EVALUATING THE EFFICACY OF NEOADJUVANT THERAPY IN CYTOREDUCTION 0F NON-METASTATIC BREAST CANCER IN PATIENTS AT KNH.

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H53/63881/10.

THIS RESEARCH PROPOSAL IS SUBMITTED IN PART FULFILLMENT FOR THE AWARD OF MASTER OF MEDICINE IN GENERAL SURGERY OF THE UNIVERSITY OF NAIROBI.

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STUDENT'S DECLARATION:

I declare that this study is my original work and has not been presented for the award of any degree at any other institution or university.

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DEPARTMENTAL APPROVAL:
This research proposal has been presented at the Department Of Surgery meeting and is hereby approved for presentation to the Kenyatta National Hospital Ethics and Research Committee.

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LIST OF ABBREVIATIONS:

CT:	Chemotherapy.
ET:	Endocrine Therapy.
Pcr:	Complete pathological response,
BCS:	Breast conserving surgery.
MRM:	Modified Radical Mastectomy.
CR:	Clinical response.
PR:	Pathological response.
KNH:	Kenyatta National Hospital.
KTC:	Kenya Texas Centre.
NH:	Nairobi Hospital.
SOPC:	Surgical Outpatient Clinic.
BCS:	Breast conserving surgery
MRM:	Modified Radical Mastectomy.
LDL:	low density lipoprotein.
ER:	Estrogen receptor.
PGR:	Progesterone receptor.
HER 2:	Human Epidermal growth factor receptor 2.
CxR:	Chest X-ray.
LD:	longest diameter.

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ABSTRACT:

Background:
Neoadjuvant therapy has been shown to be effective in breast tumor reduction. No studies have assessed the degree of this response in our context.

Objective:
To assess the efficacy of neoadjuvant therapy in patients with non-metastatic breast cancer

Patient and Methods
This was an observational study on patient with non-metastatic breast cancer seen at Kenyatta National Hospital at the breast clinic and oncology clinics between November 2017 and January 2019. All patients who met the inclusion criteria and signed the informed consent were consecutively recruited to the study. Data on demographic of the patient, clinical stage and biological characteristics of the tumour data was recorded. Neoadjuvant treatment was then prescribed by the oncologist depending on their age, clinical state and tumor biology. The patients were then followed for the entire course of neoadjuvant treatment. Clinical examination was done to assess response to treatment every time the patients come to receive chemotherapy cycle. At the end of the study, patients were assessed for response to treatment according to the WHO criteria. Data was entered and analyzed in SPSS version 21.0. Those recorded to have responded were either with complete or partial response, while non-response those whose disease progressed on chemotherapy or had stable disease. The proportion of patient who responded was analyzed. We used Chi-square to compare demographic and biological factors that may lead to such response. P - value of less than 0.05 was taken to indicate statistical significance in differences.

Results
We recruited 54 patients, but two were lost to follow-up, so only 52 were analyzed. The average age was 47 year (SD=9 years). The majority of patient in this study presented with stage II disease (56%), with most of tumour size being that of T2(57%). Luminal A were the most common molecular type (40.7%) and 37% had complete response. There was no demographic or biological factor that proved statistically significant for the response, but it was noted that most responders were younger women with higher Ki-67.

Conclusion
Looked at in the context of other earlier studies, this study finds a trend towards early presentation of breast cancer. It also notes that Neoadjuvant chemotherapy is given to patient with early breast cancer, even though the intended goal is not breast conserving surgery.

Introduction

Currently, Breast cancer is the second most common cancer in the world, and by far, the most frequent cancer among women with an estimated 1.67 million new cancer cases diagnosed in 2012 (25% of all cases) (1). Estimated cases of Breast cancer in Africa in 2008 was 92,600 compared to cervical cancer which was 80,400. Mortality from breast cancer was estimated at 50,000 whereas that of cervical cancer was 53,300[1]. According to Kenya Cancer Registry 2011 Breast cancer accounted for about 23% of all cancers in Kenya, while Cervical and Prostate cancer represent about 20% and 9.4% of all cancers respectively. At KNH, new cases of breast cancer seen in breast clinic in 2015 were 497 while those admitted to the wards in 2015 were 381. Mortality from breast cancer at KNH in 2015 was around 77 patients.

Neoadjuvant treatment of breast cancer has become established as the safe and often effective therapeutic approach of choice for larger primary and for locally advanced breast cancer (2).

The use of neoadjuvant therapy offers three clinical advantages i.e. reduction in tumor size for possible curative mastectomy or breast conserving surgery, monitoring of treatment response and biological monitoring of breast cancer treatment (2,3).

Currently neoadjuvant treatment can either be given as systemic chemotherapy or as hormonal therapy targeting the estrogen and progesterone receptors on patients who have receptor positive tumors. Hormonal therapy is either given as tamoxifen which is an estrogen receptor antagonist or as aromatase inhibitors e.g. Anastrozole that reduce synthesis of estrogen in the body.

Chemotherapy has been shown to be effective in tumor reduction but is also toxic and costly. Endocrine therapy on the other hand is cheaper and less toxic but its efficacy in cytoreduction is not very high.

Although neoadjuvant therapy is routinely used, with positive response in our set up, no study has been done to assess the degree of this response in our patients and furthermore no comparison has been made on the amount of response achieved from those patients on chemotherapy compared to those on endocrine therapy.

The purpose of this study is to assess the efficacy of neoadjuvant treatment on patients with non-metastatic breast cancer at KNH.

LITERATURE REVIEW:

Historically, neoadjuvant therapy was undertaken with the aim of shrinking the tumour in patients who were not candidates for primary curative surgery, and in the hope of allowing greater conservation of the breast. Evidence then emerged suggesting that induction of a pathological complete response (pCR) was at least to some extent predictive of long-term clinical response [4, 5]. This has enhanced the rationale to include a means of testing the activity of a therapeutic approach or the potential importance of biological factors in determining disease outcome.

Initial indications that primary therapy could favourably affect prognosis were followed by a series of randomized controlled studies in which patients were managed using either the adjuvant or neoadjuvant approaches. These studies showed that both the percentage of disease free survival at five years and percentage survival at five years was higher in the

group receiving neoadjuvant treatment than those not receiving neoadjuvant treatment before surgery. (6-10).

Chemotharapy has been the mainstay of neoadjuvant treatment for breast tumor for many years. Drugs used in chemotherapy are either Anthracyclines eg doxorubicin, epirubicin or Non Anthracycline which include taxanes eg doxetaxal, paclitaxale etc. Anthracyclines have more side effects especially cardiac and renal toxicity while taxanes are much safer but more costly. Neoadjuvant CT has been shown to be effective. In one systematic review by Scholl et al on neoadjuvant chemotherapy for operable breast cancer, patients receiving neoadjuvant chemotherapy had a lower mastectomy rate than those undergoing surgery before adjuvant chemotherapy [relative risk 0.71; 95% confidence interval (CI) 0.67–0.75](11). Neoadjuvant CT is highly effective, with a clinical response rate ranging from 50% to 90%, although with a much lower pathological complete response (pCR) rate ranging from 2% to 27% (11). The CT-induced pCR has been considered a surrogate marker for disease-free and overall survival (12, 13).

The ER status is the most commonly recorded predictor of the response to CT. At least 11 studies using different CT regimens have reported greater pCR rates in ER-negative tumours than in ER-positive ones (14–24). In the European Cooperative Trial by Gianni et al in Operable Breast Cancer, pCR after neoadjuvant chemotherapy was observed in 42% of women with ER-negative tumours, compared with 12% in the ER-positive group(25,26).

Although CT is effective, it is toxic with side effects such as cardiac toxicity, nephrotoxicity, hair loss, severe vomiting and many others. It is also very expensive. At KNH for example, each cycle of CT consisting of cyclophosphamide, Adriamycin and 5 fluorouracil costs Kshs 4500. If a taxane is included in the regimen, the cost goes up to Kshs 6500.

Neoadjuvant endocrine therapy can either be estrogen receptor modulator tamoxifen or Aromatase inhibitor's such as Anastrazole that inhibit synthesis of estrogen in the body.

Although neoadjuvant endocrine therapy has not been studied as extensively as neoadjuvant chemotherapy, several phase 2 studies have demonstrated the feasibility of various endocrine treatments in elderly breast cancer patients with advanced local regional disease, thus suggesting an alternative approach to initial surgery(27,28).

Milla-Santos et al treated 112 hormone-dependent locally advanced breast cancer postmenopausal women with anastrozole (1 mg) during 3 months. Among these patients, Milla-Santos et al reported 12% of pathological complete response (disappearance of all tumoral spread) and 71% of pathological partial response. Patients who showed no response to neoadjuvant treatment underwent radiotherapy. No adverse events were reported. For elderly patients, 4 months of letrozole resulted in improved tumour response and rates of breast conserving surgery over tamoxifen (29, 34).

At least 6 relatively small studies have evaluated neoadjuvant therapy with exemestane(35–39) Dixon et al evaluated the effect of neoadjuvant exemestane in 13 postmenopausal women with ER-positive, operable, and locally advanced breast cancer.(33) Exemestane was given for up to 3 months. Median tumour volume evaluated by clinical examination, mammography, and ultrasound was reduced by 86%, 84%, and 83%, respectively. After treatment, 10 patients had breast-conserving surgery with clear margins, and 2 underwent mastectomy.

In a phase 2 study reported by Tubiana-Hulin et al, 38 postmenopausal women with ER-positive operable breast cancer received 4 to 5 months of neoadjuvant exemestane (35).Tumour response was evaluated by using National Cancer Institute Response Evaluation Criteria in Solid Tumours(40). Six percent of patients had a clinically complete response, 65% had a partial response, 24% had stable disease, and 45% had breast-conserving surgery.

Aromatase inhibitors have shown superiority over tamoxifen in permitting breast-conserving surgery when used as preoperative therapy for 3 to 4
months (42–45)

Endocrine therapy has not been shown to have any major toxic side effects and yet is effective especially for the elderly women who cannot withstand the toxic side effects of CT. It is also much cheaper. A study by Gitonga et al at KNH showed that endocrine therapy for breast cancer was much cheaper than chemotherapy(46).

At KNH most patients receive CT. Commonest regimen given includes cyclophosphamide, adriamycin and 5 fluorouracil (CAF) for three cycles. ET is reserved for the elderly patients who cannot withstand CT and is given as tamoxifen for three months.

Response to neoadjuvant therapy is assessed according to WHO criteria:

* Complete Response (CR):	Disappearance of all target lesions
* Partial Response (PR):	At least a 30% decrease in the sum of the LD of target lesions, taking as reference the baseline sum LD
* Progressive Disease (PD):	At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions
* Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started

Adverse effects from the drugs given are graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0 and graded into one of the five grades:

Grade 1 Asymptomatic or mild symptoms, Intervention not indicated.
Grade 2 Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate Instrumental ADL*.
Grade 3 Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**.
Grade 4 Life-threatening consequences; urgent intervention indicated.
Grade 5 Death related to AE.

ADL: activities of daily living.

AE: adverse event.

STUDY JUSTIFICATION:

Breast Cancer is one of the commonest tumour's in women worldwide and locally. Neoadjuvant treatment has been shown to be effective in cytoreduction and downgrading of locally advanced breast cancer.

No study has however been done to assess the degree of response achieved on our patients post neoadjuvant therapy.

MAJOR OBJECTIVE:

To assess the efficacy of neoadjuvant therapy in cytoreduction of non-metastatic breast cancer .

SPECIFIC OBJECTIVES:

i. To assess the clinical characteristics of patients who receive neoadjuvant therapy at KNH.

ii. To assess response of neoadjuvant therapy according to WHO criteria.

PATIENTS AND METHODS:

Setting:

The study was carried at Kenyatta National Hospital (KNH) breast clinic, oncology clinic and cancer treatment centre. KNH is the national referral hospital and currently the only hospital with breast surgeons in the country which has a weekly multidisciplinary meeting.

Study Design and population

This was prospective observational study from November 2017 to January 2019

Study Population:

All patients with non-metastatic breast cancer.

Eligibility Criteria:

Inclusion Criteria:

Patient with histologically confirmed breast cancer that is non-metastatic in good condition ie. have normal Full blood count, liver, and renal functions and a negative chest X ray and abdominal u/s and biological characterization done i.e receptor status, HER2 status and Ki67

Exclusion Criteria:

Patients on prior chemotherapy or endocrine therapy or those with bilateral or inflammatory breast cancer. Also, patients with distant metastases, and other malignant diseases or on other forms of cancer treatments. Patients who decline to give consent were not be included in the study.

Method:

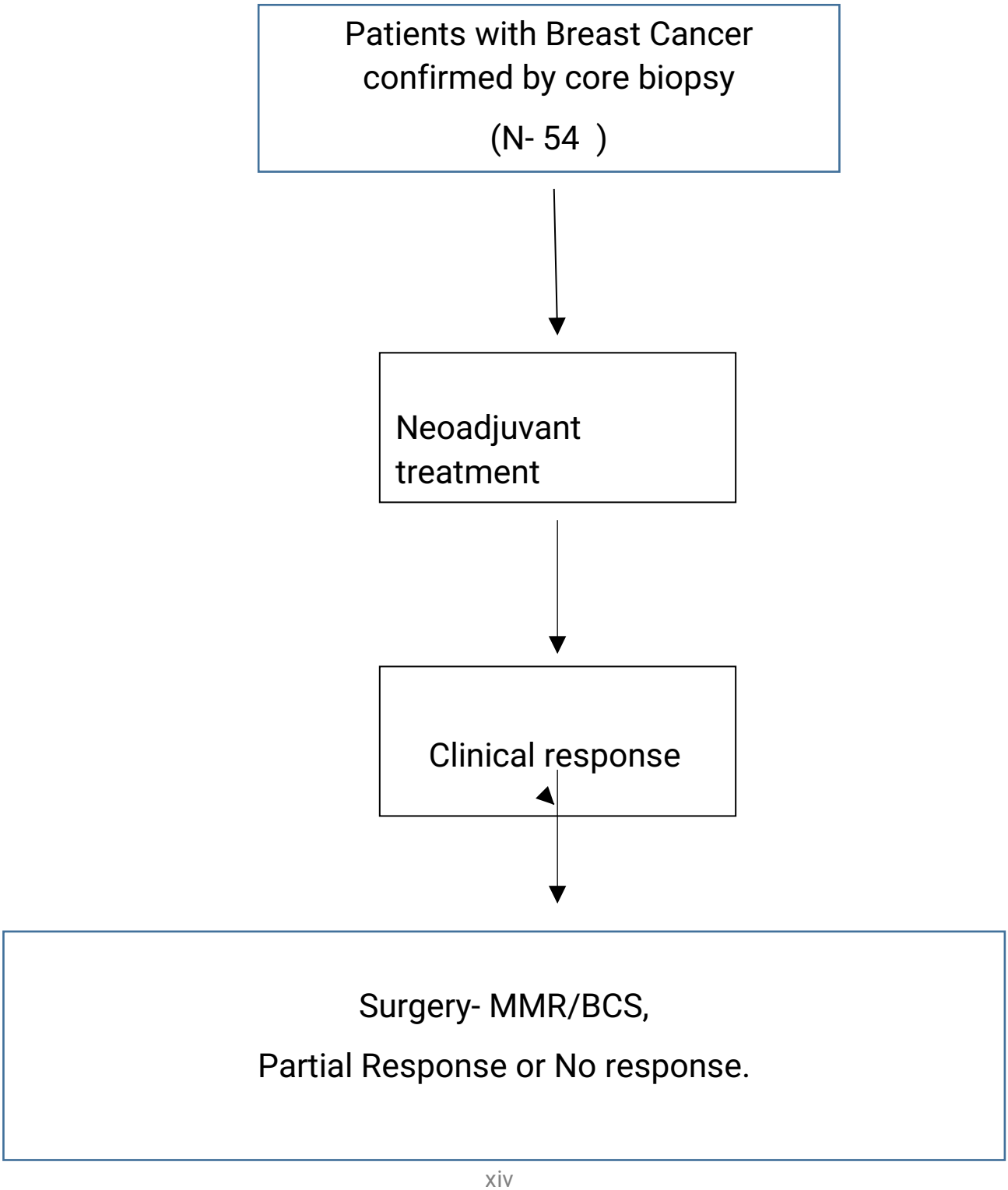
All patients who gave consent and met the inclusion criteria were included in the study. Data collected included their age, sex, grade of tumor, receptor status, Her-2 status, Ki67 level, stage , whether they are premenopausal or postmenopausal , their initial haemogram, liver and renal functions, which are routinely done by these patients. The haemogram is done at the haematology lab while the renal & liver function tests are done at the biochemistry laboratory (lab 16). A baseline Chest x-ray & and abdominal ultrasound is also routinely done by these patients to rule out metastasis at the radiology department at KNH. The laboratory and radiological department are Iso certified. Initial clinical exam findings of the breast and axilla was recorded. Patients then received neoadjuvant treatment.

At the end of neoadjuvant chemotherapy (NAC) each patient then underwent clinical exam of the breast and axilla to assess degree of response to therapy. Response to treatment was graded according to WHO criteria. Any side effects of the therapy the patients got was recorded.

Data was entered and analyzed in SPSS version 21.0. The analysis was performed for proportion that responded. Bivariate analysis using Chi-square was performed to determine any factor that could determine response or non-response.

Study End Points:
The primary efficacy end point was objective response rate defined as the percentage of patients in each treatment arm with a complete response (CR) or a partial response (PR) as determined clinically by breast palpation (CR, regression 100%; PR, regression>50%). Response categories were CR, PR, no change, progressive disease, or not assessable/not evaluable (NA/NE).

Palpable ipsilateral axillary lymph node involvement downgraded a clinically complete response (cCR) to a PR.



Statistical Methods:

Sample size calculation:

Sample size was estimated using a non-inferiority clinical trial formula as follows:

Sample size $n = [DEFF*Np(1-p)]/ [(d^2/Z^2_{1-\alpha}/2*(N-1)+p*(1-p)]$

n – sample size required.

N - the total number of the accessible population eligible for the study = 10 patients per month = 60 patients in 6 months

$Z_{1-\alpha}$ – the standard normal deviate for a two sided test at 95% CI= 1.96

P – the clinical response rate of standard treatment (chemotherapy) group = 66% (Alba et al, 2012)

d – margin of error = 5%

By substituting into the formula

N = 54

Therefore a sample of 54 patients was included in the study.

Data Collection:

All patients who met the inclusion criteria were explained to the nature and purpose of the study. Those who agreed to be part of the study, consent was obtained from them. A questionnaire was filled for every patient that included data on age, size of tumour, stage of tumour, any therapy the patient has received and receptor status of the tumor. The questionnaire was stored by the primary investigator.

Data Analysis:

Data was entered and managed in SPSS version 21.0. Demographic and clinical characteristics was summarized into proportions for categorical variables and means or medians for continuous data. Clinical response rate was calculated and presented as a proportion with 95% confidence interval. Factors associated with clinical response was assessed by analyzing demographic and selected clinical variables in patients who respond compared to those who do not respond. Chi square test was used to comparison of means/medians. Odds ratios was calculated to estimate the likelihood of response associated with the selected independent variables. All statistical tests were done at 5% level of significance.

ETHICAL CONSIDERATION:

This study was commenced after approval from the Department of Surgery UoN and the UoN-KNH Ethics and Research Committee. An informed consent was obtained from all patients. Patients were not coerced to enroll into the study. Non-participation did not affect such a patient's care in the hospital. Participation in this study did not attract extra cost to the participants. Patients' hospital file number was included into the data sheet to facilitate easy tracing and capture missed information during data collection. The data sheet was kept safely by the researcher and confidentiality maintained throughout. Electronic data file generated was encrypted with a password only availed to the research team. Any hard copy research data was kept in a safe locked cabinet only accessed by the research team. The collected data was destroyed after completion of this study. The primary data collected was

kept with the primary investigator confidentially for five years even after completion of study, before being destroyed.

RESULTS

A total of 54 women with breast cancer who underwent neo-adjuvant chemotherapy were recruited and followed up between November 2017 to January 2019 until they completed their NAC treatment and were referred for surgery. Two of the patients were loss to follow up after starting NAC. These patients were included in results analysis. The age ranged was 28-69 yrs. Mean age of patients was 47.5 (SD 9yrs). Commonest age group was 41-50yrs (Fig. 1).

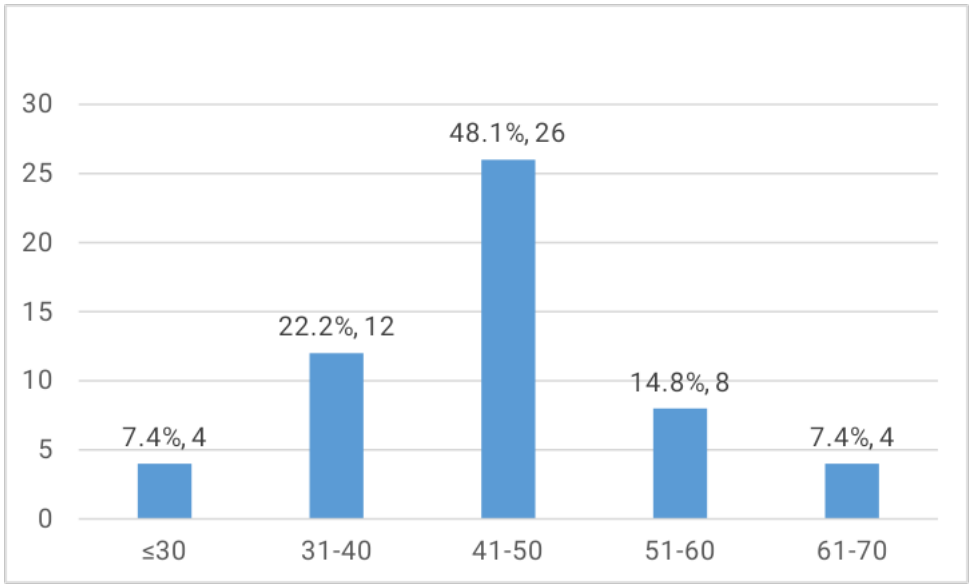


Fig 1- Age Distribution.

Stage II comprised the highest proportion of tumors at 56% while the least common was stage 1 at 7% (Fig 2).

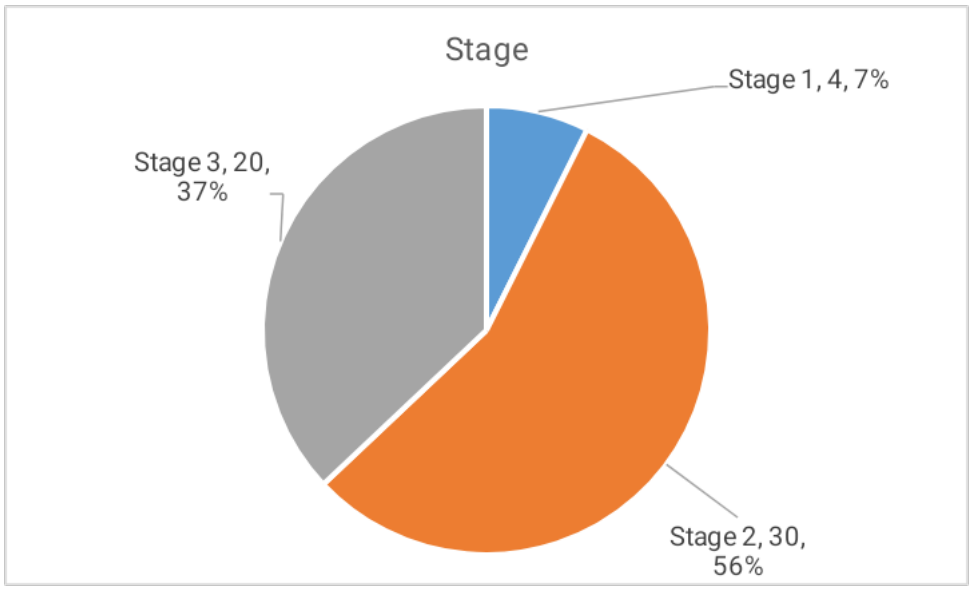


Fig 2- Frequency of different tumor stages

Commonest tumor size was between 2-5 cm (57% of the patients). Few patients came early with tumors less than 2cm (5.6%) (Fig 3).

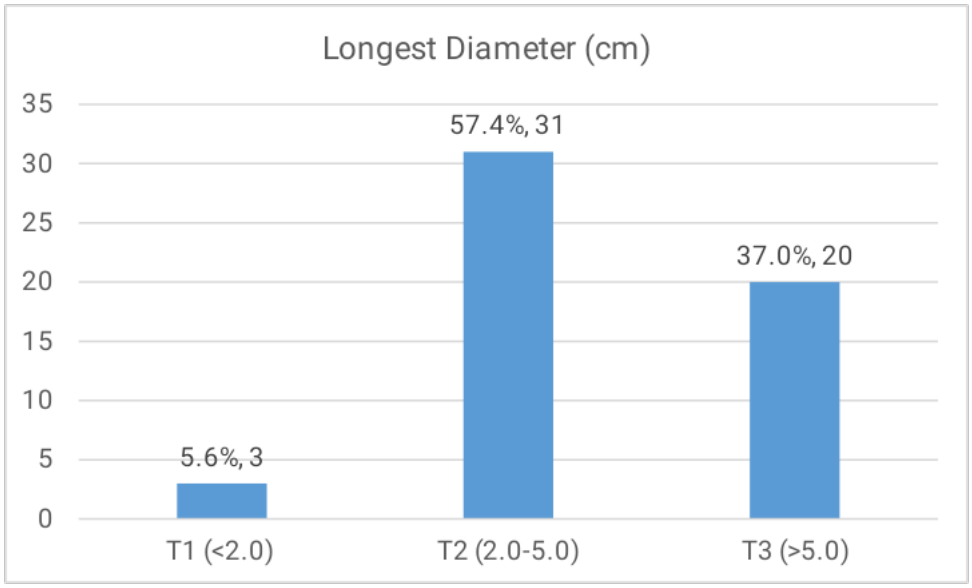


Figure 3: **Distribution of tumours by T staging**

None of the patients had low grade tumors or carcinoma in situ. All the patients had either grade 2 or 3 tumors with G2 tumors being 46.3% vs G3 tumors which were 53.7%.

ER+/PR+ patients were the commonest at 68%. Most had aggressive tumors with high Ki67 levels (72%). Her 2- tumors were commoner at 57% than Her 2+ tumors which comprises 42% (Table 1)

Table 1. Distribution by biological characteristics of the tumours.

Receptor status	
$ER^{+}PR^{-}$	2 (3.7)
$ER^{-}PR^{-}$	15 (27.8)
$ER^{+}PR^{+}$	37 (68.5)
HER-2	
Positive	23 (42.6)
Negative	31 (57.4)
Ki-67 levels (%)	
≤20	15 (27.8)
>20	39 (72.2)

Luminal A type was the commonest at 40.7%. Patients who were ER+/PR + but had aggressive features such as high Ki67 levels and younger age were classified as Luminal B tumors. Luminal A & B made around 72% of the patients. Her 2 enriched tumors were the least common at 9% (Fig 4)

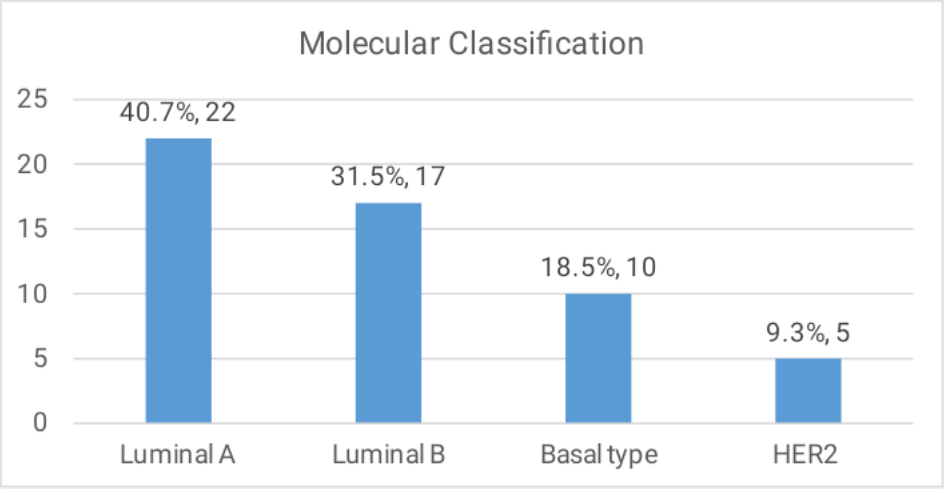


Fig 4- Distribution by molecular subtypes and their frequency

Key:
Luminal A: ER+/PR+/HER2-
Luminal B: ER+/PR+/HER2- with high Ki67 levels
Basal Like: ER-/PR-/HER2-
HER 2 enriched: ER-/PR-/HER 2+

Menopausal status of the patient was determined by asking the patients. All those who had missed periods for more than 1yr were classified as postmenopausal. Majority of our patients were premenopausal (66.7%)

Patients initially received either 3 or 4 three weekly cycles and if tumor response was adequate they were sent for surgery to be followed by adjuvant CT. Those whose tumors did not adequately shrink after the initial course, received another course of 3 or 4 three weekly cycles before going for surgery. Commonest was a course of 4 cycles (31.5%). Two of the patients opted for NAC outside KNH.

Adriamycin & Cyclophosphamide were the commonest NAC drugs given to 68.6% of the patients. Analysis of this part of the study therefore comprised of 52 patients. Herceptin was given to HER2+ patients. However, because of cost issues, it was not readily available and not all HER2+ patients received Herceptin (Table 2)

Table 2: Number of responders Vs Non-responders in the various CT gps

	Responders	Non-R	Total	
AC	24	8	32	
AC Then GC	1	0	1	
AC Than T	1	2	3	
ACH	4	1	5	
CAF	3	5	8	
TAC	1	1	2	
LTF			1	

Key:

A-Adriamycin, C- Cyclophosphamide, D-Doxorubicin, H-Herceptin, G-Gemcitabine, T-Paclitaxel, LTF-Lost to Follow-up

Response to NAC was assessed by the WHO criteria. Majority of the patients responded to CT with a total of 64.8% patients achieving either partial or complete response. Around

25.9% of the patients had progressive disease with their masses ulcerating despite being on CT (Table 3)

Table 3- Response to NAC according to the WHO criteria.

	Frequency n (%)
Partial response	15 (27.8)
Complete response	20 (37.0)
Progressive disease	14 (25.9)
Stable response	3 (5.6)
Lost to follow-up	2 (3.7)

Note:

Partial responders- reduction of > 30% in longest diameter (LD)
Complete responders-Disappearance of all target lesions
Progressive disease-at least 20% increase in the LD
Stable disease- Neither sufficient shrinkage to quantify for PR nor sufficient increase to qualify for PD, taking into consideration the LD since treatment started.

Patients with ER-PR- receptor status had a higher proportion of complete clinical response (n=13) while patients who had ER+PR+ receptor status had a higher number of responders (n=20) but most of them were partial responders (n=12 out of 20) (Table 4)

Table 4- Response according to WHO criteria in each of the molecular subtypes

	No of patients			
	CR	**PR**	**PD**	**SD**
ER^-PR^-	13	1	0	1
ER^+PR^-	1	1	0	0
ER^-PR^+	8	12	13	2
Total	**22**	**14**	**13**	**3**

Commonest side effects were Hair loss, Nausea & vomiting and weight changes, mostly weight loss. Patients also developed irregular cycles while on NAC. These effects are in keeping with common side effects of NAC reported in literature (Table 5)

Table 5- Common side effects to NAC and their frequency.

	N	Percent of Cases
Diarrhea	18	34.6%
Dizziness	8	15.4%
Fatigue	26	50.0%
Hair loss	46	88.5%
Headaches	4	7.7%
Nausea and Vomiting	40	76.9%
Loss of periods	16	30.8%
Mouth sores	18	34.6%
Nail changes	25	48.1%
Skin darkens	5	9.6%
Weight changes	34	65.4%

Comparison of responders Vs Non responders

The sample size in this study was not adequately large enough to be able to state major differences between the responders Vs the non responders. However some characteristics were more commoner in the responders Vs the non responders as shown in the table below.

Most of the responders were premenopausal women less than 50yrs (n-27), with high Ki67 levels (n=27) and Luminal A and B type of tumors (n=28)

Table 6. Comparison between responders and Non responders

	Responders	**Non Responders**	**Total**	**P value**
Age (years)				
≤30	3 (8.6)	0 (0.0)	3 (5.8)	0.542
31-40	8 (22.9)	3 (17.6)	11 (21.2)	1.000
41-50	16 (45.7)	10 (58.8)	26 (50.0)	0.555

51-60	6 (17.1)	2 (11.8)	8 (15.4)	1.000
61-70	2 (5.7)	2 (11.8)	4 (7.7)	0.589
Longest diameter (cm)				
<2.0	3 (8.6)	0 (0.0)	3 (5.8)	0.542
2.0-5.0	18 (51.4)	11 (64.7)	29 (55.8)	0.366
>5.0	14 (40.0)	6 (35.3)	20 (38.5)	0.744
Grade				
2	15 (42.9)	10 (58.8)	25 (48.1)	0.280
3	20 (57.1)	7 (41.2)	27 (51.9)	
Stage				
1	3 (8.6)	1 (5.9)	4 (7.7)	1.000
2	18 (51.4)	10 (58.8)	28 (53.8)	0.616
3	14 (40.0)	6 (35.3)	20 (38.5)	0.744
Oestrogen				
Positive	24 (68.6)	13 (76.5)	37 (76.5)	0.747
Negative	11 (31.4)	4 (23.5)	15 (28.8)	
Progesterone				
Positive	23 (65.7)	12 (70.6)	35 (67.3)	0.725
Negative	12 (34.3)	5 (29.4)	17 (32.7)	
HER-2				
Positive	14 (40.0)	7 (41.2)	21 (40.4)	0.935
Negative	21 (60.0)	10 (58.8)	31 (59.6)	
Ki-67 levels (%)				
<20	8 (22.9)	7 (41.2)	15 (28.8)	0.203
>20	27 (77.1)	10 (58.8)	37 (71.2)	
Luminal Type				
A	14 (40.0)	8 (47.1)	22 (42.3)	0.629
B	10 (28.6)	5 (29.4)	15 (28.8)	1.000
Triple negative	8 (22.9)	2 (11.8)	10 (19.2)	0.467
HER2 Positive	3 (8.6)	2 (11.8)	5 (9.6)	1.000

Menopausal status				
Premenopausal	24 (68.6)	10 (58.8)	34 (65.4)	0.488
Postmenopausal	11 (31.4)	7 (41.2)	18 (34.6)	

Discussion.

The incidence of breast cancer is known to be age related. It was found that most of the patients with non-metastatic breast cancer were between the ages of 41-50 years (48%) with a mean age of 47 yrs. The BRECC study done at KNH by Professor Abinya (36) showed that the average age of women with breast cancer was 48 yrs with an age range of 21-84 yrs . This is a relatively low age group compared to the western world where patients with breast cancer present at a later decade of life as shown by a study done by Purva sharma et al at JFK medical centre in florida (2018) (37) where 45% of the patients were above 70yrs of age. Another study by H Chen et al (38) showed that in china the commonest age range for breast cancer was 50-59 yrs with an average age of diagnosis at 56yrs. Therefore, in our setup there seems to be an upward trend of breast cancer in the younger women

Commonest tumor stage in our set up was found to be stage II (54%) which was similar to the results in the BRECC study where the commonest stage was also found to be stage II(33.7%). In the western world, breast tumor is picked up earlier as shown in review done by Ganiy et al (39) that showed that most patients are diagnosed at stage 1 (53%). The study by Purva et al also showed that the commonest tumor stage in their setup was IA (48.8%) . This was attributed to readily available screening tools to the population such as breast US and mammograms that were affordable to the general population. This higher diagnostic stage in our setup could be because of lack of awareness on breast cancer especially in lower socioeconomic population and also lack of affordability of screening tools like mammogram to a bigger proportion of the population.

Tthe commonest histological type was invasive ductal carcinoma. The BRECC study also showed that invasive ductal carcinoma was the commonest comprising 83% of all the tumor

grades. Invasive dictal carcinoma is also the commonest histological type in the west as shown by Britta et al (40) who showed that IDC comprised 80% of histological type of breast cancer.

Luminal A comprised of 40.7% of the patients in this study indicating it is the commonest luminal type in our set up, HER 2 enriched was the least common at 9% . This shows good prognosis because ER+ patients can benefit from tamoxifen as endocrine therapy. A study by Kumar et al (41) showed similar results in india with Luminal A comprising 34% of the tumors. Even in the western Borislav et al (42) that showed that Luminal A type tumors were the commonest at 72% with HER 2 enriched being the least common at 8.2%. Patients in this group were recommended to take Herceptin.

Our results show that most of the women with breast cancer in the younger age group have aggressive breast cancer. This is reflected by most tumors being grade 3 tumors (53.7%), with high ki67 levels (72% having >20%). Around 25% of the patients had progressive disease despite being on CT. These aggressive features of breast cancer in younger women has been shown by several studies including the one Paula Cabrera et al (43) which showed that patients < 65yrs presented mostly with grade III tumors and had a higher proportion of HER 2+ (22%) tumors than those who were older.

Neoadjuvant chemotherapy was given as 6 three weekly cycles to most patients and the commonest regimen used was Adriamycin and Cyclophosphamide followed by a taxane that is more commonly given as adjuvant therapy. Most studies including the review done by Rosana et al (44) also recommend an anthracycline based NAC regime followed by a taxane. A review done by Jesus Anampa et al (45) showed that the 1st line NAC regimens that brought about 35% reduction in breast cancer mortality include AC, CMF and FEC50. Complete pathological response was 37% after NAC. These results were similar to those of a study done by Alice Goodman et al (46) where 31.2% patients achieved cPR .

In this study, the women who responded to NAC were mostly premenopausal women <50yrs of age, with the longest tumor diameter being <5cm, most of them being luminal A and B who are estrogen, progesterone receptor positive and HER 2+ , the commonest tumor stage was II and had Ki67 levels >20% . These results are similar to other studies such as the study done by William Tran et al (47) that showed that among the 37 patients with breast cancer who were included in the study, the responders were 27 patients who had a median age was 50 years, the mean tumor size in longest diameter was 5.4cm (vs 7cm in the non responders), the responders were mostly ER/PR + tumors and HER2+ (Luminal A or B).

Miglietta L et al (48) also showed that downstaging of tumor was shown in patients who had pre treatment Ki67 levels > 20%, Her 2 overexpression and T2b/T3 stage .

This study also showed that patients who have ER+ or PR+ tumors show mostly partial response to CT whereas patients with ER- or PR- receptors showed mostly complete response to CT. this is in keeping with several studies including the one done by Tumofumi et al which showed that patients who were ER- were 18.6X more likely to achieve pCR (complete pathological response) than those with ER+ tumors. The European cooperative trial by Gianni et al (49) on operable breast cancers, also showed that pCR after neoadjuvant CT was observed in 42% of women with ER- tumors Vs 12% in ER+ groups (25,26)

Several studies including the one by Wei Zang et al (50) showed in HER 2+ patients , including Transtuzumab as neoadjuvant therapy to patients, increased the pCR from 30.3% to 65%. This study showed that some of the patients who were HER2+ did not receive transtumab as NAC. It is therefore recommended to give Herceptin as NAC to all HER2+ pts. The same study also showed that HER 2+ pts responded well to CT than HER2- pts. In this study, the responders group had more HER2- than HER2+ pts. We think this could be because nor all of the HER2+ patients received Herceptin & this made their response to NAC less effective.

On the comparison for the response rate of CT to ET, the study found that ET was not given to any of the patients in the neoadjuvant setting and therefore it was not possible to make a comparison between effectiveness of ET vs CT in the neoadjuvant setting. Studies such as the one by Milla Santos et al have shown upto 12% of cPR & 71% of partial response when anastrozole was used as neoadjuvant therapy especially on postmenopausal women. Since ET has less side effects than CT and is cheaper than CT (Gitonga at KNH) it is recommended that ET should be considered as neoadjuvant therapy especially in the elderly & postmenopausal women. ET is also recommended especially for ER-ve breast cancers than ER+ tumors as shown in several studies (14-24) however the results from this study show that all patients at KNH were put on CT irrespective of their receptor status.

Among the patients who responded to CT neither of the clinical characteristics studied here were statistically significant enough between the responders Vs the non responders. Probably further studies should be done to assess characteristics that make certain patients

respond to CT and others not such as BRCA gene mutations in the responders Vs non responders and positivity of family history in the past generations between the two groups.

Study limitation.

The tumor measurements were done using clinical examinations and therefore tumor staging and response to NAC can be quite subjective.

Conclusions

The study concluded that breast cancer is becoming increasingly common in the younger age group of women with most tumours being grade 3 tumors with a high ki67 levels. Commonest neoadjuvant CT regimen used at KNH is AC and majority of the patients respond to it however 25% of the patients get progressive disease despite being on CT. pCR is better achieved by patients who are ER or PR negative and petients who are ER/PR potitive have better prognosis than patients with basal like and HER 2 enriched tumors.

Recommendations

We recommend that there should be more accurate method of measuring tumor size and axillary nodal involvement prior to neoadjuvant therapy such as breast US and axillary US so as to objectively measure therapy response.

The results show that not all patients who were HER2 + received Herceptin due to lack of availability of Herceptin which is mostly due to its high cost. We recommend Herceptin should be made available to all HER2+ patients.

A large percentage of 25% of the patients progressed with their disease despite being on NAC. It is recommended to study these patients further to try and establish the cause of failed CT in these patients.

Around 3 patients received CT regimen of ACH. Both Adriamycin and Herceptin are cardiotoxic and are not routinely given together. It is recommended that the medical practitioners prescribing the CT are well aware of the side effects of the chemo drugs.

As discussed in the literature review, ET has been shown to be effective in the neoadjuvant setting especially in the elderly age group and in patients with other comorbidities such as cardiovascular issues since it is less toxic than CT. It is recommended that ET should be considered in selected patients as neoadjuvant therapy.

It is recommended that another study be done with a large sample size that can identify clinical characteristics of patients who respond to neoadjuvant treatment Vs those who do not.

Appendix

Study time frame:

ACTIVITY	Aug 201	Sep 201	Oct 201	Nov 201	Dec 201	Jan 201	Feb 201	Mar 201	Apr 201	May 201	Jun 201	Jul 201	Aug 201	Sep 201
Proposal developm														
Ethical Approval														
Data Collection														
Data Analysis														
Dissertation Writing and presentation														

Budget:

Budget Item	Amount(Kshs)
Research Fees.	2,000
Stationary.	5,000
1 Statistician	30,000
1 Research Assistant.	30,000
Printing and Binding.	20,000
Contingencies.	20,000
Total	**107,000**

Informed Consent:

English version

EFFICACY OF NEOADJUVANT THERAPY IN CYTOREDUCTION OF NON METASTATIC BREAST TUMOUR .

This informed consent is for patients with locally advanced, receptor positive women presenting at the Adult Accident and Emergency Department, breast clinic and oncolocy unit, KNH. This consent will be administered to the patients themselves. We are requesting these patients to participate in this research project whose title is “Efficacy of neoadjuvant therapy in cytoreduction of locally advanced breast tumour in receptor positive breast cancer patients.”

Principal investigator: Dr. Iram Shabir.

Institution: School of Medicine, Department of surgery,

University of Nairobi

Supervisors: Dr Joseph Githaiga.

. Dr, Daniel Ojuka.

This informed consent has three parts:

- Information sheet (to share information about the research with you)
- Certificate of Consent (for signatures if you agree to take part)
- Statement by the researcher

You will be given a copy of the full Informed Consent Form.

Part i: Information sheet

Introduction

My names are Dr Iram Shabir; I am a post graduate student at the University Of Nairobi School Of Medicine, department of general surgery. I am carrying out a study to validate the Efficacy of neoadjuvant therapy in cytoreduction of non metastatic breast tumour in breast cancer patients. This would be possible through data collection by filling in a data collection tool.

Study Procedure

Eligible patients who willingly give consent will randomly be assigned to receive neoadjuvant therapy. All patients will undergo monthly clinical examination to assess response to treatment. After the patient completes her treatment she will be assessed for cytoreduction of tumor by clinical exam .

Voluntary Participation/Right to Decline or Withdraw

An invitation to participate in this study is hereby extended to you. You will have the opportunity to ask questions before you decide on your enrollment. You may seek clarification regarding any bit of the study from my assistant(s) or me should any part be unclear. The decision to participate in this study will be entirely voluntary after you have comprehensively understood the details herein. By refusing to participate in the study, you will not be denied medical care. Furthermore, you may stop participating at any time with no consequences whatsoever.

Confidentiality

All the information which you provide regarding yourself will be kept confidential; only the researchers will access this information. They will be identified by a number and only the researchers can relate the number to the patient. The information will not be shared with anyone else unless authorized by the Kenyatta National Hospital/University of Nairobi – Ethics and Research Committee (KNH/UoN-ERC).

Cost and Compensation

There will be no extra cost incurred by you (or your kin) from participation in this study, and there is also no compensation.

Sharing of information

Following authorization by the Kenyatta National Hospital/University of Nairobi – Ethics and Research Committee (KNH/UoN-ERC), which is a committee whose work is to make sure research participants are protected from harm, relevant medical information yielded from this study may be

shared with fellow doctors through scientific seminars, workshops and publications. Personal information will not be disclosed whatsoever

Who to contact

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Mobile phone 0711444234

Part i: Statement by the researcher

I have accurately read out the information sheet to the participant, and to the best of my

ability made sure that the participant understands the following:

Refusal to participate or withdrawal from the study will not compromise the quality of care and treatment given to the patient.

All information given to us will be treated with confidentiality.

The results of this study may be published to enhance knowledge and to help improve utility/management of peritoneal dialysis surgical complications.

I confirm that the participant was given the chance to ask questions about the study, and all such questions have been answered correctly and to the best of my ability. I confirm that the individual has not been coerced into giving consent, and the consent has been given freely and voluntarily.

A copy of this Informed Consent Form has been provided to the participant.

Name of researcher taking consent……

Signature of researcher taking the consent……

Date……

ii) Participants Consent

I …… willingly accept to be part of this study being conducted by Dr Iram Shabir. I fully understand the nature of the study as has been explained to me by her/ her research assistant. I am aware that my participation is voluntary and as such I can withdraw from the study at any point and that this will not affect the care given to me at the hospital.

Signature…….. Date……..

Left Thumb print of Participant if unable

To sign

Kiswahili Version:

FOMU YA MAKUBALIANO YA KUJIUNGA NA UTAFITI

EFFICACY OF NEOADJUVANT THERAPY IN CYTOREDUCTION OF NON METASTATIC BREAST CANCER PATIENTS.

Fomu hii ya makubaliano ni kwa wagonjwa na “Breast Cancer” ambao wanahudumiwa kwenye Idara ya Ajali na Dharura katika hospitali ya KNH na wamealikwa kujiunga na utafiti, **“EFFICACY OF NEOADJUVANT THERAPY IN CYTOREDUCTION OF NON METASTATIC BREAST CANCER PATIENTS’.**

Mtafiti mkuu: Dkt. Iram Khan.

Kituo: Kitengo cha Upasuaji, Shule ya Afya, Chuo Kikuu cha Nairobi.

Fomu hii ya makubaliano ina sehemu tatu:

- Habari itakayo kusaidia kukata kauli
- Fomu ya makubaliano (utakapo weka sahihi)

- Ujumbe kutoka kwa mtafiti

Utapewa nakala ya fomu hii.

SEHEMU YA KWANZA: Ukurasa wa habari

Kitambulizi

Jina langu ni Dkt. Iram Khan. Mimi ni daktari ninayesomea upasuaji katika Chuo Kikuu cha Nairobi. Ninafanya utafiti kuhusu, "**EFFICACY OF NEOADJUVANT THERAPY IN CYTOREDUCTION OF NON METASTAIC BREAST CANCER PATIENTS.**

Ushiriki wa Hiari/Haki ya Kukataa

Ningependa kukualika ushiriki katika utafiti huu. Utapata nafasi ya kuuliza maswali kuhusu utafiti huu, aidha kutoka kwangu au kutoka kwa wasaidizi wangu. Baada ya kuelewa maelezo ya utafiti, ushiriki wako utakuwa wa hiari. Iwapo utaamua kutoshiriki katika utafiti, hautanyimwa matibabu. Isitoshe, ukishaamua kushiriki, ni haki yako kukataa kuendelea na ushiriki huo wakati wowote ule bila madhara yoyote.

Taadhima ya Siri

Ujumbe wote utakaotokana nawe utahifadhiwa kwa siri, na utatumika tu na wahusika wa utafiti kwa malengo ya utafiti pekee. Jina lako halitaorodheshwa popote katika utafiti huu; nambari spesheli itatumika katika utambulizi wako.

Utumizi wa Matokeo ya Utafiti

Nakala za matokeo ya utafiti huu zitahifadhiwa kwa siri katika maktaba ya Idara ya Upasuaji, Chuo Kikuu cha Nairobi. Kwa minajili ya kuendeleza ujuzi wa Sayansi ya Utabibu, huenda haja ya kuarifu matabibu wengine kuhusu utafiti huu itokee. Cha muhimu ni kwamba, ruhusa itaombwa kutoka kwa Afisi ya Maadili ya Utafiti inayosimamia utafiti katika Hospitali kuu ya Kenyatta na Chuo Kikuu cha Nairobi, kabla ya kutumia matokeo ya utafiti huu katika warsha za Sayansi au kuyachapisha katika majarida ya Sayansi. Nyakati hizo, ujumbe wa kibinafsi hautafichuliwa kamwe.

Madhara

Utafiti huu hauna madhara yoyote kwako.

Gharama/Malipo

Hakuna gharama ya ziada wala malipo utakayopata kutokana na kushiriki kwako katika

utafiti

SEHEMU YA PILI: Fomu ya makubaliano

Nimeelezewa utafiti huu kwa kina. Nakubali kushiriki utafiti huu kwa hiari yangu. Nimepata wakati wa kuuliza maswali na nimeelewa kuwa iwapo nina maswali zaidi, ninaweza kumwuliza mtafiti mkuu au watafiti waliotajwa hapa juu.

Jina la Mshiriki_____

Sahihi ya mshiriki _____

Tarehe_____

Kwa wasioweza kusoma na kuandika:

Nimeshuhudia usomaji na maelezo ya utafiti huu kwa mshiriki. Mshiriki amepewa nafasi ya kuuliza maswali. Nathibitisha kuwa mshiriki alipeana ruhusa ya kushiriki bila ya kulazimishwa.

Jina la shahidi_____

Sahihi la shahidi_____

Tarehe _____

Alama ya kidole cha mshiriki

SEHEMU YA TATU: Ujumbe kutoka kwa mtafiti

Nimemsomea mshiriki ujumbe kiwango ninavyoweza na kuhakikisha kuwa mshiriki amefahamu yafuatayo:

- Kutoshiriki au kujitoa kwenye utafiti huu hautamdhuru kupata kwake kwa matibabu.

- Ujumbe kuhusu majibu yake yatahifadhiwa kwa siri.
- Matokeo ya utafiti huu yanaweza chapishwa ili kuwezesha kuzuia na kutibu matatizo yanayosababishwa na breast biopsy.

Ninathibitisha kuwa mshiriki alipewa nafasi ya kuuliza maswali na yote yakajibiwa vilivyo. Ninahakikisha kuwa mshiriki alitoa ruhusa bila ya kulazimishwa.

Mshiriki amepewa nakala ya hii fomu ya makubaliano.

Jina la mtafiti _____

Sahihi ya Mtafiti _____

Tarehe_____

STUDY DATA COLLECTION FORM:

1) Patient Hospital No: ……
2) Patient Age: ……
3) Tumor size at presentation: .....
4) Blood works results:

    Haemogram: .....

UEC: .....

LFT: .....

5) Core Biopsy Results:

……

……

6) Receptor status of the tumour

Oestrogen:

Progesteron:

7) Ultrasound and CxR results at presentation:

……

……

8) Under the study, patient received Neoadjuvant therapy as:

Chemotherapy: …….

Endocrine Therapy: …….

9) Duration of neoadjuvant therapy: …….. Months.

10) Menopausal Status of the patient:

Premenopausal…….

Postmenopausal……

11) Study Results as follows:

- Tumour Size: ……..
- Clinical Response: .....
- Ultrasound results:

……

……

- The patient qualifies for:

  BCS: ……..

  MRM: …….

12) Side Effects of Neoadjuvant Endocrine Therapy (if applicable):

……

……

……

13) Side Effects of Neoadjuvant ChemotherapY (if applicable):

……..…….....
.....

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