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Pathologic response after primary chemotherapy for breast cancer : outcome from two South African breast centres

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PATHOLOGIC RESPONSE AFTER PRIMARY CHEMOTHERAPY FOR BREAST CANCER : OUTCOME FROM TWO SOUTH AFRICAN BREAST CENTRES

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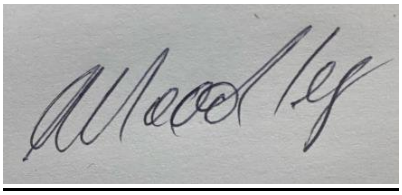


A Research Report submitted to the Faculty of Health Sciences, University of the Witwatersrand, in fulfilment of the requirement for the degree Master of Medicine

Johannesburg 2021

Declaration

I, Treven Moodley, declare that this Research Report is my own, unaided work. It is being submitted for the Degree of Master of Medicine at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at any other University.



Treven Moodley

21 day of **November** 2021

Dedication

I wish to dedicate this work to my loving wife Louise Moodley and our first child Treyen Moodley. Also a loving thought to my parents, Loganathan and Pushpakanthi Moodley for always being there to support me and encouraging me to pursue my dreams.

I also wish to thank my supervisors being Sarah Nietz, Herbert Cubasch and Maureen Joffe. Thank you for your time, patience and guideance and for being there every step of the way.

Abstract

Background: Neoadjuvant chemotherapy (NACT) has evolved to become an integral component in the management of both early and locally advanced breast cancer. Histologic response classification systems make use of pathologic complete response (pCR) which is also a surrogate endpoint for estimation of long term clinical outcome such as disease free survival and overall survival. This study aimed to evaluate pCR rates and the use of histopathological reporting systems among breast cancer patients receiving NACT in two Johannesburg breast units.

Methods : This is a retrospective review of prospectively collected data from the South African Breast Cancer and HIV Outcomes (SABCHO) study. Patients were selected from the respective databases of two academic hospitals based in Johannesburg. All histopathological specimens were assessed by the National Health Laboratory Service (NHLS).

Results : A total of 399 patients were enrolled for NACT but only 321 proceeded to surgery. 40 patients (12.5%) had a pCR with tumour grade ($P = 0.005$), receptor status ($P = 0.004$) and clinical response being predictive values of a pCR ($P = 0.038$). 61 specimens were reported using the Sataloff method, 15 specimens were reported using the Miller-Payne method and the remaining majority had no documented classification system.

Conclusion: Our pCR rate of 12.5% is much lower than reported in other studies. Triple negative breast cancer achieved the highest pCR rates. Histopathological reporting post chemotherapy needs to improve and there should be uniformity in reporting.The Sataloff method is favoured as it easier to apply and takes into consideration tissue response both in the breast and lymph nodes.

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Nomenclature

American Joint Committee on Cancer - AJCC

Breast cancer – BC

Breast conserving surgery - BCS

Chris Hani Baragwanath Academic Hospital - CHBAH

Charlotte Maxeke Johannesburg Academic Hospital - CMJAH

Ductal carcinoma in situ – DCIS

Oestrogen receptor - ER

Food and Drug Administration - FDA

Human epidermal growth factor receptor-2 – HER2

Hormone-receptor positive – HR+

Hormone-receptor negative – HR

Immunohistochemistry – IHC

Neoadjuvant chemotherapy - NACT

National Health Laboratory Services - NHLS

National Surgical Adjuvant Breast and Bowel Project - NSABP

Pathologic complete response - pCR

Pathologic no response – pNR

Pathologic partial response - pPR

Progesterone receptor – PR

Pathologic Response after Primary Chemotherapy for Breast Cancer: Outcomes from Two South African Breast Centres

1. Introduction

Breast cancer treatment involves three core modalities: surgery, systemic therapy, and radiation therapy.[1] Traditionally, systemic therapy was given to breast cancer patients once surgery was completed. Neoadjuvant chemotherapy (NACT) was initially reserved for those with non-resectable locally advanced breast cancer (LABC).[2] In the past decade, the systemic therapy approach to those presenting with early breast cancer has undergone a dramatic change with neoadjuvant chemotherapy now being a preferred option for selected patients.[3] Although studies have not shown any improvement in survival when compared to adjuvant chemotherapy, clinical trials have shown the following potential advantages of neoadjuvant chemotherapy.[4-5]

1. Downstaging of the tumour and involved lymph nodes thus creating opportunities for less extensive surgery.
2. Monitoring of tumour response with the opportunity to change treatment regimens.
3. Tumour response is a short-term endpoint for clinical trials and NACT can be used as an early surrogate endpoint.

Pathological complete response (pCR) after NACT is commonly used as a surrogate endpoint and is a powerful prognostic factor for disease-free survival and overall survival.[6] NACT causes various morphological changes with the most desirable outcome being a pCR with complete disappearance of invasive tumour in the breast and lymph nodes. pCR rates differ based on the immunohistochemical subtype of

breast cancer and the therapeutic regimen given. Other possible outcomes of NACT include partial tumour regression, stable disease or progressive tumour growth during treatment.[7]

Clinical examination and routine imaging provide gross indicators of response after NACT but a histological examination of the breast specimen is the gold standard to assess the breast and lymph nodes for residual tumour.[5] Currently, there are various histopathological classification systems available for the pathologic response to NACT and include the Chevallier method, NSABP-18 (National Surgical Adjuvant Breast and Bowel Project), Residual Cancer Burden system (RCB), Miller-Payne system and Sataloff method.[8-9] In general, all systems distinguish a category of pathologic complete response (pCR) and a category of partial or no response.[5] Classification systems that incorporate routine staging and grading parameters (e.g. tumour size, lymph node involvement, tumour grade) are easier to apply than those that require dedicated measurements to obtain the necessary information in the grossing area or at the microscope (e.g. celluraity estimation).[8] There is no consensus on a standardised histopathology reporting system in South Africa to date.

In our units, NACT is generally given to patients with locally advanced breast cancer and early breast cancer receive primary surgery regardless of immunohistochemical subtype.[10] Response to NACT has not been evaluated in South Africa and very scarce data is available from Sub-Saharan institutions.[11] We aimed to evaluate NACT response and the use of histopathological classification systems in two Johannesburg units.

2. Methods

This is a retrospective review of prospectively collected data from the South African Breast Cancer and HIV Outcomes (SABCHO) study.[12] We included patients who were enrolled by the breast units at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) and Chris Hani Baragwanath Academic Hospital (CHBAH) between July 2015 and September 2017. Only patients who were referred for NACT were selected for analysis, those patients who underwent primary surgery or palliative chemotherapy for metastatic disease were excluded. Chemotherapy is provided by a single institution in the greater Johannesburg area at CMJAH.

Histopathological specimens were evaluated by the National Health Laboratory Service (NHLS) laboratories of the respective hospitals. We used immunohistochemistry as surrogates for intrinsic subtype allocation with a Ki67 cut-off of 15% to distinguish between luminal subtypes. Luminal A subtypes have a Ki-67 value <15% and are HER2 receptor negative whereas Luminal B tumours have a Ki-67 index of 15 or above and/ or are HER2 positivite.[13] Pathological response outcomes were sub-grouped into those achieving no pathological response (pNR), pathological partial response (pPR), residual DCIS in the breast but no invasive tumour and negative lymph nodes (pCR with DCIS) and those with no residual invasive tumour or DCIS in breast and lymph nodes (pCR). Only those patients who had completed >70% of their NACT were included in the analysis.

Tumour size was approximated by initial clinical TNM entry and grouped in less than 5cm (T1 and T2) and larger than 5cm in size (T3 and T4).

Data on ethnicity was included to account for potential differences in population characteristics affecting tumour biology and treatment response. Ethnicity was self-reported by patients during their initial SABCHO enrolment.

Frequency and percentages were reported for categorical variables while summary statistics were reported for continuous variables. The pCR of each immunohistochemical breast cancer subtype was compared using a Pearson's Chi-Squared test or Fisher's exact test where appropriate. The association between ethnicity and response was evaluated using Pearson's Chi-Squared test. Statistical tests were interpreted as two-sided and P=< 0.05 was considered significant. Data was analysed with Stata version 14.[14]

This study was approved by the Human Research Ethics Committee (Medical) of the University of the Witwatersrand (M150351).

3. Results

This study comprised 399 patients with 226 patients from CHBAH and the remaining 173 from CMJAH. 390 (97.7%) patients completed >70% of their NACT regimen whilst nine (2.3%) patients received <70% of their NACT regimen. Of these nine patients, five demised whilst on treatment and the other four patients had their therapy terminated due to serious adverse events (two had bone marrow failure and two developed kidney failure).

321 (82.3%) patients underwent surgery (either breast conserving or mastectomy) whilst 69 (17.7%) patients were not operated on (figure 1). From the operative group, histopathology results revealed that 40 (12.5%) patients had a pCR post NACT

(inclusive of six patients that had pCR with residual DCIS), 276 (86%) had remnant disease (pNR or pPR) and the remaining five (1.5%) patients histopathology results were untraceable and documented in this study as missing. The missing histopathology reports were the consequence of strike action during the study period by the NHLS staff.

From the non-operative group, five (7.3%) patients refused surgery whilst eleven (15.9%) were lost to follow-up. A further five (7.3%) patients had no surgery because of medical conditions (three patients had pulmonary embolus and two had myocardial infarctions). Ten (14.5%) patients had no clinical response to NACT and their tumours were noted to be irresectable whilst the remaining 38 (55%) patients were noted to have disease progression during NACT (19 patients had tumour enlargement clinically and the remaining 19 patients developed metastases). The outcomes of patients are summarized in figure 1.

Demographics and clinicopathological features of the cohort are shown in table 1. The majority of patients were black (88.7%). Most presented with locally advanced stage 3 disease (89%), only 11% were stage 2 and none were stage 1. Most patients had hormone receptor-positive tumours of the luminal B group (Luminal B / HER2 – (39.8%) and luminal B / HER2 + (22.1%), hormone receptor-negative tumours accounted for 25.3%.

Of the 321 patients that underwent surgery, 316 specimens were available for pathological reporting. Fifteen (4.7%) specimens were reported using the Miller-Payne method whilst 61 (19.3%) patients had their reports categorized using the Sataloff

method. The remaining 240 (76%) patients had no pCR classification system on their histopathology reports.

Outcomes of pathological response are shown in table 2.

Ethnicity, age and clinical stage showed no significant differences in pCR rates. 34 (12.3%) black patients obtained a pCR and both the white (15.8%) and the coloured race (18.8%) groups had three patients each that attained a pCR result. 166 patients were below the age of 50 whilst 150 were ≥ 50 years old. Both age categories had 20 patients each that had obtained a pCR. 34 (12.3%) patients with clinical stage 3 disease and 6 (15%) patients with stage 2 disease obtained a pCR.

All twelve grade 1 tumours failed to demonstrate a pCR. Those with grade 2 tumours had a pCR rate of 6.6% whereas those with grade 3 tumours attained an 18.1% pCR rate (*P*= 0.005).

Receptor status (*P-value* 0.004) was also shown to be a positive predictor for pCR. 235 patients were noted to have Luminal tumours with 21 patients (8.9%) within this group having achieved a pCR. The highest pCR rate achieved in the luminal group was the luminal B (HER2+) subset with a pCR rate of 11.6%.

The non-luminal group consisted of a total of 19 (24.1%) patients that achieved a pCR. The highest pCR responders were those with triple-negative breast cancer with 15 (26.30%) patients obtaining a pCR followed by HER2 enriched tumours with four (18.20%) patients obtaining a pCR. Thus, the non-luminal group obtained an overall pCR rate of 24.05% when compared to the Luminal group which achieved a pCR rate of 8.94%. Two pathology reports failed to document the specimen's receptor status and these were classified as unknown.

A total of 79 patients were diagnosed Human Immunodeficiency Virus (HIV) positive whilst for five patients the HIV status was not known. The HIV negative group attained a higher pCR rate of 14.2% compared to the HIV positive group of 8.9%.

Chemotherapy was either anthracycline-based, taxane or a combination of the two. The majority of patients received combination therapy and this resulted in 35 (13.5%) patients obtaining a pCR. The anthracycline based group had 4 (7.8%) patients achieving a pCR whilst the taxane based regimen obtained a pCR rate of 16.7% but only consisted of a single patient.

Clinical response was a significant predictor in this study with a *P-value* of 0.038. Of the 62 patients that were noted to have had a complete clinical response, 14 (22.6%) patients achieved a pCR. 248 patients were recorded as partial/stable disease of which 26 (10.5%) had a pCR. Six patients had clinical progression of disease.

Figure 3.1: Summary of NACT outcomes

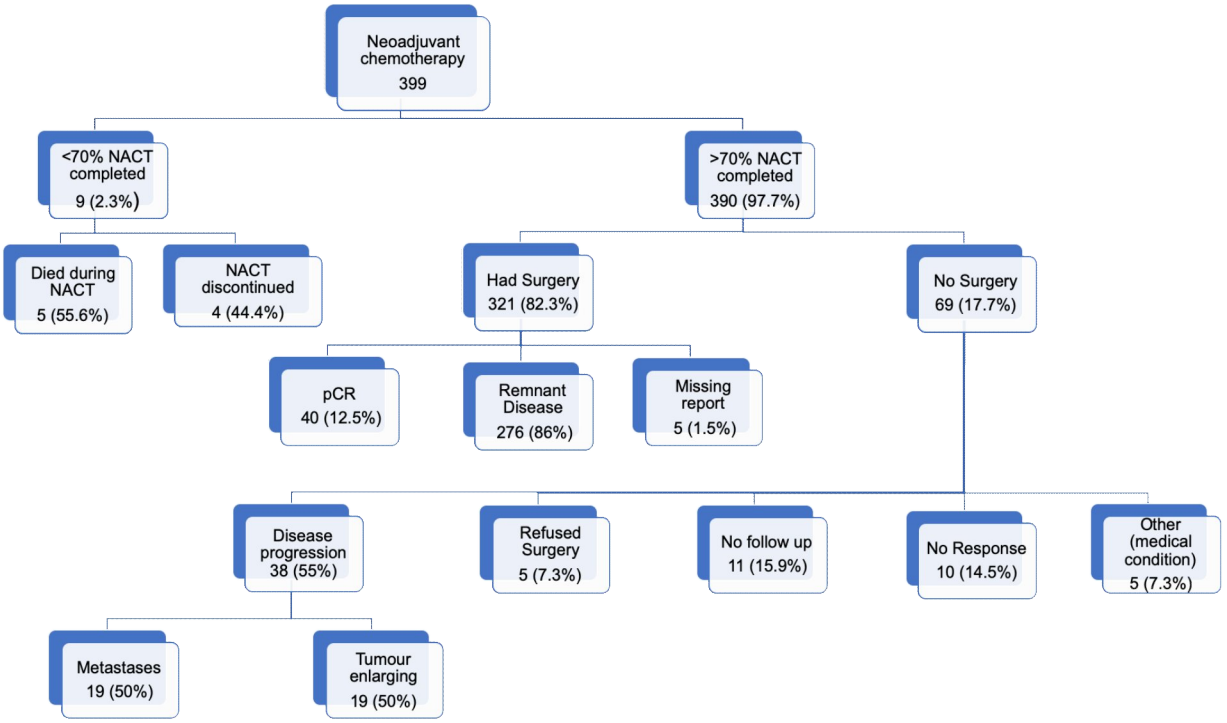


Table 3.1 : Overview of cohort

Category	Number of patients	Percentage
Hospital		
CHBAH	226	56.6%
CMJAH	173	43.4%
Total	399	100%
Ethnicity		
Black	354	88.7%
White	20	5%
Indian	4	1%
Coloured	21	5.3%
Total	399	100%
Clinical Staging		
Stage 2	44	11%
Stage 3	355	89%
Total	399	100%
Receptor Status		
Luminal A	49	12.3%
Luminal B / HER2 -	159	39.8%
Luminal B / HER2 +	88	22.1%
HER2 Enriched	27	6.8%
Triple Negative	74	18.5%
Unknown	2	0.5%
Total	399	100%
Histopathology System		
Miller Payne	15	4.7%
Sataloff	61	19.3%
Unknown	240	76%
Total	316	100%

Table 3.2: Pathological Response Outcomes Post Neoadjuvant Chemotherapy

Category	Remnant Disease (pPR)		Complete Response (pCR)		Total		P-value
	N = 276	Percentage	N = 40	Percentage	N = 316	Percentage	
Ethnicity							**0.724***
Black	243	87.7%	34	12.3%	277	100%	
Indian	4	100%	0	0%	4	100%	
White	16	84.2%	3	15.8%	19	100%	
Coloured	13	81.3%	3	18.8%	16	100%	
Total	276	87.3%	40	12.7%	316	100%	
Age							**0.732**
<50	146	88%	20	12%	166	100%	
>=50	130	86,7%	20	13,3%	150	100%	
Total	276	87,3%	40	12,7%	316	100%	
Clinical Staging							**0.634**
Stage 2	34	85%	6	15%	40	100%	
Stage 3	242	87,70%	34	12,30%	276	100%	
Total	276	87,30%	40	12,70%	316	100%	
Tumour Staging							**0.445***
T1	12	92,3%	1	7,7%	13	100%	
T2	53	81,5%	12	18,5%	65	100%	
T3	90	88,2%	12	11,8%	102	100%	
T4	121	89%	15	11%	136	100%	
Total	276	87,3%	40	12,7%	316	100%	
Tumour Grade							**0.005***
1	12	100%	0	0%	12	100%	
2	127	93,4%	9	6,6%	136	100%	
3	131	81,9%	29	18,1%	160	100%	
Total	270	87,7%	38	12,3%	308	100%	
Unknown	6		2		8		
Receptor status							**0.004***
Luminal A	41	97,6%	1	2,4%	42	100%	
Luminal B/HER2-	112	90,3%	12	9,7%	124	100%	
Luminal B/HER2+	61	88,4%	8	11,6%	69	100%	
HER2 enriched	18	81,8%	4	18,2%	22	100%	
Triple negative	42	73,7%	15	26,3%	57	100%	
Total	274	87.3%	40	12.7%	316	100%	
Unknown	2		0		2	100%	
Receptor status							**<0.001**
Luminal	214	91,1%	21	8,9%	235	100%	
Non-luminal	60	75,9%	19	24,1%	79	100%	
Total	274	87,3%	40	12,7%	314	100%	
Unknown	2		0		2		
HIV status							**0,321**
Negative	199	85,8%	33	14,2%	232	100%	
Positive	72	91,1%	7	8,9%	79	100%	
Total	271	87,1%	40	12,9%	311	100%	
Unknown	5		0		5		
Chemotherapy regimen							**0.515***
Anthracycline based	47	92,2%	4	7,8%	51	100%	
Taxane based	5	83,3%	1	16,7%	6	100%	
Anthracycline and taxane	224	86,5%	35	13,5%	259	100%	
Total	276	87,3%	40	12,7%	316	100%	
Clinical response							**0.038***
Complete	48	77,4%	14	22,6%	62	100%	
Partial/stable	222	89,5%	26	10,5%	248	100%	
Progression	6	100,0%	0	0,0%	6	100%	
Total	276	87,3%	40	12,7%	316	100%	

***Fishers Exact test**

4. Discussion

Our study demonstrated an overall pCR rate of 12.5%. This result is lower than reported in the NSABP B18 and B27 trials which attained pCR rates of 13% and 26% respectively and a pCR rate of 19% was achieved in an American study by Haque *et al.* of nearly 14 000 participants.[15,16]

There are different potential reasons to explain this lower pCR rate. A lower pCR rate could be an indication of undertreatment. This can include situations where women were not able to complete their chemotherapy regimen, had dosage reductions or treatment delays. Unfortunately, we did not have dose-intensity data available. Furthermore, the majority of our cases were locally advanced with very large tumours which may have reduced the pCR rate in this study. South Africa is an upper middle-income country with great socioeconomic inequality. Many patients have very limited education and language barriers may exist. These factors may lead to patients not understanding their treatment. In addition, some may not have financial support to attend hospital for treatment what may contribute to under-treatment.

4.1 Predictive Parameters

Non-luminal molecular subtype and higher histological grade were positive predictors of a pCR in our study. Those with a TNBC subtype ($P = 0.004$) or a histological grade 3 tumour ($P = 0.005$) have a higher chance of obtaining a pCR result. Although TNBC is known to be an aggressive tumour with poor biological characteristics such as higher pathological grade, decreased survival and greater frequency of tumour invasion; their increased response to NACT is based on their higher mitotic rate, greater mutational

spectrum and an increased amount of tumour infiltrating lymphocytes.[19-21] Patients who have achieved a pCR result have a better survival irrespective of molecular subtype whereas those with TNBC and residual disease post NACT have a shorter disease free survival time and higher recurrence rate when compared to patients with non-TNBC and residual tumour burden.[22] Thus the response to NACT can be related to the proliferative rate of the tumour subtype.

The most common receptor sub-group was luminal B and 74.2% of our study population had hormone receptor-positive disease. A study based in Kenya by Sayaed *et al.* found that approximately 60% had hormone receptor positive tumours.[23] A study by Jiagge *et al.* showed patients of West African ancestry had a higher incidence of TNBC compared to those of East African ancestry.[24] Our data indicate that there is no increased rate of TNBC in our population. Further work is required to collect population based data on breast cancer incidence, molecular subtype and mortality in different parts of Africa.

Clinical response was also found to correlate with pathological response. Although in some patients there may be clinical signs of palpable disease it must be understood that a key feature of tumour response to NACT is a loss of cellularity even though there may not be a marked reduction in the size of the tumour. Loss of cellularity correlates with clinical response and prognosis.[5] In those patients obtaining a pCR but demonstrating only a partial/stable clinical response, a residual palpable mass is likely due to fibrosis.[8] Clinical response remains valuable in the early detection of progression of disease in patients who are undergoing NACT. In such cases, treatment can be stopped or modified.

4.2 Non-Predictive Factors

Our study showed that pCR rates were not linked to ethnicity and this result is similar to that found in other studies. An important consideration relating to race is that it could be a predictor of worse disease free survival and overall survival.[25] A study based at M. D. Anderson Cancer Center with a cohort of 2140 patients discovered a poorer survival amongst black patients and although the causal factors for this observation are poorly understood, they have suggested biological differences.[26] However, pCR rates have not differed in studies which take tumour and treatment heterogeneity in to account.[27,28]

Age was another non-associated factor ($P = 0.732$) but Chou *et al.* have demonstrated in their study that younger age (< 50 years) together with three molecular subtypes (Luminal B/HER2+, HER2 enriched and TNBC) were predictive factors for a pCR.[29] They noted that this was most likely due to younger women having more hormone receptor negative tumours which in turn are more susceptible to chemotherapy when compared to hormone receptor-positive tumours.

Tumour size and clinical staging are important for clinical decision making but both exhibited no benefit in predicting pCR rates in our study. Although the Neoadjuvant Breast Symphony Trial (NBRST) study revealed that tumour size was correlated inversely with the frequency of a pCR result, a multivariate logistic regression analyses of this study had shown that tumour subtype was still the most important factor in predicting a pCR.[30] Goorts *et al.* analyzed data from the nationwide cancer registry in the Netherlands and concluded that clinical tumour size is an independent predictor of

pCR.[31] Clinical staging was an independent and stronger predictor of pCR than hormone receptor subtype and histological grade. Smaller tumours (< 5cm) had greater pCR rates (up to 31%) than larger tumours (≥ 5cm) with pCR rates of 17%. In developing countries such as South Africa, breast cancer patients often present late and with more advanced disease. Many have lymph node-positive disease and advanced primaries at initial presentation. In our study, the majority of patients were stage 3 and numbers were too limited to offer comparison to early-stage breast cancers.

Approximately 70% of the world's HIV infected population live in sub-Saharan Africa.[10] With the introduction of anti-retroviral therapy (ART), life expectancy of HIV positive patients is increasing and many women are affected by HIV and breast cancer simultaneously. Our study found that approximately one in four patients were infected. HIV did not show any association with pCR due to decreased sample size in our study. However, a recent publication on the entire SABCHO cohort has clearly documented a decreased pCR response in HIV-infected compared to non-infected women, especially in the those with hormone receptor positive disease.[32]

Anthracycline and taxanes (in combination or alone) are commonly used chemotherapeutic agents for NACT at our institution and the choice of agents did not predict pCR. However, our study numbers are too small to explore differences and the majority of patients received a combination of both agents.

4.3 Histopathological Classification Systems

A standardized communication of histopathological response to the treating clinician is critical as it predicts long-term outcome. In our study, the majority of pathology reports did not refer to the actual histopathological system that was used to evaluate the breast specimens. In those that did, the Sataloff classification was most commonly used. The Sataloff method looks at response in both the breast and lymph nodes but does not cater for lymphovascular invasion.[5] It is an easy classification system to understand and apply.

Table 4.3.1 Sataloff Method[5] **Tumour**	
T-A	**Total or near total therapeutic effect (pCR)**
T-B	**> 50% therapeutic effect, but less than total or near total (pPR)**
T-C	**< 50% therapeutic effect, but effect evident (pPR)**
T-D	**No therapeutic effect (pNR)**
Nodes	
N-A	**Evidence of therapeutic effect, no metastatic disease**
N-B	**No nodal metastasis or therapeutic effect**
N-C	**Evidence of therapeutic effect, but nodal metastasis present**
N-D	**Viable metastatic disease, no therapeutic effect**

The Miller-Payne classification was used for reporting in only a minority of specimens. It is a 5 point scale that focuses on the reduction of tumour cellularity when compared to the initial specimen (before the induction of chemotherapy). In this classification system, histopathologists must use their discretion in order to estimate the the celluar tumour reduction if present.

Table 4.3.2 Histological grading system ('Miller and Payne system')[33]	
Grade 1	**No change or some alteration to individual malignant cells but no reduction in overall cellularity**
Grade 2	**A minor loss of tumour cells but overall cellularity still high; up to 30% loss**
Grade 3	**Between an estimated 30% and 90% reduction in tumour cells**
Grade 4	**A marked disappearance of tumour cells such that only small clusters or widely dispersed individual cells remain; more than 90% loss of tumour cells**
Grade 5	**No malignant cells identifiable in sections from the site of the tumour; only vascular fibroelastic stroma remains often containing macro- phages. However, ductal carcinoma in situ (DCIS) may be present**

Currently, there is no standard protocol of reporting within our facilities and South Africa. Ideally, there should be a general consensus.

A specific mention deserve the five specimens that were lost. Clearly, important information has gone missing resulting in potential over- or undertreatment of individual patients. Appropriate measures need to be in place to ensure that all surgical specimens reach the laboratory for timeous processing.

4.4 Limitations

The greatest limitation of this study was the limited sample size. Although we evaluated the data retrospectively, the collection was prospective and only minimal data were missing. No dose-intensity data were available to evaluate potential

treatment heterogeneity. The size of tumour had to be approximated based on clinical staging since no actual size measurements were available.

5. Conclusion

We found an overall pCR rate of 12.5% and that is lower than reported in similar studies from high-income countries. Predictive factors for pCR included tumour grade, clinical response and receptor subtype. TNBC was the most responsive subtype with the highest pCR rates.

The histopathological reporting of response to chemotherapy has gained importance and a standardized classification system would improve communication with the treating clinicians. The Sataloff method is easier to understand and apply and takes into consideration treatment response in breast tissue and lymph nodes and is also the most commonly used reporting system in our setting. The Miller Payne grading system only takes into consideration resonse to treatment in the breast tissue and relies on the estimation of the percentage of tumour seen on slides in order to categorize the response.Individual estimations may vary and the results produced may not be reliable. It has been noted Eradication of tumours from both breast and lymph nodes (ypT0 ypN0) had a stronger association with improved EFS and OS than did eradication of tumour from the breast alone and that the prognostic value is greatest in aggressive tumour subtypes.[34]

6. Conflict of Interest

The author confirms that there is no conflict of interest to declare.

7. Funding

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Appendix A – Ethical Clearance

R14/49 Dr Herbert Cubasch

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M150351

NAME: (Principal Investigator)	Dr Herbert Cubasch
DEPARTMENT:	Surgery Chris Hani Baragwanath Academic Hospital Charlotte Maxeke Johannesburg Academic Hospital
PROJECT TITLE:	Factors Influencing Outcomes of Breast Cancer Including HIV (NIH/NCI Grant Ref 1R01CA192627-01)
DATE CONSIDERED:	27/03/2015
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	
APPROVED BY:	Professor P Cleaton-Jones, Chairperson, HREC (Medical)
DATE OF APPROVAL:	06/05/2015

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Secretary in Room 10004, 10th floor, Senate House, University.

I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report.**

Principal Investigator Signature

Date 6.5.2015

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

Appendix B – Turnitin Report and Approval

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ORIGINALITY REPORT			
11% SIMILARITY INDEX	4% INTERNET SOURCES	10% PUBLICATIONS	1% STUDENT PAPERS

PRIMARY SOURCES

Sarah Nietz, Paul Ruff, Wenlong Carl Chen, Daniel S. O'Neil, Shane A. Norris. "Quality indicators for the diagnosis and surgical management of breast cancer in South Africa", The Breast, 2020 Publication	%
"30th Annual San Antonio Breast Cancer Symposium – December 13–16, 2007", Breast Cancer Research and Treatment, 2007 Publication	%
www.researchsquare.com Internet Source	
Sarah Nietz, Daniel S O'Neil, Oluwatosin Ayeni, Wenlong Carl Chen et al. "A comparison of complete pathologic response rates following neoadjuvant chemotherapy among South African breast cancer patients with and without concurrent HIV infection", Breast Cancer Research and Treatment, 2020 Publication	



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Sun, 24 Jan at 18:19

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Kind Regards
Emmanuel

Appendix C – Protocol

CANDIDATE SURNAME: MOODLEY | FIRST NAME: TREVEN | STUDENT NUMBER: 1878003

CURRENT

QUALIFICATIONS: MBChB

TEL: N/A CELL: 084 500 4899 E-MAIL: treven_moodley@yahoo.com

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DEGREE FOR WHICH PROTOCOL IS BEING SUBMITTED: M. Med (Surgery)

PART-TIME OR FULL-TIME: Full-time

FIRST REGISTERED FOR THIS DEGREE: TERM : 01 YEAR:01

2017

DEPARTMENT: GENERAL SURGERY

TITLE OF PROPOSED RESEARCH: Pathologic Response after Primary Chemotherapy for Breast

Cancer: Outcomes from Two South African Breast Centers

CANDIDATE'S SIGNATURE: DATE: 09/10//2017

SPERVISOR 1 (NAME& SURNAME): Dr. Sarah Nietz 80% Supervision

SUPERVISOR'S QUALIFICATIONS MD (Hamburg) MMed (Surg) FCS (SA)

SUPERVISOR'S DEPARTMENT: Department of Surgery, University of the Witwatersrand, Breast Unit CMJAH

SUPERVISOR'S ADDRESS / TEL / E-MAIL: 073 313 1366/ sarah.nietz@gmx.de

SUPERVISOR 2 (NAME& SURNAME): Dr. Herbert Cubasch

10% Supervision

SUPERVISOR'S QUALIFICATIONS: Ärztliche Prüfung (München), FCS(SA). Department of Surgery, University of the

Witwatersrand, Breast Unit CHBAH

SUPERVISOR'S ADDRESS / TEL / E-MAIL: hcubasch@gmail.com

SUPERVISOR 3 (NAME & SURNAME): Dr. Maureen Joffe
10% Supervision

SUPERVISOR'S QUALIFICATIONS: PhD

SUPERVISOR'S ADDRESS / TEL / E-MAIL: 0112749356/ mjoffe@witshealth.co.za

SYNOPSIS OF RESEARCH:

[Use reverse side of this page if

more space is required]

ETHICS PENDING:

Y ETHICS APPROVED:

N

(circle appropriate symbol)

IF Y SUPPLY

ETHICS

CLEARANCE No:

SIGNATURE OF SUPERVISOR/S: Herbert Cubasch

Sarah Nietz

Maureen Joffe

SIGNATURE PG OFFICE STAFF

……..

REGISTERED

YES….. NO….
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STAMP

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List of Abbreviations

American Joint Committee on Cancer - AJCC

Breast cancer – BC

Breast conserving surgery - BCS

Chris Hani Baragwanath Academic Hospital - CHBAH

Charlotte Maxeke Johannesburg Academic Hospital - CMJAH

Ductal carcinoma in situ - DCIS

European Medicines Agency - EMA

Oestrogen receptor - ER

Food and Drug Administration - FDA

Human epidermal growth factor receptor-2 – HER2

Hormone-receptor positive – HR+

Hormone-receptor negative – HR-

Immunohistochemistry - IHC

Low to middle income country - LMIC

Neoadjuvant chemotherapy - NACT

National Health Laboratory Services - NHLS

National Surgical Adjuvant Breast and Bowel Project - NSABP

Pathologic complete response - pCR

Pathologic no response - pNR

Pathologic partial response - pPR

Progesterone receptor - PR

Residual cancer burden - RCB

Surveillance, Epidemiology and End Results Program - SEER

Pathologic Response after Primary Chemotherapy for Breast Cancer: Outcomes from Two South African Breast Centers

Abstract

Neoadjuvant chemotherapy is increasingly used as the primary treatment modality for operable breast cancer. The highest rates for pathologic complete response have been reported in patients with triple-negative and HER-2 positive disease. This study aims to determine pathologic response rates, compare rates among population groups and breast cancer subtypes and evaluate the impact of tumour size. This will be the first study on pathologic response after neoadjuvant chemotherapy in South Africa.

Literature review

Breast cancer (BC) is the most common cancer among females worldwide. The incidence has significantly increased in low to middle income countries (LMIC) and an increased burden on health care systems is expected[12]. South Africa had an age-standardized BC incidence of 25.86 per 100 000 women in 2010 but rates varied by ethnicity[3].

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Higher proportions of hormone-receptor negative (HR-) tumours and triple-negative breast cancer have been reported in African populations[4]. However, the validity of pathology and immunohistochemistry (IHC) in many African countries is questionable possible resulting in overreporting of hormone-receptor negative breast cancers[5]. Recent studies suggest that the majority of breast cancers in sub-Saharan Africa are actually HR+, with the exception of some countries in the West African region[67]. Within the United States, HR- tumours appear to be more prevalent among African Americans compared to white Americans[8]. Data from the American Surveillance, Epidemiology and End Results Program (SEER) also suggested that patients were younger at diagnosis and presented with larger tumours[9].

Primary chemotherapy, most commonly referred to as neoadjuvant chemotherapy (NACT) in the literature, refers to the administration of chemotherapy before definite surgical excision of a carcinoma and has gained significant therapeutic application in the treatment of breast cancer. NACT was initially reserved for non-resectable locally advanced breast cancer (LABC) and inflammatory breast cancer but has been increasingly used for early-stage operable breast cancer[10]. Studies have not shown any improvement in survival compared to adjuvant chemotherapy[1112] but have shown several potential benefits including the downstaging of the primary to allow breast conserving surgery (BCS), in vivo assessment of therapeutic efficacy and downstaging of the axillary nodes with a reduced need for axillary lymph node dissection[12131415]. Furthermore, pathologic complete response (pCR) after NACT has been identified as a powerful prognostic factor for disease-free survival and overall survival and enables research to identify radiological, histological, and molecular predictors of response[161718]. The US Food and Drug Administration (FDA) and the

European Medicines Agency (EMA) acknowledge pCR as an acceptable endpoint in NACT trials and for drug approval[19].

NACT causes various morphological changes in tumours as well as lymph nodes, the most desirable outcome being a pCR with complete disappearance of invasive cancer. Other possible outcomes of NACT include partial tumor regression, stable disease or progressive tumor growth during treatment[20].

Clinical examination and routine imaging provide gross indicators of response after NACT but careful histological examination of the breast specimen is required to assess the breast and lymph nodes for residual tumor[21]. A tumor that shows a complete clinical response can still demonstrate residual carcinoma on microscopic examination and histopathology remains the gold standard in the assessment of response to NACT[22]. Currently there are various classification systems for the pathologic response to NACT and there is no standard definition of pCR. Variations among classifications of pCR are based on the inclusion or exclusion of lymph node status and residual ductal carcinoma in situ (DCIS)[21]. Classification systems include the AJCC (American Joint Committee on Cancer) "y" classification[23], Chevallier method[24], NSABP-B18[25](National Surgical Adjuvant Breast and Bowel Project), residual cancer burden (RCB) system[26], Miller-Payne system[27] and the Sataloff method[28] (Appendix 1). In general, all systems distinguish a category of pathologic complete response (pCR) and a category of partial or no response[21].

Von Minckwitz et al demonstrated that pCR in the most strict definition as no invasive and no in situ residuals in breast and nodes most accurately predicts clinical outcomes and recommended that residual DCIS in the breast or involved lymph nodes should

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not be considered as pCR[29]. Mazouni et al on the other hand, showed that residual DCIS did not alter patient outcome as long as both the breast and lymph nodes showed no residual invasive disease[30]. There is no standardized reporting system in South Africa but the Sataloff method and Miller-Payne system are the most commonly used.

A regimen with an anthracycline, cyclophosphamide and a taxane is a common regimen and offered to high-risk patients in our local oncology units in the neoadjuvant setting[19].

Systemic therapy was initially a "one size fits all approach" but has since been modified according to breast cancer subtype[19]. Breast cancer subtypes were initially defined by microarray gene expression but this is expensive to perform and hence not routinely used in clinical practice. The more practical IHC classification system uses oestrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor-2 (HER-2) and Ki-67 as a surrogate markers to identify tumor subtypes (see Table 1)[31].

The response to NACT is not uniform and is better in triple-negative and HER-2 positive breast cancers. Rouzier et al demonstrated pCR rates of 45% for triple- negative and HER-2 positive tumours, respectively, but only 6% for HR+ tumours[32]. The response among HR+ tumours has been further evaluated and patients with high grade tumours and negative PR are more likely to benefit from NACT[33]. Tumour size appears to have no impact on response to NACT[34].

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Table 1: Adapted from Goldhirsch *et al.*[31]

Intrinsic Subtype	Clinico-pathological Definition
Luminal A	**'Luminal A'** ER and/or PgR positive HER2 negative Ki-67 low (<14%)
Luminal B	**'Luminal B (HER2 negative)'** ER and/or PgR positive HER2 negative Ki-67 high **'Luminal B (HER2 positive)'** ER and/or PgR positive Any Ki-67 HER2 over-expressed or amplified
Erb-2 Over-expression	**'HER2 positive (non-luminal)'** HER2 over-expressed or amplified ER and PgR absent
'Basal Like'	**'Triple Negative (ductal)'** ER and PgR absent HER2 negative

Killelea et al. noted that women of African ancestry have significantly poorer pathologic response rates for both triple-negative and HER-2 positive tumours compared to

Caucasian and Hispanic women[9]. Another study showed no racial difference in pCR rates but outcome disparity only in HR+ patients[35].

The response to NACT in South Africa has not been studies yet and very scarce data come from sub-Saharan Africa[36–38]. The majority of our patients are black and many present with large tumours and at an advanced stage[39]. Breast units at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) and Chris Hani Baragwanath Academic Hospital (CHBAH) are part of the prospective South African Breast Cancer and HIV Outcomes (SABCHO) study in 2015[40]. A clinical database has since been used and offers the opportunity to study the response to NACT in our patients.

Study Objectives

Primary objectives:

- To evaluate the pathologic response to NACT
- To document the use of the histopathological classification systems for pathologic response

Secondary objectives:

- To compare response rates between intrinsic subtypes of breast cancer
- To compare response rates between population groups (self-assessed race)
- To evaluate the impact of tumour size on response

Methods

Study Design

Secondary analysis of prospective cohort study

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Study Sites

CMJAH and CHBAH breast units.

Study Population

Patients enrolled in the SABCHO study[40].

Sampling

Subjects will be recruited from the existing clinical databases of the respective breast units. Time period for review will be patients entered from 1st of July 2015 to 30th of September 2017 with an estimated sample size of 600 patients. To accommodate for patients enrolled at the end of the time period the prospective cut-off for evaluation of the surgical specimen will be 1st of June 2018.

Inclusion criteria:

- Histologically confirmed primary invasive breast cancer cases enrolled in the SABCHO study
- Patients who were referred for NACT

Exclusion Criteria:

- Patients who underwent primary surgery
- Patients referred for palliative chemotherapy
- DCIS
- Benign disease
- Age below 18 years
- Significant cognitive deficit

- Previous cancer diagnosis (other than non-melanoma skin cancer or in situ cervical cancer)
- Patients failing to complete neoadjuvant chemotherapy

Study groups

Patients will be grouped into patients referred for NACT but no surgery performed (disease progression on NACT, death or lost to follow-up) and NACT and surgery performed.

For the evaluation of pathologic response outcomes will be grouped into the following subgroups

- Pathologic no response (pNR)
- Pathologic partial response (pPR)
- Residual DCIS in the breast but no invasive tumour and negative lymph nodes (pCR with DCIS)
- No residual invasive tumour or DCIS in breast and lymph nodes (pCR)

For evaluation of the use of systems to categorize pathologic response all described methods will be included and their corresponding categorization into study subgroups is depicted in Appendix A.

For the groups of intrinsic breast cancer subtype the criteria in table 1 will be applied[31].

Race is self-assessed by the patient as per SABCHO protocol[40].

Tumour size is assessed clinically by examination and ultrasound on presentation and grouped into no larger than five cm and larger than five cm.

Measuring Tool

Patient records will be accessed via the clinical databases of the respective breast units. Histopathology is recorded on the clinical database for each patient but reports will be reassessed via the National Health Laboratory Services (NHLS) system and other laboratory services if required.

Data Collection

Two datasheets will be used. The first data sheet will contain patient name, folder number and study number. The second data sheet will be deidentified and contain extractable parameters, which are listed in Appendix A. Source data on the clinical databases will be cleaned and updated during data collection.

Sources of bias

Bias is expected to be minimal as the study is an audit on prospectively collected clinical data. Possible bias through missing or incomplete records will be minimized by thorough perusal of the data and all available records. A further source of bias may arise by enrolment into the study as patients may have benefited from improved clinical performance and follow-up compared to other SA women with breast cancer.

Data Analysis

Analysis will be carried out with Stata version 14 (StataCorp Limited, Texas, United States of America). Descriptive statistics will be carried out with response to NACT as the outcome variable. Frequency and percentages will be reported for categorical variables while summary statistics will be reported for continuous variables.

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Frequencies and percentages will be for classification systems used pathologic response.

The pCR of each intrinsic subtype will be compared using Pearson's Chi squared test or Fisher's exact test where appropriate. The association between race and response rate will be evaluated using Pearson's Chi squared test. Statistical tests will be two-sided, and $P < .05$ will be considered significant.

Benefits

There is no data on the response to NACT from South Africa. The study will provide valuable information on local response rates and histopathological reporting systems used. This will offer opportunity for review of clinical decision-making and could highlight areas requiring future research.

Ethics

Ethical clearance to proceed with this retrospective study will be obtained from the ethics committee of the University of the Witwatersrand. This is a secondary analysis on the SABCHO cohort for which ethical clearance was obtained from the ethics committee of the University of the Witwatersrand (clearance certificate number M150351).

13. Limitations

Immunohistochemistry and FISH testing may be a limiting factor in terms of pathology report availability. Another limitation is that patients may be given different chemotherapy regimens and this may affect the pathological response

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Budget

The cost of this MMED will be approximately R1000 due to the cost of printing and will be funded solely by the researcher

Time Table

	July 17	Aug	Sep	Oct	Nov	Dec	Jan 18	Feb	Mar	Apr	May	June
Literature review	x	x										
Preparing protocol		x	x									
Protocol assessment				x								
Ethics application				x								
Collecting data					x	x	x	x				
Data analysis									x			

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Writing up - thesis										x		
Writing up - paper										x	x	

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Appendix A

Criteria used in different systems for categorizing response to NACT and Study group categorization, adapted from Sahoo & Lester, 2009[21]

Described Systems	Criteria	Study Group Categorization
NSABP B-18[25]		
pCR	No recognizable invasive tumour cells present	pCR
pPR	The presence of scattered individual or small clusters of tumour cells in a desmoplastic or hyaline stroma	pPR
pNR	Tumours not exhibiting the changes listed above	pNR
Miller-Payne System[27]		
Grade 1	No change or some alteration to individual malignant cells, but no reduction in overall cellularity (pNR)	pNR
Grade 2	A minor loss of tumour cells, but overall cellularity still high; up to 30% loss (pPR)	pPR
Grade 3	Between an estimated 30% and 90% reduction in tumour cells(pPR)	pPR
Grade 4	A marked disappearance of tumour cells such that only small clusters or widely dispersed individual cells remain; > 90% loss of tumour cells (almost pCR)	pPR
Grade 5	No malignant cells identifiable in sections from the site of the tumour; only vascular fibro-elastic stroma remains, often containing macrophages ; however	pCR or pCR with DCIS

	ductal carcinoma in situ may be present (pCR)	
Chevallier Method [24]		
Class 1	Disappearance of all tumour (pCR)	pCR
Class 2	Presence of DCIS in the breast, no invasive carcinoma and negative lymph node (pCR)	pCR with DCIS
Class 3	Presence of invasive carcinoma with stromal alteration (pPR)	pPR
Class 4	Few modifications of the tumour appearance (pNR)	pNR
Sataloff Method[28]		
Tumour-A	Total or near total therapeutic effect (pCR)	pCR if nodes not involved; otherwise pPR
Tumour-B	Subjectively > 50% therapeutic effect, but less than total or near total (pPR)	pPR
Tumour-C	> 50% therapeutic effect (pPR)	pPR
Tumour-D	No therapeutic effect evident	pNR
Nodes-A	Evidence of therapeutic effect, but no metastatic lesion (pCR)	pCR if Tumour-A; otherwise pPR
Nodes-B	No nodal metastasis or therapeutic effect	pCR if Tumour-A; otherwise pPR
Nodes-C	Evidence of therapeutic effect but nodal metastasis still present	pPR
Nodes-D	Viable metastatic disease, no therapeutic effect	pNR if Tumour-D; otherwise pPR
RCB System[26]		
RCB-0	No residual disease	pCR
RCB-1	Minimal residual disease	pPR
RCB-2	Moderate residual disease	pPR
RCB-3	Extensive residual disease	pNR
AJCC 'y' classification[23]		

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pCR	No invasive carcinoma in breast nor nodal tissue. Carcinoma in situ after treatment constitutes a pCR.	pCR
pPR	Need to compare pre-treatment clinical categories (cT and cN)with clinical post therapy categories (ycT and ycN)	pPR
No response (pNR)	No change or an increase in either the T or N category	pNR

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Appendix B

First data sheet

- Name
- GT Number
- Study number

Second deidentified data sheet

- Study number
- Age at presentation
- Race (self-assessed)
- Hospital site
- Laboratory site
- Clinical stage (cTNM)
    - Clinical tumour size
        - § No larger than 5 cm
        - § Larger than 5 cm
- Pathologic stage (ypTN)
    - Pathologic tumour size
- Histologic type
- Intrinsic subtype
    - Luminal A
    - Luminal B/HER-2 negative
    - Luminal B/HER-2 positive ○ HER-2 overexpressed
    - Basal-like

response

- None
- Sataloff
- Miller-Payne
- Chevallier
- RCB
- NSABP-B18
- Other

- NACT regimen
  - Completion of regimen
  - Adverse events
  - Less than 70% of treatment completed
    - Pathologic response
  - pCR
  - pCR with DCIS
  - pPR
  - pNR
- Clinical course on NACT
  - Had secondary surgery
  - Did not have secondary surgery
    - § Disease progression
    - § Death
    - § Lost to follow-up