ADEQUACY OF AXILLARY LYMPH NODE DISSECTION IN THE MANAGEMENT OF BREAST CANCER AT KENYATTA NATIONAL HOSPITAL

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A dissertation submitted as part fulfillment of the requirements of the University of Nairobi for award of the degree of Master of Medicine (MMed) in General Surgery.

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Declaration

Candidate's declaration

I hereby declare that this study is my original work and has not been presented at any other university.

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List of abbreviations

ALND	-	Axillary Lymph Node Dissection
KNH	-	Kenyatta National Hospital
NCCN	-	National Comprehensive Cancer Network
LN	-	Lymph node
SLN	-	Sentinel Lymph Node
MRM	-	Modified Radical Mastectomy
ER	-	Estrogen receptor
PR	-	Progesterone receptor
HER2	-	Human Epidermal Growth Factor Receptor 2
pN	-	Pathological nodal status
T1	-	Tumor ≤ 2cm in the greatest dimension
T2	-	Tumor >2cm but ≤ 5cm in the greatest dimension
T3	-	Tumor > 5cm in the greatest dimension
T4	-	Tumor of any size with direct extension to the chest wall and or to the skin
RUOQ	-	Right upper outer quadrant
RLOQ	-	Right lower outer quadrant
RUIQ	-	Right upper inner quadrant
RLIQ	-	Right lower inner quadrant
LUOQ	-	Left upper outer quadrant
LLOQ	-	Left lower outer quadrant
LUIQ	-	Left upper inner quadrant
LLIQ	-	Left lower inner quadrant
RO	-	Complete resection of tumor without involved margins
R1	-	Resection with involved margins at pathology

Definitions of operational terms

- Modified radical mastectomy (MRM) – This refers to total mastectomy plus level II axillary lymph none dissection.
- Axillary lymph node dissection – Level II axillary lymphadenectomy i.e. all ipsilateral axillary nodes posterior to and lateral to pectoralis minor muscle
- Adequate Axillary Lymph node dissection – This refers to retrieval of 10 or more nodes in an axillary lymph node dissection specimen
- Consultant surgeon – A General surgeon registered by the medical practitioners and dentist board i.e. at least 2 years post qualification.

Summary

Background: Axillary lymph node status is the most important prognostic factor in the management of breast cancer and is used to guide adjuvant treatment. When axillary lymph node dissection (ALND) is done, retrieval of at least 10 lymph nodes for histopathology analysis is considered optimal. This is to avoid stage migration. Although mastectomy plus ALND is a common operation in our setting we do not know the adequacy of the dissection.

Objective: To determine the adequacy of ALND in the management of breast cancer at Kenyatta National hospital (KNH).

Study design: Cross-sectional study done over one year.

Setting: KNH general surgical wards, and histopathology laboratory.

Patients and methods: Seventy three consenting female patients with histologically confirmed breast cancer who underwent modified radical mastectomy (MRM) were recruited into the study. Patient's demographic data and histopathology data for the ALND specimen were recorded. Histopathology evaluation was performed by the pathologists assisted by technicians. Data on tumor histology, size and number of nodes retrieved was filled into the data sheet.

Main outcome measures: This was done by analysis of number of retrieved lymph nodes as the dependent variable and its association to the patients' demographic data and histopathology data.

Data analysis: The number of lymph nodes retrieved was analyzed as both a continuous and a categorical variable (<10 or ≥10 nodes). Adequacy of ALND was defined as the presence of 10 or more lymph nodes (LN) in the ALND specimen.

Results: The mean number of LN retrieved was 12.12 (median 11, mode 10) and 62 (84.9%) of patients had ≥10 lymph nodes retrieved. Adequacy of ALND was not associated with patients' demographics, tumor factors or the surgeon i.e. consultant surgeon or supervised surgical resident.

Conclusion: Axillary dissection nodal yield is a surrogate marker for the quality of the accuracy of ALND for staging and locoregional control of breast cancer. Surgeons should be aware of current guidelines on adequate axillary dissection for consistency in the extent of ALND.

Introduction

The incidence of breast cancer and associated disease burden is rapidly rising in developing countries. A higher proportion of the cancer burden occurs in less developed regions of the world, both in terms of cancer incidence (56% of new cancer cases in 2008 occur within developing regions) and cancer mortality (63% of cancer deaths) (1).

Axillary lymph node dissection (ALND) provides important prognostic information that influences crucial management decisions. Historically, its role has been in staging and planning adjuvant chemotherapy and also in local control of cancer in both node positive and node negative tumors (2). Node positive status and a higher number of nodes containing metastases are associated with an increased risk of local recurrence and disease progression (3).

A minimum of 10 lymph nodes is required in the ALND specimen for the dissection to provide accurate information for staging (3, 4). This recommendation is derived from a mathematical model developed by Kiricuta and Tausch in 1992 in which they determined that the retrieval of 10 axillary lymph nodes was the cut-off value to allow a 90% certainty of a true negative axillary status after ALND (3). Therefore, number of lymph nodes removed should be at least 10 to exclude misclassification of node-positive patients as node negative (5). This will allow accurate LN staging and hence appropriate adjuvant therapy.

At the Kenyatta national hospital (KNH) sentinel lymph node biopsy is not routinely done and so ALND is almost standard during mastectomy for breast cancer management. As stated earlier a minimum of 10 lymph nodes should be provided for pathologic evaluation in an ALND specimen to accurately stage the axilla (3, 4, and 6). The purpose of this study was to determine the adequacy of axillary lymph node dissection in the management of breast cancer at the KNH by assessing the nodal harvest during MRM.

Literature Review

Cancer of the breast accounts for 5% of all malignancies in Kenya and only second in number to cancer of the cervix with an incidence rate in females of 1.08 per 100,000 person-years (7).The primary site of lymphatic drainage of the breast is the axillary region and, therefore the axillary lymph nodes are often involved in regional metastatic disease in breast cancer. The standard treatment of axillary lymph node metastasis has been axillary lymph node dissection (ALND) though recently the use of sentinel node biopsy has increased and the role of elective ALND both as a staging and therapeutic procedure in clinically node-negative patients is currently questioned (8). However, ALND is indicated for those whom SLN specimen is positive for tumor and for those with clinically positive axillary nodes and remains a widely accepted standard (8, 9). Dissection of the axilla and analysis of the axillary lymph nodes has prognostic and therapeutic impacts. Information about the number or ratio of positive lymph nodes is important for prognostic purposes and helps to determine the need for adjuvant systemic therapy like chemotherapy, endocrine, and targeted biological therapy, and for radiotherapy (10). In addition, the nodal status has been used in the predictive survival scoring systems such as the Nottingham Prognostic Index (9).

Surgical anatomy of the axilla

Axillary lymph nodes have been divided by anatomic levels reflecting the traditional concept that nodal metastases extend sequentially from lateral to medial (11). Level I includes all lymph nodes situated laterally to the lateral margin of the pectoralis minor muscle, level II includes the lymph nodes situated behind the pectoralis minor muscle, and the level III includes the nodes located medially to the medial margin of the muscle, in the space commonly defined as the apex of the axilla.

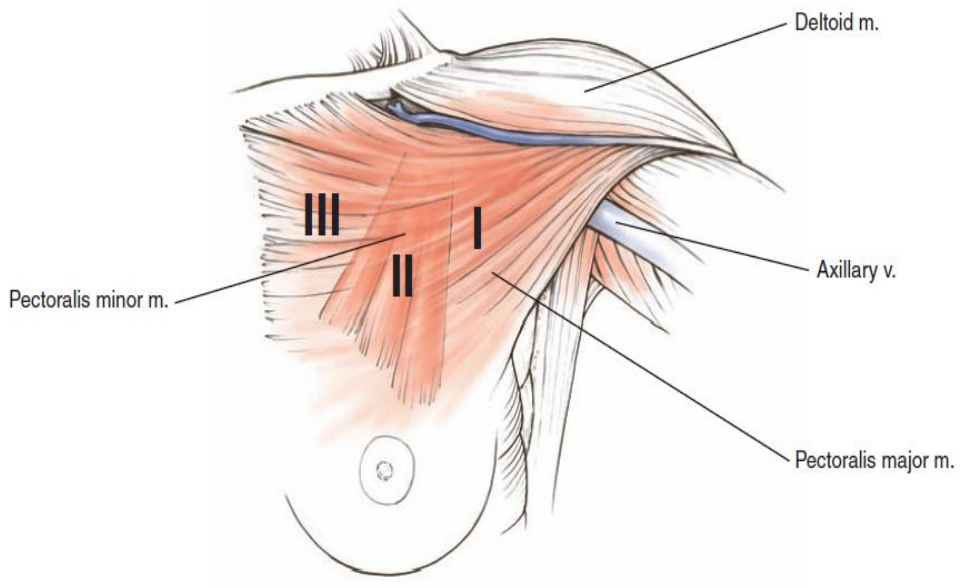


Figure 1: Levels of axillary lymph nodes (Adapted from, Anatomic Basis of Tumor Surgery 2nd Edition, William C. Wood and others)

Kircuta et al (4) found that the total number of axillary lymph nodes to be 21: Level I had 13, Level II had 5, and Level III had 3. However, according toVeronesi et al. the average number of nodes found per patient was 20.3, with 13.5 in Level I, 4.5 in Level II, and 2.3 in Level III (12). Kircuta et al (4) found that in patients with T1, T2 and T3 primary breast cancers a cut off level for a true No axillary status 10 level I lymph nodes should be examined to achieve a 90% probability that there is no other nodal involvement.

ALND can either be complete or partial. Complete ALND involves removal of levels I, II and III axillary nodes while partial ALND involves removal of levels I and II (or any ill-defined portion thereof), and axillary sampling removes a randomly selected node or nodes from the "lower" axilla. The detection of tumor-involved axillary lymph nodes is directly related to the extent of ALND. Hence, the false-negative rate is quite high for both axillary sampling (40%) and level I ALND (10-15%). Level I and II ALND carries only a 2-3%false-negative rate (due to metastasis above levels I and II). Although complete ALND has the highest rate of tumor detection, its high morbidity has led to recommendations against its routine use (13).

Axillary lymph node dissection (Levels I and II) is the recommended staging study in women with stage III breast cancer. It is also indicated in women found to have more than 2 lymph nodes with breast cancer on sentinel lymph node dissection (14).

The NCCN consensus states that at least 10 LN should be provided for pathologic evaluation in order to accurately stage the axilla (14). A lower number of evaluated nodes could lead to stage migration, i.e. the migration of patients into a less advanced nodal stage by investigating fewer lymph nodes. When fewer nodes are examined, lymph node metastases could be missed that would have been demonstrated when more lymph nodes would have been investigated. Four or more positive nodes and 10 or more positive nodes in the axilla change the stage, the definition of the proportions of patients with 4 or more and 10 or more positive nodes is crucial for an accurate staging in lymph node–positive patients (15). Node positive status and the number of nodes containing metastases are associated with an increased risk of local recurrence and disease progression. A cancer with four or more positive nodes has a particularly aggressive phenotype. Nodal status is also considered to be a surrogate marker for the number of acquired and expressed genetic alterations (16).

Nodal retrieval rates vary from study to study. Stravar et al (17) had a node retrieval of less than 10 lymph nodes at 6.3%, Somner et al (16) reported 8% of patients had 10 or fewer lymph nodes collected, Chagpar et al (18) found that 77.8% of the patients had an adequate lymph node dissection and Chakrovarty et al (19) reported 16% node retrieval less than 10%. A local study had a lymph node retrieval of ≥10 lymph nodes of 30% (20).

Factors influencing node retrieval

Predictors of nodal metastases include tumor size, lymphovascular invasion, tumor grade, and patient age. Receptor status, DNA content (ploidy), tumor location, method of detection, and presence of casting-type calcifications on mammography have some predictive value (21). However, no combination of predictors of axillary node status has replaced histopathology examination of ALND specimen which is thought to be the most accurate assessment for presence of nodal metastasis (3, 21).

Primary systemic therapy or neoadjuvant chemotherapy is increasingly being implemented in the treatment of breast cancer. Recent published studies have demonstrated decreased axillary lymph node retrieval in patients after neoadjuvant therapy, resulting in a general acceptance of a low lymph node count after neoadjuvant chemotherapy. Basliam et al (22) and Neuman et al(6) reported significantly lower mean node retrieval for patients treated with neoadjuvant chemotherapy, compared to those without. However, Straver et al (17) did not find decreased lymph node retrieval after neoadjuvant chemotherapy. This brings to question whether administration of neoadjuvant chemotherapy solely is a valid reason for a lower lymph node yield at ALND. They postulated that the contrary results in lymph node retrieval might be due to differences in pathologic assessment and surgical technique. Fibrotic replacement in the axilla in the neoadjuvant group complicates the performance of an accurate lymph node dissection and the pathological workup. The subjective point of view of the surgeon, performing an ALND in a patient who already received systemic therapy with a possible complete axillary remission, may have an impact on the extent of the ALND. On the other hand, the assessment of the dissection specimen by specialized technicians, who have sufficient time to accurately prepare the specimen for the pathologist, might result in a higher lymph node count (17).

It is well established that the number of involved axillary lymph nodes is related directly to the size of the primary carcinoma (12). However, tumor size as an independent predictor of adequacy of ALND has had varying result (18).

There was no difference in node retrieval rates among supervised senior trainees, operating clinical fellows and consultant breast surgeons (19). Chagpar et al (18) found that an increasing percentage of breast practice was associated with a lower rate of adequate ALND. Surgery in an academic setting has been associated with higher lymph node retrieval. This has been attributed to not only academically affiliated surgeons, but also academic pathologists and a laboratory that may have greater resources (23).

Increasing age has been shown to be associated with declining nodal yield. A number of plausible explanations have been put forth, such as surgical pragmatism - older patients are less likely to benefit from potentially small survival advantages conferred by extended ALND whereas the morbidity may have significant functional implications (19).

This may simply reflect either the regression of some lymph nodes spontaneously with older age or presence of fewer nodes in older patients (15, 18).

Axillary nodal yields are not just surgeon dependent but also rely on a careful and thorough pathological analysis of scarred and sometimes fragmented ALND tissue. The diligence with which pathologists search for lymph node, is critical in obtaining an adequate number of nodes for pathological evaluation (18).Nodal yield is a surrogate marker for quality of the accuracy of ALND as a staging procedure and of the completeness of ALND when used for therapeutic purposes (4,5).

Kuru et al (15) found that tumor grade, lymphovascular invasion, ER status, histologic type, and systemic treatment were not independently associated with the number of nodes removed. However, tumor size, patient age, four or more positive nodes, invasion level, pN status, and stage were correlated with the number of removed nodes.

Study Question

What is the adequacy of ALND in the management of breast cancer at KNH?

Study justification

Axillary node status is the single most important prognostic indicator for patients with primary breast carcinoma. The presence of LN metastases decreases 5year survival by approximately 40%. (24). It has been well established that the number of positive lymph nodes (LN) identified in the axilla is related to the adequacy of the axillary dissection and the number of LN removed (25, 26).

Current guidelines recommend dissection of level I and II axillary nodes, which should ensure the removal of 10 nodes (14). An awareness of the variation in the number of lymph nodes examined, the factors associated with it, and the significance of the extent of axillary dissection, in addition to the current guidelines, should lead to greater consistency in the extent of axillary dissection (23).

Study objectives

Main objective

To determine the adequacy of ALND in breast cancer management in KNH.

Specific objectives

- To determine the total nodal harvest after ALND.
- To determine whether there is a difference in nodal harvest depending on level of qualification of the surgeon i.e. surgical resident versus consultant surgeon.
- To determine the effect of patient's age, tumor size, tumor location, hormonal receptor status, HER2 status, tumor grade and use of neoadjuvant chemotherapy on nodal harvest

Methodology

Study design: This was a cross sectional study over a period of twelve months.

Study setting: Kenyatta National Hospital General surgical wards and histopathology laboratory

Study population: Adult female patients with confirmed breast cancer undergoing MRM.

Sampling Procedure: Patients eligible for the study were enrolled consecutively.

Inclusion criteria: All consenting patients with histologically confirmed breast cancer admitted for MRM.

Exclusion criteria: Those with known history of distant metastasis and previous ipsilateral axillary surgery were excluded

Sample size calculation: The sample size was calculated using the formula $n = z^2pq/d^2$

Where

n = sample size

z= standard normal variant corresponding to the 95% confidence interval, and is 1.96

p= prevalence of breast cancer at KNH. Previous study showed that breast cancer accounts for 5% of all malignancies presenting at KNH (7).

q=1-p ; d=the required precision of estimate (0.05)

$n= (1.96)^2 x 0.05 (1-0.05)/ (0.05)^2$

n=73

Data collection:

The patients for the study were enrolled in the general surgical wards by the principal investigator. These were female patients with histologically confirmed breast cancer who had been routinely admitted in the wards for surgery (MRM). Informed consent for participating in the study was administered and routine physical examination done.

The following data about the patient was entered in the standard data collection form: the patient's hospital number, the study number, and the age in years. The size of the tumor was also entered in a pre-prepared data sheet. Data on the use of neoadjuvant therapy was collected. After surgery the level of qualification of the surgeon (whether a consultant or surgical resident) was also sought from the theatre notes and filled in.

In the histopathology laboratory all MRM and ALND specimen was evaluated by the pathologists assisted by the technicians. The procedure included careful gross dissection of the specimen to identify and isolate all palpable lymph nodes including those in the axillary tail. The rest of the adipose tissue remaining and axillary tail was serially sectioned in 2-3 mm to identify small non palpable nodes. The total number of nodes was entered in the data sheet. All retrieved LNs were submitted for histological evaluation and the total number of those positive with tumor entered in the data sheet.

The rest of the breast including the primary tumor was sectioned and the pathologist data on histological type, tumor size, tumor grade presence or absence of lymphovascular invasion and status of resection margins was included in the data sheet. Data on ER, PR receptor status and HER2 status was also included.

Data management and analysis

The data obtained was coded and entered in a Microsoft excel spread sheet by the principal investigator. The number of lymph nodes retrieved was analyzed as both a continuous and a categorical variable (<10 or ≥ 10 nodes) and was treated as dependent variable. Adequacy of ALND was defined as the presence of 10 or more LN in the ALND specimen. Univariate analysis of independent variables; the effect of patient demographic data, histologic data (tumor size, tumor grade, presence of lymphovascular invasion and tumor location), surgeon's experience and use of neoadjuvant chemotherapy on adequacy of ALND was performed using chi-square test for dichotomous variables and student t test for continuous variables. The size of the tumor in the pathological staging was used for analysis. Statistical analysis was performed using SPSS Version 17.0 (Chicago, IL), with significance level set at $p = 0.05$.

Ethical consideration

Institutional consent was sought and granted from the Department of surgery, University of Nairobi (UON) and the Ethics and Research Committee of KNH.

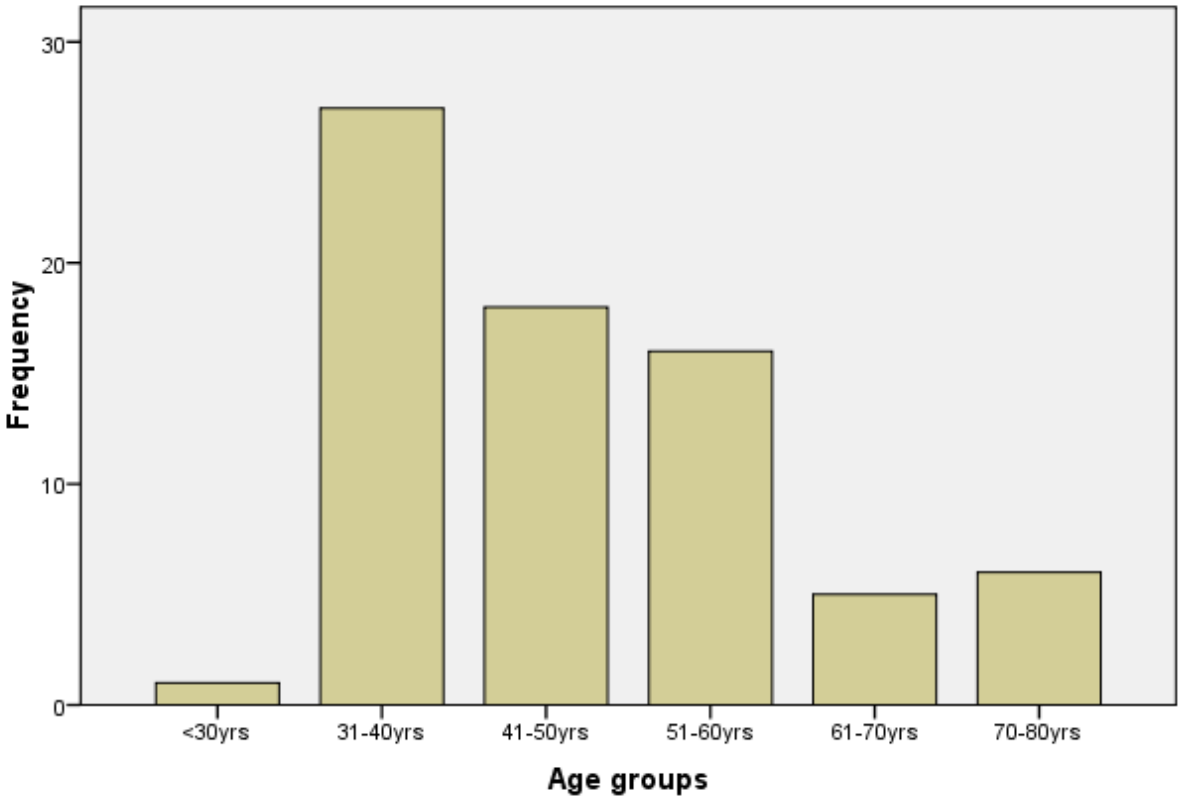
Informed consent was sought from the participants.

Confidentiality and privacy was observed.

Results

The study cohort comprised of 73 women with breast cancer undergoing modified radical mastectomy. The cohort had a mean age of 48 years (range 30-80 years).

Figure 2: Age distribution



All patients had a palpable breast tumor. The tumor was located in the upper outer quadrant in 39.7% of the patients (Table 1). Most tumors were in T2 (52.1%) stage at the time of surgery. Consultant surgeons performed the surgery (modified radical mastectomy) in 44 (60.3%) of the patients.

The histology of the tumor was ductal carcinoma in 66(90.3%) of the patients with tumor grade 2 and 3 comprising 90.4%. Lymphovascular invasion and positive resection margins were found in 53 (72.6%) and 10 (13.7%) of the submitted specimens respectively. The hormonal and HER2 receptor status was done in 59 (80.8%) of the submitted specimens. Twelve (20.3%) of these specimens had triple negative breast cancer.

Table 1: clinicopathological characteristics of the breast cancer

Characteristics	No of cases (%)
Tumor size	
T1	12(16.4%)
T2	37(50.7%)
T3	24(32.9%)
Site	
Upper outer quadrant	29(39.7%)
Lower outer quadrant	12(16.4%)
Upper inner quadrant	22(30.1%)
Lower inner quadrant	6(8.2%)
Central	4(5.5%)
Histology	
DCIS	2(2.7%)
Ductal	66(90.4%)
Lobular	4(5.5%)
Other	1(1.4%)

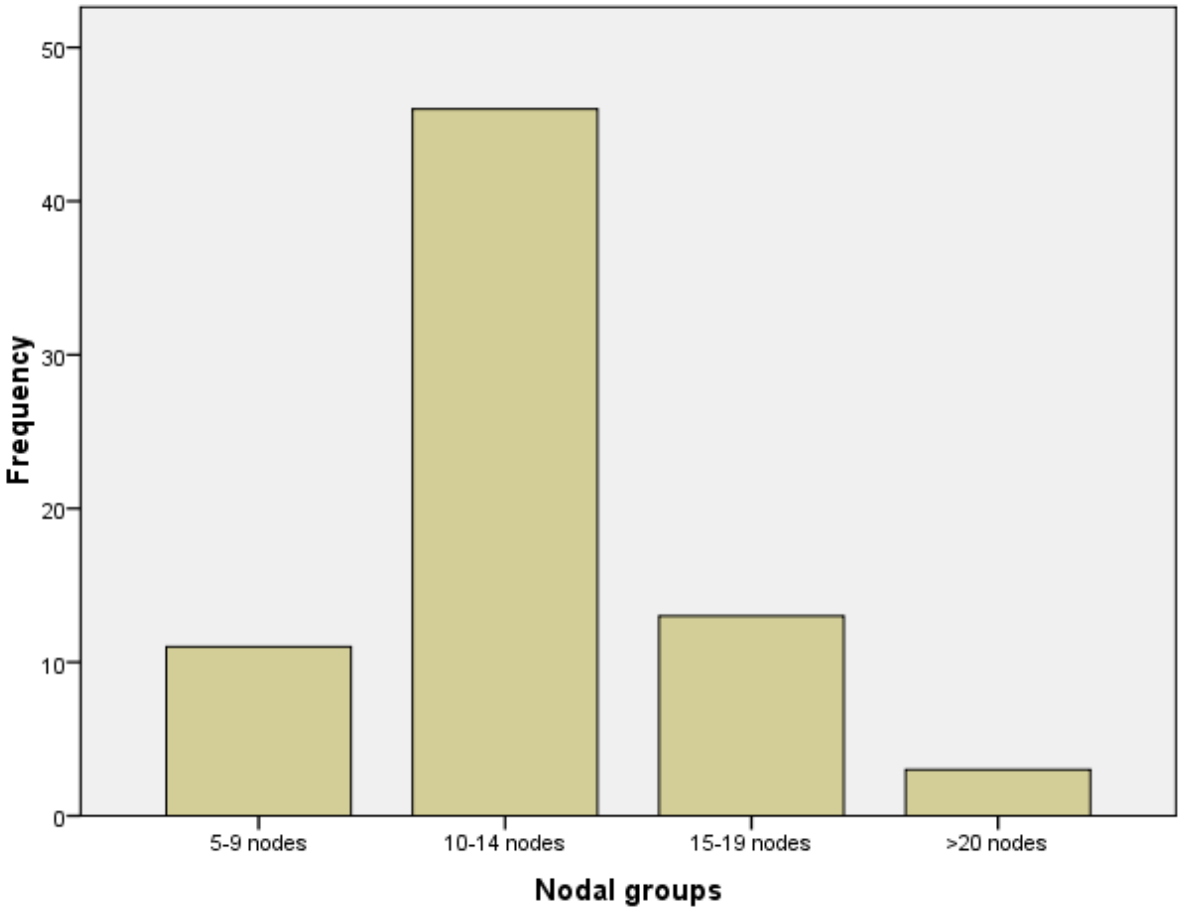
Tumor grade	
I	**7(9.6%)**
II	**35(47.9%)**
III	**31(42.5%)**
Lymphovascular invasion	
Yes	53(72.6%)
No	20(27.4%)
Resection margins	
R0	63(86.3)
R1	10(13.7)
Receptor status	
ER negative	21(28.8%)
ER positive	38(52.1%)
PR negative	22(30.1%)
PR positive	37(50.7%)
HER2 negative	47(64.4%)
HER2 positive	12(16.4%)

Receptor status was not done in 14 (19.2%) of the specimens

Nodal harvest

The average total lymph node harvest was 12.12 (Median 11, mode 10). Sixty-two (84.9%) of the patients had an adequate axillary lymph node dissection (recommended number of lymph node harvest of 10 or more).

Figure 3: Total nodal harvest



Nodal harvest and surgeon's qualification

There was no difference between consultant surgeons and residents in the total nodal count, positive nodes and adequacy of axillary lymph node dissection. Though the positive resection margins were higher in surgeries done by residents (17.25% vs 12.8%) , it was not statistically significant (p= 0.505).

Table 2: Surgeon qualification and nodal harvest

	Consultant	Resident	p-value
Total nodal count mean	12.18	12.03	0.869
Positive nodes mean	3.68	3.20	0.668
Adequate nodal harvest (>10)	38(86.3%)	24(82.75%)	0.744

On univariate analysis no factor correlated with adequacy of ALND (table 3)

Table 3: Univariate analysis

Characteristic	No. of cases (%) adequate ALND	P value
Patients age		0.828
Tumor		0.613
T1	11(91.7%)	
T2	30(81.1%)	
T3	21(87.5%)	
Site		0.245
Upper outer quadrant	24(82.7%)	
Lower outer quadrant	11(91.7%)	
Upper inner quadrant	19(86.4%)	
Lower inner quadrant	6(100%)	
Central	2(50%)	
Neoadjuvant therapy		0.569
Yes	4(80%)	
No	58(85.3%)	
Histology		0.840
DCIS	2(100%)	
Ductal	56(84.8%)	
Lobular	3(75%)	
Other	1(100%)	

Tumor grade		0.977
I	6(85.7%)	
II	30(85.7%)	
III	26(83.9%)	
Number of Positive nodes		0.218
Lymphovascular invasion		0.716
Yes	44(83%)	
No	!8(90%)	
Resection margins		0.641
R0	54(85.7%)	
R1	8(80%)	
ER		0.829
positive	33(86.8%)	
negative	17(81%)	
PR		0.885
positive	32(86.5%)	
negative	18(81.8%)	
HER2		0.213
positive	12(100%)	
negative	38(80.9%)	

Discussion

Axillary lymph node dissection in patients with breast cancer has therapeutic and prognostic applications. It offers local control that prevents axillary recurrences and the information obtained from the number of positive lymph nodes allows for accurate staging and adjuvant treatment decisions (18). It is recommended to offer post mastectomy radiation therapy in patients with 4 or more positive lymph nodes as it indicates a more aggressive disease (14). Adequate axillary lymph node dissection, to adequately stage the axilla, involves the submission of a minimum of 10 lymph nodes for pathological evaluation (3, 14, 18).

The results have demonstrated comparable median nodal yields and adequacy of ALND as other studies, such as Chagpar et al (18). This study had median nodal yields of 11 and adequate ALND rates of 84.9%. The adequacy of ALND reported in other studies ranges from 49% (23) to 93% (17). A local study done previously had shown adequate ALND dissection rates of 30% (20). The increase in the level of adequate ALND could be attributed to the improvement in the quality of management of patients with breast cancer and also perhaps an indicator of increased vigilance at pathology. This study did not find a difference in the number and adequacy of nodal retrieval rates between the consultant surgeons and supervised surgical residents. The present study was done in an academic institution; the surgical residents were being supervised by consultant surgeons hence the lack of difference in the nodal retrieval rates. In addition, it has been reported that academic affiliation of the surgeons and surgery in a teaching hospital has been associated with adequate ALND (18, 23). Chakravorty et al (19) found no difference in nodal retrieval rates among supervised senior trainees, operating clinical fellows and consultant breast surgeons.

Age, tumor site and size, tumor grade, lymphovascular invasion, histology type, neoadjuvant chemotherapy, hormonal and HER2 receptor status have been reported to correlate with nodal retrieval rates (6, 15, 17, 18, 22, 23). The influence of these factors in nodal retrieval rates vary between studies. In the current study no correlation was found between these factors with the nodal retrieval rates and adequacy of ALND. Kuru et al (15) and Chagpar et al (18) reported tumor factors such as size, grade, lymphovascular invasion, to correlate with the number of lymph nodes retrieved. However, Petrik et al (23) found no association between tumor factors and nodal retrieval rates but found association between age (younger age < 40yrs) and surgeon's academic affiliation to be associated with high nodal retrieval rates. Petrik et al (23) in addition,

mentioned a Danish study with >13000 patients that did not find association between age and nodal retrieval. Concerning nodal retrieval rates after neoadjuvant chemotherapy, Straver et al (17) did not find decreased lymph node retrieval while Neumann et al (6) and Baslian et al (22) reported significantly lower nodal retrieval rates. In our study, the number of patients on neoadjuvant chemotherapy was too low (n=5, 6.5%) for proper analysis.

Due to variation in association between studies, and lack of association in the current study we look forward to further studies with larger sample sizes in our location.

Conclusion

Axillary dissection nodal yield is a surrogate marker for the quality of the accuracy of ALND for staging and locoregional control of breast cancer. Surgeons and pathologists should be aware of current guidelines on adequate axillary dissection and it's importance in the evaluation of the axilla. The study has adequacy of 84.9% which is desirable and compares favorably with other studies.

Recommendations

Further studies with larger sample sizes and also incorporating outcome data in our setting would be welcome since our results did not show any correlation of adequate ALND with any of the variables being studied and the fact that there is no consensus from literature.

Study time frame

Activity	Feb – June 2012	July – Nov 2012	Dec 2012 – Dec 2014	Jan 2014 - Mar	April 2014.
Proposal writing & presentation to department of surgery					
Submission for ethical approval					
Data collection					
Data analysis & dissertation writing					
Presentation of results					

Budget estimates

ITEM	**COST**
Research fees (KNH/ERC)	1,500
Technicians' honoraria	20,000
Stationery	25,000
Statistician	25,000
Dissertation writing & printing	25,000
Miscellaneous	10,000
Total	**106,500**

Budget explanation

- Technicians' honoraria – This was meant to motivate the technicians assisting the pathologist.
- No money was budgeted for ER, PR AND HER 2 receptor status testing since this was already routinely being done as part of the BRECC registry.
- **NB**: The study was funded by the principal investigator.

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Appendices

Appendix 1: Data collection sheet

1. Study number ☐ 2. Hospital number ☐ 3. Weight (Kg) ☐ 4. Height (Cm) ☐ Age_____

5. Breast lump ◯ Y ◯ N (specify location and size below)

a. ☐ T1 b. ☐ T2 c. ☐ T3 d. ☐ T4

6. ☐ RUOQ 7. ☐ RLOQ 8. ☐ RUIQ 9. ☐ RLIQ

10. ☐ LUOQ 11. ☐ LLOQ 12. ☐ LUIQ 13. ☐ LLIQ 14. ☐ Peri areolar

15. Neoadjuvant therapy given ◯ Y ◯ N

16. Surgeon: ☐ Consultant ☐ Resident

Pathology

1. Tumor Size

a. ☐ No carcinoma identified T0

b. ☐ Tumor < 2cm diameter T1

c. ☐ Tumor 2-5cm diameter T2

d. ☐ Tumor >5cm diameter T3

e. ☐ Tumor fixation to chest wall/skin T4

2. Histological type

a. ☐ DCIS

b. ☐ LCIS

c. ☐ Ductal ca

d. ☐ Lobular ca

e. Other _____

3. Tumor Grade : ☐ I ☐ II ☐ III ☐ Not done

4. Axillary lymph nodes: ☐ Total nodal harvest ☐ No of positive nodes

5. Lymphovascular invasion ◯ Y ◯ N

6. Resection margins : ☐ Clear ☐ Not Clear ☐ Not reported

7. Hormonal receptor status

a. ER ◯ +ve ◯ -ve ◯ not reported

b. PR ◯ +ve ◯ -ve ◯ not reported

c. HER2 ◯ +ve ◯ -ve ◯ not reported

Appendix 2: Study Consent form

Adequacy of axillary lymph node dissection in the management breast cancer at Kenyatta National Hospital

English version

This Informed Consent form is for adult female patients with confirmed breast cancer admitted at Kenyatta National Hospital for surgery – modified radical mastectomy. We are requesting these patients to participate in this research project.

Principal investigator: Dr. Gichere Nderitu Raphael
Institution: School of Medicine, Department of surgery- University of Nairobi
Supervisors: Dr. Joseph Githaiga, Prof. Saidi Hassan and Dr. Parmenas Okemwa.

This informed consent has three parts:

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

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

Part I: Information sheet

My name is Dr. Gichere Nderitu Raphael, a post graduate student at the University of Nairobi's School of Medicine. I am carrying out a study to determine the adequacy of ALND in the management of breast cancer and the factors that may affect it at KNH. This will be determined by doing a formal node retrieval and count in the laboratory after your surgery. I will also do some clinical examination on you and check some clinical notes from your file on staging of the disease. However I will not be involved in your actual surgery or management process as this has been / will be discussed by the ward doctors concerned. The results of this study will be useful in letting us know whether that aspect of the surgery is up to required standard.

I am inviting you to participate in my study out of your own free will. You will be given the opportunity to ask questions before you decide and you may talk to anyone you are comfortable with about the research before making a decision. After receiving this information concerning the study, please seek for clarification from either myself or my assistant if there are words or details which you do not understand.

If you agree to participate, you will be asked to provide personal information and other details related to breast cancer. All the information which you provide will be kept confidential and no one but the researchers will see it. Your name will not appear in any document or any specimen container. The information about you will be identified by a number and only the researchers can relate the number to you as a person. Your 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).

Your involvement in this research will be through an interview, clinical evaluation and laboratory evaluation of the mastectomy specimen. You will not expose yourself to any risks if you consent to participate in the study and you will not be denied medical care if you decline to participate in the study. There will be no extra cost incurred for participating in the study. You may stop participating at any time with no consequences whatsoever. All the information that you give us will be used for this research only.

This proposal has been reviewed and approved by the KNH/UoN-ERC which is a committee whose work is to make sure research participants like you are protected from harm. The contact information is given below if you wish to contact any of them for whatever reason;

- Secretary, KNH/UoN-ERC
  P.O. Box 20723 KNH, Nairobi 00202
  Tel 726300-9
  Email: uonknh_erc@uonbi.ac.ke

- University of Nairobi research supervisors
  Dr. Joseph Githaiga, MMed FCS (ESCA)
  Senior Lecturer and Thematic Head, Department of Surgery,
  University of Nairobi.
  jackiegithaiga@yahoo.com
  P.O. Box 19676 KNH, Nairobi 00202
  Tel # 0202726300

  Prof. Saidi Hassan, BSc (Anat), MMed, FCS (ESCA), FACS
  Associate Professor, Department of Human Anatomy,
  University of Nairobi.
  hsaidi@uonbi.ac.ke
  P.O. Box 19676 KNH, Nairobi 00202
  Tel # 0202726300

- Dr. Parmenas Okemwa Miinda (MMed. Pathology)
  Lecturer, Department of Pathology,
  University of Nairobi.
  P.O. Box 19676 KNH, Nairobi 00202
  Tel # 0202726300

- Principle researcher:
  Dr. Gichere Nderitu Raphael
  Department of Surgery, School of Medicine, University of Nairobi
  P.O. Box 19676 KNH, Nairobi 00202
  Mobile phone 0722659864

Part ii: Consent certificate by patient

I……..freely give consent of myself or for my proxy (Name…….) to take part in the study conducted by Dr. Gichere Nderitu Raphael, the nature of which has been explained to me by him/his research assistant. I have been informed and have understood that my participation is entirely voluntary and I understand that I am free to withdraw my consent at any time if I so wish and this will not in any way alter the care being given to me or my proxy. The results of the study may not directly be of benefit to me or my proxy but may benefit the Medical professionals to better understand whether ALND as explained is adequately done or improvements are needed.

……

Signature/left thumb print (Participant/Next of kin)

Date……

Day/Month/Year

Thumb print of participant if Unable to sign due to illiteracy

Statement by the witness if participant is illiterate

I have witnessed the accurate reading of the consent form to the participant, and the individual has had the opportunity to ask questions. I confirm that the individual has given consent freely.

Name of witness……

Signature of witness……..

Date……

Day/Month/Year

Part iii: 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 in any way compromise the quality of care and treatment given to the patient.
- All information given will be treated with confidentiality.
- The results of this study might be published to enhance knowledge and to help improve the quality of care for patients undergoing breast cancer management.

I confirm that the participant was given an opportunity to ask questions about the study, and all the questions asked by the participant 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……

Day/Month/Year

Appendix 3: Fomu ya idhini

(i) Sehemu ya kwanza – Maelezo ya Daktari mtafiti.

Mimi ni Daktari Gichere Nderitu Raphael, kutoka shule ya Elimu ya Afya idara ya upasuaji Chuo Kikuu cha Nairobi (University of Nairobi). Ninafanya utafiti kuchunguza utoshelevu wa kiwango cha upasuaji katika matibabu ya saratani ya matiti. Utafiti huu ninafanya kwa kuchunguza nambari ya lymph nodes baada ya upasuaji katika maabara. Mimi mwenyewe sitahusika kwa upasuaji ama hali ya kuchagua jinsi ya matibabu – hii itakuwa kazi ya daktari wako kama vile ameshakueleza ama atakavyokuelezea. Katika utafiti huu utatakiwa kutoa tarifa yako binafsi. Habari zote zitakazokusanywa zitashughulikiwa kwa siri na hazitasambazwa ila tu kwa ruhusa kutoka kwa mkurughenzi mkuu wa utafiti wa chuo kikuu cha Nairobi na hospital kuu ya Kenyatta.

Utafiti huu utawasaidia madaktari kuulewa kama wanafanya upasuajiwa kamili na hivyo basi kuweza kuwahudumia wagonjwa wao kwa ubora zaidi. Kuhusika kwako kwenye utafiti huu hauna malipo yeyote ila ni kwa hiari yako mwenyewe na pia unaweza kujiondoa kwa utafiti wakati wowote bila kuhatarisha matibabu yako katika Hospitali Kuu ya Kenyatta. Naomba mimi ama wasaidizi wangu wakuulize maswali ambayo yatajibiwa kwa fomu maalum. Habari yote ambayo utatuarifu ni ya siri kati yako na watafiti na haitaenezwa kwa watu wengine.

Jina lako halitaandikwa kwenye fomu yoyote inayotumika na watafiti isipokuwa zile za kawaida za hospitali.

Unaweza kuuliza maswali yoyote kuhusu utafiti huu na ukiridhika tafadhali ijaze fomu ya idhini iliyopo hapa chini. Unaweza pia kuuliza swali lolote baadaye kwa kupiga simu ya mtafiti mkuu ama mkuu wa idara ya upasuaji katika chuo kikuu cha Nairobi ama walimu wasimamizi wa utafiti ukitumia nambari za simu zifuatazo;

- Katibu wa utafiti, Hospitali kuu ya Kenyatta na Chuo kikuu cha Nairobi. Sanduku la Posta 20723 KNH, Nairobi 00202. Nambari ya simu 726300-9.

Walimu wakuu wa Chuo kikuu cha Nairobi:

1. Daktari Joseph Githaiga,
   MBChB, M.Med Surgery, F.C.S (ECSA)
   Sanduku la Posta 19676 KNH, Nairobi 00202. Nambari ya simu: 0202726300
2. Profesa Saidi Hassan,
   BSc. (Anat) ,MBChB (U.O.N), M.Med Surgery, F.C.S (ECSA),FACS.Sanduku la Posta 19676 KNH, Nairobi 00202. Nambari ya simu: 0202726300
3. Daktari Parmenas Okemwa,
   MBChB, M.Med Pathology
   Sanduku la Posta 19676 KNH, Nairobi 00202. Nambari ya simu: 0202726300

- Mtafiti: Daktari Gichere Nderitu Raphael,
  Idara ya Upasuaji ya Shule ya Afya – Chuo kikuu cha Nairobi,
  Sanduku la Posta 20154 GPO Nairobi 00100. Nambari ya simu ya mkononi 0722659864

(ii) Sehemu ya pili – Idhini ya mgonjwa.

Mimi (Jina)……..kwa hiari yangu ama kwa hiari ya mgonjwa wangu (Jina la Mgonjwa.....
…….) nimekubali kushiriki katika utafiti huu unaofanywa na Daktari Gichere Nderitu Raphael kutokana na hali ambazo nimeelezwa nasio kwa malipo ama shurutisho lolote.

Nimeelewa kwamba ninaweza kujiondoa wakati wowote nitakapo na hatua hii haitahatarisha matibabu ninayopata ama anayoyapata mgonjwa wangu. Matokeo ya utafiti hayana manufaa kwangu binafsi lakini yaweza kuwa na manufaa kwa wagonjwa wengine kwa jumla na hata madaktari wenyewe, kwa kuendeleza elimu.

……

Sahihi/ama alama ya kidole cha gumba katika sanduku →

Tarehe…….....

Siku/Mwezi/Mwaka

Jina la shahidi……

Sahihi…….

Tarehe…….

(Siku/Mwezi/Mwaka)

(iii) Sehemu ya tatu – Dhibitisho la mtafiti

Hii ni kuidhinisha ya kwamba nimemueleza mshiriki ama msimamizi wake kuhusu utafiti huu na pia nimempa nafasi ya kuuliza maswali. Nimemueleza yafuatayo;

- Kwamba kushiriki ni kwa hiari yake mwenyewe bila malipo.
- Kushuriki hakuta sababisha madhara ama kuhatarisha maisha kamwe.
- Anaweza kujiondoa kutoka kwa utafiti huu wakati wowote bila kuhatarisha matibabu anayoyapata katika hospitali kuu ya Kenyatta.
- Habari ambazo atapeana hazitatangazwa hadharani bila ruhusa kutoka kwake (mshiriki) napia kutoka kwa mdhamini mkuu wa utafiti wa hospitali kuu ya Kenyatta na chuo kikuu cha matibabu.

Jina la mtafiti ama msimamizi wake……

Sahihi……..

Tarehe…….

(Siku/Mwezi/Mwaka)

Appendix 4: Declaration Form for Students

UNIVERSITYOFNAIROBI

Declaration of Originality Form

This form must be completed and signed for all works submitted to the University for examination.

Name of Student_____

Registration Number_____

College _____

Faculty/School/Institute_____

Department_____

Course Name_____

Title of the work_____

DECLARATION

1. I understand what Plagiarism is and I am aware of the University's policy in this regard
2. I declare that this_____(Thesis, project, essay, assignment, paper, report, etc) is my original work and has not been submitted elsewhere for examination, award of a degree or publication. Where other people's work, or my own work has been used, this has properly been acknowledged and referenced in accordance with the University of Nairobi's requirements.
3. I have not sought or used the services of any professional agencies to produce this work
4. I have not allowed, and shall not allow anyone to copy my work with the intention of passing it off as his/her own work
5. I understand that any false claim in respect of this work shall result in disciplinary action, in accordance with University Plagiarism Policy.

Signature_____

Date_____

Appendix 5: Declaration Form for Staff

UNIVERSITY OF NAIROBI

Declaration of Originality Form

This form must be completed and signed for all scholarly works produced.

Name of Staff _____

Payroll Number _____

College _____

Faculty/School/Institute_____

Department _____

Title and bibliographic details of the work

_____

DECLARATION

1. I understand what plagiarism is and I am aware of the University's policy in this regard.

2. I declare that this _____ scholarly work (Paper, book chapter, monograph, review, etc) is my original work. Where other people's work, or my own work has been used, this has properly been acknowledged and referenced in accordance with

The University of Nairobi's requirements.

3. I have not allowed, and shall not allow anyone to copy my work with the intention of passing it off as his/her own work.

4. I understand that any false claim in respect of this work shall result in disciplinary action, in accordance with University Plagiarism Policy.

Signature _____

Date _____

Appendix 6: Copy of ethical approval

UNIVERSITY OF NAIROBI
COLLEGE OF HEALTH SCIENCES
P O BOX 19676 Code 00202
Telegrams: varsity
(254-020) 2726300 Ext 44355
Ref: KNH-ERC/A/339

KNH/UON-ERC
Email: uonknh_erc@uonbi.ac.ke
Website: www.uonbi.ac.ke
Link:www.uonbi.ac.ke/activities/KNHUoN

KENYATTA NATIONAL HOSPITAL
P O BOX 20723 Code 00202
Tel: 726300-9
Fax: 725272
Telegrams: MEDSUP, Nairobi
13 December 2012

KENYATTA NATIONAL HOSPITAL APPROVED 13 DEC 2012 ETHICS & RESEARCH COMMITTEE

Dr. Gichere Raphael Nderitu
Dept. of Surgery
School of Medicine
University of Nairobi

Dear Dr. Nderitu

RESEARCH PROPOSAL: ADEQUACY OF AXILLARY LMPH NODE DISSECTION IN THE MANAGEMENT OF BREAST CANCER AT KENYATTA NATIONAL HOSPITAL (P401/07/2012)

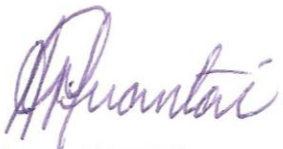
This is to inform you that the KNH/UoN-Ethics & Research Committee (KNH/UoN-ERC) has reviewed and **approved** your above revised proposal. The approval periods are 13th December 2012 to 12th December 2013.

This approval is subject to compliance with the following requirements:

a) Only approved documents (informed consents, study instruments, advertising materials etc) will be used.
b) All changes (amendments, deviations, violations etc) are submitted for review and approval by KNH/UoN ERC before implementation.
c) Death and life threatening problems and severe adverse events (SAEs) or unexpected adverse events whether related or unrelated to the study must be reported to the KNH/UoN ERC within 72 hours of notification.
d) Any changes, anticipated or otherwise that may increase the risks or affect safety or welfare of study participants and others or affect the integrity of the research must be reported to KNH/UoN ERC within 72 hours.
e) Submission of a request for renewal of approval at least 60 days prior to expiry of the approval period. (*Attach a comprehensive progress report to support the renewal*).
f) Clearance for export of biological specimens must be obtained from KNH/UoN-Ethics & Research Committee for each batch of shipment.
g) Submission of an *executive summary* report within 90 days upon completion of the study
This information will form part of the data base that will be consulted in future when processing related research studies so as to minimize chances of study duplication and/or plagiarism.

For more details consult the KNH/UoN ERC website **www.uonbi.ac.ke/activities/KNHUoN**

Yours sincerely



PROF. A.N. GUANTAI
SECRETARY, KNH/UON-ERC

c.c. The Deputy Director CS, KNH
The Principal, College of Health Sciences, UoN
The Dean, School of Medicine, UoN
The Chairman, Dept.of Surgery, UoN
The HOD, Records, KNH
Supervisors: Dr. Joseph Githaiga, Prof. Said Hassan, Dr. Parmenas Okemwa Miinda