progressive Disease (PD):	At least a 20% increase in the LD of the initial radiological measurement compared to resected specimen
Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD

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 scarcity of adequate resources. Therefore, the tumour size on the pathology specimen at surgery was measured post-NACT. The axillary response was assessed on the excision nodal specimen. If no disease was found on the nodal excision specimen, it was recorded as N0, and if any disease was present, it was recorded as N1. 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, with non-parametric data described with median and interquartile range. Data was categorised using numerical variables with Pearson's chi-squared test and Fisher's exact test used for analysis. A P-value of 0.05 was used to show statistical significance, rejecting the null hypothesis.

Study Approval

This study was approved by the Human Research Ethics Committee of the University of Cape Town (HREC 761/2021)

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 us with 160 tumours for analysis. Amongst these cases, 97.5% were found in females, while the remaining 2.5% occurred in 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. Among this group, 9.4% received docetaxel as an adjunct to their chemotherapy.

Response to chemotherapy

A comprehensive evaluation of pathological response was conducted among the patients subjected to neoadjuvant chemotherapy (NACT). The response outcomes were categorised as follows: Complete Response (CR) was observed in 21% of cases, Partial Response (PR) in 31%, No Response (NR) in 31%, and Progressive Disease (PD) in 17%. Collectively, responders comprised 52% of the cohort, while the remaining 48% were non-responders. (See table 2)

Table 2: Clinical response

Clinical Response	Frequency	Percent
Complete Response	34	21
Partial Response	49	31
No Response	50	31
Progressive Disease	27	17
Total	160	100

The median tumour size on imaging, before neoadjuvant chemotherapy was 31.5 mm (IQR 23-49). The median tumour size on the pathology specimen, post neoadjuvant chemotherapy, was 25 mm (IQR 2-40).

Subtype-specific Responses

Subtypes of the tumours exhibited distinctive response rates. Triple negative tumours exhibited the highest pCR rate at 31.9%, followed by HER2+/ER+ tumours at 29.4%. Conversely, ER-/HER2+ tumours exhibited a modest response rate of 6.7%, and ER+ve/HER2- tumours demonstrated the lowest response rate at 2%. On further statistical analysis, it was found that triple negative and ER+ve/Her 2 -ve had a statistically significant response ($p<0.05$). However, triple negative favours responders to chemotherapy while ER+ve /HER2-ve subtype favours non responders. (See table 3)

Table 3: Response to neoadjuvant chemotherapy and association with different variables is depicted

Characteristic	N	Overall, N = 160	CR, N = 34	PR, N = 49	SD, N = 50	PD, N = 27	p-value
Age category	160						*0.294
<= 50		79 (49%)	20 (25.3%)	21 (26.6%)	26 (32.9%)	12 (15.1%)	
> 50		81 (51%)	14 (17.2%)	28 (34.6%)	24 (29.1%)	15 (18.5%)	
ER	160						*0,72
Positive		76 (48%)	11 (14.5%)	21 (27.6%)	30 (39.5%)	14 (18.4%)	
Negative		84 (52%)	23 (27.4%)	28 (33.3%)	20 (23.8%)	13 (15.5%)	
PgR	160						*0.096
Positive		4 (2.5%)	1 (25%)	2 (50%)	1 (25%)	0 (0%)	
Negative		78 (49%)	22 (28.2%)	23 (29.5%)	19 (24.4%)	14 (17.9%)	
Not recorded		78 (49%)	11 (14.1%)	24 (30.8%)	30 (38.5%)	13 (16.7%)	
Her2	159						*0,805
Positive		49 (30.8%)	11 (22.4%)	18 (36.7%)	16 (32.7%)	4 (8.2%)	
Negative		111 (68.2%)	23 (20.7%)	31 (27.9%)	34 (30.6%)	23 (20.7%)	
Grade	160						**0.8607
1		15 (9.4%)	0 (0%)	7 (46.7%)	7 (46.7%)	1 (6.7%)	
2		60 (38%)	1 (1.7%)	24 (40%)	22 (36.7%)	13 (21.7%)	
3		50 (31%)	1 (2.0%)	15 (30%)	21 (42%)	13 (26%)	
Type of tumour	160						**0.8206
IDC		151 (94%)	33 (21.9%)	48 (31.8%)	49 (32.5%)	21 (13.9%)	
ILC		6 (3.8%)	1 (16.7%)	1 (16.7%)	0 (0%)	4 (66.7%)	
Mixed		1 (0.6%)	0 (0%)	0 (0%)	1 (100%)	0 (0%)	
Other		2 (1.3%)	0 (0%)	0 (0%)	0 (0%)	2 (100%)	
ER pos / HER 2 neg	160						*0.0005
Yes		42 (26.3%)	1 (2.9%)	10 (23.8%)	20 (47.6%)	11 (26.2%)	
No		118 (73.8%)	33 (28%)	39 (33.1%)	30 (25.4%)	16 (13.5%)	
ER pos / HER 2 pos	160						*0.248
Yes		34 (21.3%)	10 (29.4%)	11 (32.4%)	10 (29.4%)	3 (8.8%)	
No		126 (78.7%)	24 (19%)	38 (30.2%)	40 (31.7%)	24(19%)	
ER neg / Her 2 pos	160						*0.147
Yes		15 (9.4%)	1 (6.7%)	7 (46.7%)	6 (40%)	1 (6.7%)	
No		145 (90.6%)	33 (22.8%)	42 (29%)	44 (30.3%)	26(17.9%)	
Triple neg	160						*0.0419
Yes		69 (42.5%)	22 (31.9%)	21 (30.4%)	14 (20.3%)	12 (17.4%)	
No		91 (57.5%)	12 (13.2%)	28 (30.8%)	36 (39.6%)	15 (16.5%)	
Interval days between	160						*0.244
< 30 days		20 (12%)	7 (21%)	7 (14%)	5 (10%)	1 (3.7%)	
31 - 60 days		85 (53%)	19 (56%)	28 (57%)	24 (48%)	14 (52%)	
61 - 90 days		40 (25%)	5 (15%)	12 (24%)	15 (30%)	8 (30%)	
> 90 days		15 (9.4%)	3 (8.8%)	2 (4.1%)	6 (12%)	4 (15%)	
Interval days between Surgery and last dose of chemo	160						*0.671
< 30 days		20 (12%)	6 (18%)	4 (8.2%)	8 (16%)	2 (7.4%)	
31 - 60 days		98 (61%)	21 (62%)	28 (57%)	29 (58%)	20 (74%)	

61 - 90 days		34 (21%)	6 (18%)	13 (27%)	12 (24%)	3 (11%)	
> 90 days		8 (5.0%)	1 (2.9%)	4 (8.2%)	1 (2.0%)	2 (7.4%)	
n (%)							
*Pearson's Chi-squared test; **Fisher's exact test							

Waiting Time and Response

The interval between diagnosis and initiation of NACT, as well as the period from the last dose of NACT to surgical intervention, exhibited no statistically significant impact on response rates. Waiting times varied between 30 to 90 days, with the majority falling within the 30–60-day range.

The waiting time from diagnosis of breast cancer 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. (See table 3)

Tumour Size and Response

Significant correlations emerged between the initial tumour stage 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 stages. (see table 4)

Table 4: Stage migration before and after chemotherapy

		Post Chemotherapy Tumor Size					Total
		T0	**T1**	**T2**	**T3**	**T4**	
Pre-Chemotherapy Tumour Stage	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

Nodal Stage and Response

The relationship between the nodal stage and the response rate was explored. Of the patients evaluated, 52.9% who achieved pCR exhibited nodal regression. Of the patients who were initially node positive, 42.4 % converted to nodal negative post NACT.

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., with a smaller group of 52 patients, reported a complete pathological response of 9.6% and an overall response rate of 84.6%[11]. Taucher S et al. demonstrated a pathological complete response rate of 5.9% and an overall response rate of 56.2%[12].

Study	**Size of study**	**Complete pathological response**	**Overall response**
Sude NS (2022) [13]	n=52	9.6%	84.6%
Taucher S (2008) [1]	n=203	5.9%	56.2%
Nietz S (2020)[8]	n=715	14.5%	
Cortazar P (2014)[13]	n=11955	18%	
This study	n=160	21%	52%

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 the 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 ($p=0.248$). Our study findings are similar to a study by Qian et al. in terms of PCR in ER+ve/HER2+ve patients[14]. They found a pCR rate in this group of 28% Our pCR in the triple negative group was also similar in a large study by Cortazar et al[13]. They 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.

Study	Hormone receptor	Size	pCR
Qian et al (2022) [14]	Triple negative	40	11(26.2%)
	(ER/HER2)+ve	44	12(28.6%)
	ER+ve	23	0
Cortazar P (2014) [13]	Triple negative	1157	33.6%
	(ER/HER2)+ve	701	18.3
	ER+ve	2616	9.6%
	HER2+ve/ER-ve	471	30.2%

The added effect of Trastuzumab on pCR is not disputed. Cortazar et al. 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. and Schettini et al. on HER2+ve tumours demonstrated that targeted therapy to HER2 receptors significantly improved the pCR, especially in HER2-enriched (ER-ve/HER2+ve) tumours[15][16]. The Noah trial indicated that adding Trastuzumab nearly doubled the pCR from 19% to 38% and improved disease-free survival[17]. Untch et al. showed a response rate of 20% when Trastuzumab was not used and 39% when Trastuzumab was used[18]. Similarly, Budzar et al. showed a complete pathological response rate of 25% without trastuzumab use and 66.7% when Trastuzumab was used[19].

This study showed a pCR in patients ER-ve/HER2+ve in only 1/15 (6%), which is much lower than what is expected. Cortazar et al. 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 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, in fact, 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 31mm (IQR 11-100). Similarly, our study shows timing of chemotherapy had no impact

on tumour size, thereby implying that all responses were most likely as a result of tumour biology. Introducing Trastuzumab into the treatment regimen for our patients could potentially have improved our response rates.

Only one patient (2.9%) in the ER+ve/HER2-ve group achieved a pCR. Livingston-Rosanoff et al. had a response rate of 9% in this subgroup, while Cortazar et al. had a response rate of 7.5% in their meta-analysis[13,20]. 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 the time of our study, the hospital did not perform Ki-67 testing, so we were unable to explore this specific subtype in our analysis. Several studies have highlighted that Ki-67 plays a significant role in predicting treatment response[21–23].

This study found no association between histologic grade and response to NACT. A meta-analysis of chemotherapy trials in Germany, by Von Minckwitz et al, showed that histological grading was associated with a pathological response[24]. Our conflicting result may be attributed to a lower sample size.

In this study, we made noteworthy observations regarding the tumour size and response rates in patients. 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 Dieras et al. showed an incidence of 25% in their study[12,25]. 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 (downstaging). 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 Linvingston-Rosanoff et al., 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[20]. In support of our observations, Goorts et al. and Ben Qian et al. have also demonstrated that tumour staging size has a significant impact on response rates[14,26]. 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 neoadjuvant chemotherapy.

Finally, we observed a 42% response rate to neoadjuvant chemotherapy in relation to axillary nodal status. It is crucial to highlight that our evaluation of the axilla included both clinical examination and ultrasound. However, we did not conduct routine biopsies of nodes considered pathological, which could potentially lead to under or overestimation of node-positive patients before neoadjuvant chemotherapy. Nevertheless, our study findings are supported by a review conducted by Edge et al., who identified seven studies showing pCR rates limited only to axillary nodal status, ranging from 38% to 49%[27]. These outcomes align with the results we obtained in this study.

Our study faced significant limitations that could impact its findings. A lack of data regarding Ki-67 and progesterone receptor status on our histological specimens hindered our ability to comprehensively compare the efficacy of existing treatment regimens on different tumour biology. Having access to this crucial information would have strengthened our study's conclusions. Another limitation was related to the measurement of tumour size, which was assessed using a combination of radiology and pathology methods. This approach introduced potential bias into the study since different modalities were employed to monitor the treatment response from pre-treatment to post-treatment stages. Ideally, if we had the resources, we could have measured the response using both radiology and pathology and assessed the discrepancy. We classified equivocal HER2-neu (2+) as negative, because the majority of these (60%) would be Her2-ve on FISH testing[28]. 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 and allow for more accurate and reliable comparisons across treatment regimens.

Conclusion

This retrospective study, spanning two years, marks a significant milestone as the first of its kind in South Africa, shedding light on patients who underwent neoadjuvant chemotherapy at a single tertiary centre. By focusing on a middle-income country with limited access to Trastuzumab, this study contributes to the literature concerning the response to NACT in these patients. The results of this study reveal a noteworthy finding: triple negative 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 disease-free survival. Incorporating such targeted therapies as the standard of care in South Africa can enhance treatment outcomes and ultimately benefit patients with HER2+ve cancers.

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03 December 2021

HREC REF: 761/2021

Dr F Malherbe
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Dear Dr Malherbe

PROJECT TITLE: PATHOLOGICAL RESPONSE TO NEOADJUVANT CHEMOTHERAPY FOR BREAST CANCER AT A SINGLE TERTIARY BREAST CENTER with NO ACCESS TO TRASTUZUMAB·MMED CANDIDATE-DR ARVIN KHAMAJEET

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee (HREC) for review.

It Is a pleasure to Inform you that the HREC has **formally approved** the above-mentioned study.

This approval Is subject to strict adherence to the HREC recommendation■ regarding research Involvlng human participants during COVID -19, dated 17 March 2020; 06 July 2020 & 01 July 2021.

Approval la granted for one year until the 30 December 2022.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form If the study Is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethlcs/forms)

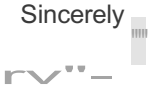
The HREC acknowledge that* the *student: Dr Arvin Khamajeet will also* be *Involved in this study.

Please quote the HREC REF 761/2021 In all your correspondence.

Please note that the ongoing ethical conduct of the study remains the responsibility of the prlnclpal investigator.

Please note that for all studies approved by the HREC, the principal investigator must obtain appropriate Institutional approval, where necessary, before the research may occur.

Yours Sincerely



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CHAIRPERSON. FACULTY OF HEALTH SCIENCES HUMAN RESEARCH ETHICS COMMITTEE

Federal Wide Assurance Number: FWA00001637.
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This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug In patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), Internatlonal Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use: Good Clinical Practice (ICH GCP), South African Good Clinical Practice Guidelines (DoH 2020), based on the Association of the British Pharmaceutical Industry Guldellnes (ABPI), and Declaration of Helsinki (2013) guidelines. The Human Research Ethics Committee granting this approval is in compliance with the ICH Harmonised Tripartite Guidelines E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and FDA Code Federal Regulation Part SO, 56 and 312.

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