HISTOPATHOLOGY REPORTING AND BIOMARKER TESTING OF INVASIVE BREAST CANCER AT KENYATTA NATIONAL HOSPITAL: AN AUDIT OF THE SYNOPTIC REPORTS AND DETERMINATION OF ER/PR/HER2 RECEPTOR PROFILES

A DISSERTATION SUBMITTED IN PARTIAL FULFILLMENT FOR THE AWARD OF DEGREE IN MASTERS OF MEDICINE, HUMAN PATHOLOGY, AT THE UNIVERSITY OF NAIROBI

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DECLARATION

I, Dr Priscilla Githinji, declare that this is my original work and has not been presented in any other university or learning institution.

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DEDICATION

I dedicate this work to Andrew Karani, my parents Mr. and Mrs. Githinji, my brother Erastus and my sisters Roselyn and Joan.

LIST OF ABBREVIATIONS AND ACRONYMS

ASCO-	American Society of Clinical Oncology
BRCA-	Breast cancer
CAP-	College of American Pathologists
CME-	Continuous Medical Education
CSF-	Cerebrovascular fluid
DAB-	Diaminobenzidine
DCIS –	Ductal carcinoma in situ
DISH-	Dual in-situ hybridization
EDTA-	Ethylene Diamine tetra-acetic acid
ER -	Estrogen receptor
ERC-	Ethical Research Committee
FISH-	Fluorescent in situ hybridization
GIT-	Gastrointestinal tract
H&E-	Hematoxylin and Eosin
HER 2-	Human epidermal receptor 2
KNH-	Kenyatta National Hospital
LCIS-	Lobular carcinoma in situ
NGS-	Nottingham Grading System
NST-	No special type
PBS-	Phosphate buffered saline
PI-	Principal Investigator
PR-	Progesterone receptor
SOP-	Standard Operating Procedures
TNM-	Tumor, Node, Metastasis
UON-	University of Nairobi

OPERATIONAL DEFINITIONS

Synoptic Reporting is the use of structured checklists to produce standardized clinical documentation.

Biomarker testing is a group of tests that assess molecular signs of health e.g. cancer. It's useful in screening, diagnosis and treatment planning of various cancers. In breast cancer it involves the testing for ER/PR/HER2 receptors. These receptors have predictive and prognostic significance.

Clinical audit is a quality improvement process that seeks to improve patient care and outcomes through a systematic review against explicit criteria and the implementation of change.

Quality Assurance is any systematic process of determining whether a product or service meets specified requirements.

ABSTRACT

Background

Breast cancer is the leading cause of cancer morbidity and the third cause of cancer mortality after esophageal and cervical cancer among women in Kenya. Breast cancer histopathology reports form the basis upon which management and prognosis of the breast cancer is based. As a result, continued efforts have been made to improve reporting standards and ensure that histopathology reports are complete and contain all relevant clinical information.

Traditionally at Kenyatta National Hospital, a narrative reporting system was used. Since 2016 synoptic reporting was implemented to improve reporting standards. To ensure that the standards of reporting breast cancer histopathology are maintained continuous audits and feedback should be done routinely.

Main Objective: To audit the synoptic reporting of invasive breast cancer histopathology at Kenyatta National Hospital laboratory and determine the Estrogen receptor/Progesterone receptor/Human Epidermal Growth Factor Receptor profiles.

Design: Laboratory based retrospective cross sectional study

Setting: University of Nairobi/ Kenyatta National Hospital Anatomic Pathology Laboratory

Study population: Invasive breast carcinoma synoptic reports, immunohistochemistry reports and tissue blocks from January 2016 to December 2018.

Results: The age of patients ranged from 23 to 80 years with the most affected age group being 40-49 years with 39.8%. The surgical procedure done was documented in 96.7% of the reports, laterality in 96%, specimen integrity in 89.4%, tumor size in 100%, specimen gross description in 76.4%, lymph node sampling in 100%, tumor site in 89.4% and tumor focality in 91.9%. For microscopic details histologic type and grade was indicated in 100%, presence or absence of ductal carcinoma in-situ in 97.6%, extensive intraductal component in 45.8%, architecture in 69.4%, nuclear grade in 55.6% and necrosis 47.2%. Presence or absence of lobular carcinoma in situ was indicated in 47.2%. Margin closest to tumor and distance was indicated in 69.4% of the reports and where the margin was involved the margin was indicated in 100% of the reports. Presence or absence of Paget's disease was reported in 91.9%, lymphovascular invasion

in96.7%, skin involvement in 81.3%, skeletal muscle involvement in 80.5%, treatment effect in 47.5%, staging in 83.7% and microcalcifications in 88.6%. The number of Lymph node involved was indicated in 100% of the reports. In 65% of the reports 10 or less lymph nodes had been sampled. Micrometastasis was indicated in 26% while extranodal extension was indicated in 73.1%.

ER/PR receptors were reported as per the Allred score and college of American pathologists guidelines while HER2 was reported as per the ASCO guidelines. Receptor profiles seen were as follows: ER positive tumors were 69.9%, PR positive 62.6% and HER2 positive 18.7%. ER/PR positive and HER2 negative tumors were 60.2%, triple positive tumors were 8.1% and triple negative tumors were 18.7%.

Grade 3 tumors were seen in younger patients and also in triple negative hormonal status. ER/PR positive and HER2 negative receptor profile was associated with lower histological tumor grades.

Triple negative receptor status was associated with higher histological grades

Conclusion: The introduction of synoptic reporting has led to an increased level of completeness of pathology reports with an average level of completeness of 82%. The reporting of extensive intraductal component, architectural pattern, nuclear grade and necrosis in Ductal carcinoma in situ, microscopic margins, treatment effect and presence or absence of Lobular carcinoma in situ is still sub-optimal.

Recommendations: Anatomic Pathologists/registrars should be sensitized on the clinical utility and need to report DCIS, LCIS, microscopic margins and treatment effect. Based on observed incompleteness, periodic audits should be carried out with a target of achieving complete reports.

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1.0 INTRODUCTION

Breast cancer is the leading cause of cancer morbidity and mortality among women. Globally it's the second most common cancer in women and the leading cause of cancer deaths among women. Due to its increasing incidence; a lot of effort has been made to improve screening, laboratory diagnosis and treatment (1,2).

In Kenya, the Kenya cancer control strategy 2017-2022 aims to improve laboratory services as regards cancer screening and diagnosis (3). As knowledge on cancers improves there is need to keep up to date with the diagnosis and reporting of cancers.

Histopathology reports form the basis on which management of breast cancer is based. It is therefore paramount to ensure that all the reports contain all the relevant information important to the clinician(4). Several organizations including the college of American pathologists and the Royal College of pathologists have set guidelines for the handling and reporting of breast cancer specimens (5,6).

Previously pathology reports were narrated or dictated. This led to incomplete reports that lacked important information needed for management of cancer. This has led to the introduction of synoptic reporting which aims to improve pathology reports. Synoptic reports are standardized as they use a pre-defined checklist. This aims to improve accuracy, timeliness, completeness and proper information transfer (7).

Auditing is a useful tool in a laboratory quality management system. It seeks to improve patient care and outcome. It evaluates laboratory processes against set standards and it serves to ensure compliance to set standards, identify problem areas and offer corrective measures (8). Auditing in the histopathology laboratory is part of the internal quality assessment system. It serves to assess, monitor and evaluate histopathology services. Retrospective analysis of performance of new methods is often employed(9). Assessing adequacy of pathology reports involves examining both gross and microscopic descriptions. This helps to determine the completeness of reports (10).

2.0 LITERATURE REVIEW

2.1 Breast Cancer Epidemiology

In 2018 the global cancer burden was estimated at 18.1 million new cancer cases and 9.6million cancer deaths. Breast cancer is the second most common cancer overall after lung cancer (2.1 million cases, 11.6%). It is the commonest cancer in women and accounts to about 25% of all cancers in women. It is the leading cause of cancer deaths among women in both developed and developing countries though death rates have reduced in developed countries e.g. the US, UK, France, Australia due to efforts to improve early detection and improved treatment. Increased incidence in many African and Asian countries is due to changes in reproductive patterns, physical inactivity, obesity, increase in breast cancer awareness and screening activities as well as social and economic development (2)(1).

Cancer burden in Africa is increasing. This is due to the increase in the risk factors for cancer e.g. smoking, obesity, physical inactivity and reproductive behaviors. Cancer statistics are also deficient due to lack of cancer registries and limited resources. In 2012 there were an estimated 847,000 new cancer cases and 591,000 cancer deaths. In Africa breast cancer is the most commonly diagnosed cancer and is the second leading cause of death after cervical cancer. It accounts for 27.6% of all the cancer in women. In sub-Saharan Africa it accounts for about 25.5% of cancers in women and is the leading cause of death. South Africa has the highest incidence of breast cancer. Breast cancer in African women is likely to be of early onset, higher grade and estrogen receptor negative (11).

In Kenya the annual incidence of cancer is close to 37,000 new cases and an annual mortality of over 28,000. Cancer is the third leading cause of death after infectious and cardiovascular diseases. The 2018 globocan placed Breast cancer as the commonest cancer in women followed by cervical cancer. It is also the third leading cause of cancer deaths (1). The incidence of breast cancer is about 40.3/100,000. Due to the rise in cancer incidence several strategies have been put in place to improve prevention, screening, diagnosis and treatment of cancer cases.

2.2 Breast Cancer Tumor Characteristics

Histopathology reports form the basis on which treatment and management of breast cancer is based. As a result pathology reports need to be thorough. Information on specimen and tumor description, orientation and analysis of surgical margins, and full reporting of histologic features should be included (4).

The prognosis of breast cancer is influenced by several variables. These variables include tumor invasion and size, extent of lymph node involvement, distant metastases, histologic grade, the histologic type of carcinoma, the presence or absence of estrogen or progesterone receptors and expression of HER2/NEU (12).

Handling of breast specimens is a very important aspect. Good fixation helps to preserve morphological details of breast specimens. Poor fixations alter mitotic figures, estrogen receptor expression and Lympho vascular invasion. Orientations of surgical specimens are important in evaluation of tumor margins (5).

The histologic type of breast cancer is an important entity. Prognosis varies with different histological types. Mucinous carcinoma, tubular carcinoma, invasive cribriform carcinoma, infiltrating lobular carcinoma and tubulo-lobular carcinoma carry a better prognosis that invasive carcinoma of no special type. For lobular carcinoma the classical type has a better prognosis than the solid variant. Medullary carcinoma has a moderate prognosis though patient may have a better survival than those with ductal carcinoma of no special type grade III. Survival is also better in patient with node negative typical medullary carcinoma. Mixed tumors with distinct ductal and special components show a better prognosis than ductal carcinoma of no special type (13).

Vascular invasion is an important prognostic variable. There is increased incidence of axillary lymph node metastases and poorer survival in patients with blood vessel or lymphatic invasion. Vascular invasion also increases the risk of local recurrence (14).

Extensive intraductal component and predominant intraductal component are associated with an increased incidence of multicentric and also multifocal tumors and can be seen in the remaining breast after breast conservative surgeries. It has also been associated with local tumor recurrence

even after radiotherapy in breast conservation treatment (15). This shows the importance of indicating the presence of DCIS when reporting invasive breast cancer histology.

The presence of lobular carcinoma in situ or lobular neoplasia co-existing with invasive breast carcinoma is also a very important variable. The risk of developing bilateral breast carcinoma is more frequent in patients with co-existing lobular neoplasia and carcinoma (16). Invasive ductal carcinoma with lobular features is associated with increased risk of nodal and distant metastasis especially to the bone. The presence of lobular features also infer the need for re-excision to achieve adequate margins (17).

Hormonal receptor expression is an important prognostic and predictive factor. Response to therapy depends on the presence and quantity of the hormone receptors. Estrogen receptor negative tumors have a higher rate of recurrence and poor survival. ER positive breast cancer responds better to endocrine therapy. A higher ER content gives a better response rate. Progesterone receptors also predict response to endocrine therapy. Therapeutic response is better when both ER and PR are present. Some tumors which are ER negative but PR positive also respond to endocrine therapy (18). Due to different platforms that can be used for the testing of estrogen and progesterone receptors, currently the ASCO/CAP guidelines are used to interpret the receptor status. These guidelines also guide on the laboratory processes e.g. internal quality assurance, method validation, proficiency testing and external quality assurance. A tumor is positive for estrogen or progesterone receptors when more than 1% of the tumor nuclei are immunoreactive (19).

HER 2/neu receptor is a transmembrane tyrosine kinase receptor of the epidermal growth factor receptor family. It's overexpression in breast cancer is associated with higher grades, high proliferation rate, p53 mutations and adverse outcomes e.g. metastasis and invasiveness. Its expression in benign breast disease confers an increased risk of subsequent invasive breast cancer. It's a poor prognostic indicator. Determination of HER2 status in breast cancer is important since it's a target of the monoclonal antibody trastuzumab. These breast cancers are also resistant to hormonal therapy and are more sensitive to cytotoxic therapies. Its expressed in all breast epithelial cells thus testing of its status in breast cancer is quantitative rather than qualitative. In breast cancer it's measured using immunohistochemistry, DISH or FISH (20,21). A tumor is considered positive if the cells show circumferential membrane staining that is

complete and intense and is given a designation of 3+. Equivocal results i.e. 2+ and negative results of 1+ or 0 should be confirmed using DISH or FISH (22).

2.3 Invasive Breast Cancer Histopathology

Invasive breast cancer is divided into various subtypes. The most common subtype is invasive ductal carcinoma. It accounts for about 70-80% of the invasive cancers. It can be associated with DCIS and rarely LCIS. About two thirds express estrogen or progesterone receptors and a third overexpress HER2/NEU (12).

Lobular carcinoma is the second most common subtype. About 66% are associated with an adjacent LCIS. They frequently spread to cerebrovascular fluid, serosal surfaces, gastrointestinal tract, ovary, uterus and bone marrow. It can be multicentric and bilateral. Almost all express hormone receptors but HER2/NEU overexpression is rare.

Inflammatory carcinoma is a rare subtype characterized by enlarged, swollen, erythematous breast without a palpable mass. It's poorly differentiated and diffusely infiltrative. It has a poor prognosis.

Medullary carcinoma is another rare subtype accounting for less than 1% of breast cancers. Clinically it can be mistaken for a fibro adenoma. It has minimal or no DCIS. It's associated with BRCA1 mutations. It's usually triple negative.

Colloid or mucinous carcinoma is a subtype characterized by abundant extracellular mucin. Tubular carcinoma is also a rare subtype. These two subtypes express hormone receptors but do not show HER2/NEU overexpression.

Invasive breast carcinoma can also be subdivided based on the histological grade. Currently the Nottingham Grading System also known as the modified bloom Richardson classification is used. Grading is based on degree of tubule formation, nuclear pleomorphism and mitotic count. The histologic grade can be; grade 1 (well differentiated), grade 2 (moderately differentiated) or grade 3 (poorly differentiated) (23).

The staging of breast cancer is by the TNM system and is from stage 0 to 4. This is determined by the presence and size of the primary tumor, the status of the regional and distant lymph nodes and the presence of metastasis (24).

2.4 Molecular Classification of Breast Cancer

Breast cancer is divided into several molecular subtypes based on hormonal receptor and HER2 receptor expression. Luminal A consists of breast cancers with ER regulated genes overexpression, under expression of HER2 gene clusters and under expression of proliferation related genes. Tumors in this group have a good prognosis and respond better to endocrine therapy. Luminal B tumors have lower expression of ER genes and a higher expression of proliferation genes. They also harbor TP53 mutations and have a poorer prognosis. HER2 enriched breast cancer subtype account for about 20-30% of all breast cancers. They are characterized by high expression of HER2/neu proliferation genes. They are mostly HER2 positive and ER/PR negative. Triple negative and basal breast cancer are however not synonymous. Triple negative breast cancer (TNBC) represents a phenotype characterized by lack of ER,PR and HER2 expression while basal like breast cancer subtype consists of tumors with gene expression similar to basal epithelial cells and have a strong expression of cytokeratin 5,6 and 17, are associated with BRCA1 mutations and are usually ER/PR/HER2 receptor negative.. (25,26,27).

In the United States the surveillance, epidemiology and end results (SEER) registries analyzed data on HER2 status to demonstrate breast cancer subtypes. ER, PR positive and HER2 negative tumors accounted for 72.7%, triple negative tumors were 12.2%, ER, PR and HER2 positive tumors were 10.3% while ER, PR negative and HER2 positive tumors accounted for 12% (28).

In a study done in Soweto South Africa analyzed 1218 breast cancer cases and found ER positive tumors at 64.9%, PR positive tumors 53.1% and HER2 positive tumors 26%. Luminal A tumors were 53.7%, luminal B 14.6%, HER2 enriched 11.4% and triple negative tumors were 20.4% (29).

In Uganda Indrojit et al analyzed 45 cases. ER positive tumors were 60% and majority of them were grade 2 tumors while grade 3 were ER negative. HER2 overexpression was seen in 11% of the tumors all of which were grade 3. Triple negative tumors were 36% (30).

A study done at Aga Khan University Hospital Kenya by Sayed et al that analyzed 301 breast cancer cases showed ER positivity at 72.8%, PR positivity at 64.8% and HER2 positivity at

15.3%. Luminal A tumors constituted 61.2% of the cases and luminal B 10.8%. Triple negative cancers were 20.2% of the cases (31).

2.5 Audit of Breast Histopathology Reports

A study done by macharia et al in 2006 that reviewed mastectomy specimens from 2001-2005 showed that there was incomplete reporting of tumor characteristics due to lack of standardization. Histology reports produced were dependent on the pathologists reporting them. The main areas of incomplete reporting were ; histological grading which was indicated in 66.3% of the cases, tumor margins in 75%, axillary node status in 92.3%, tubular formation only in 5.7% of the cases, Paget's disease in 36.8%, ductal carcinoma in situ in only 13.8 % and vascular invasion only stated in 25% of the case. The use of a standard proforma used in the study improved the completeness of the histopathology reports and ensured that tumor characteristics were adequately filled. The recommendation of this study was that use of a standard proforma be adopted at KNH (56).

An audit of breast histopathology reports at Aminu Kano Teaching Hospital in Nigeria revealed that use of standard text reports led to the omission of vital clinical information. Being a training institution, the need to develop a standardized reporting method was recommended for trainee pathologists. The need for continuous audits e.g. every two years was also emphasized (32).

The need to improve histopathology reports has led to the development of synoptic reporting and standard proforma. The aim is to ensure completeness of reports, accuracy and reduce the turnaround time needed to generate a report. Synoptic reports are easier to interpret i.e. are user friendly. They are also better when extracting information useful for cancer registries, and for policy formulation (33).

 The Royal College of Pathologists developed guidelines to guide pathologists in handling breast cancer cases and ensure pathology reports are consistent. The breast datasets developed provide recommendations on handling of specimens e.g. trimming and fixation, structure of the request form, a checklist of important histological features to include, reporting of immunohistochemistry results and quality assurance both internal and external (5).

The College of American Pathologists (CAP) also developed a proforma that has been largely adopted. It provides a structured format for the reporting of breast cancer histopathology. It outlines the various tumor characteristics whose presence or absence can be indicated in a structured manner (6).

A study done at the department of surgery, Royal Victoria Infirmary compared standard text reports and the use of a proforma. The use of a proforma improved the reporting of certain tumor characteristics to upto 100%. These characteristics include the presence of micro calcification, coexistent ductal carcinoma in situ, hormonal receptor status. The use of a proforma was shown to optimize the amount of histopathological information given (34).

In Ontario Cancer Care the impact of using standardized synoptic cancer pathology reporting was assessed among pathologists, physicians, surgeons and oncologist. Reports were found to be complete for the purposes of making clinical decisions. Synoptic reports improve efficiency as finding the relevant information is made easier. Also there was a reduction in errors as all the parameters significant to a cancer were included (35).

An audit of pathology reports of breast cancer in Australia also showed that lack of a standard checklist led to incompleteness of pathology reports. It also showed that completeness was also based on reporting volumes in different laboratories. Completeness was more in teaching hospital (36).

A study done at the University of Wales to show the effectiveness of audits in improving histopathology reporting standards showed that performance may deteriorate if audits are not done regularly. This is because guidelines tend to be filed away and not implemented. Also new employees may not be made aware of the recommended guidelines and thus will not follow them. The study showed that continuous audits are important to ensure that standards are maintained and that guidelines are reviewed and modified. The need to do audits every two years or less was shown to be effective. The study also showed that introduction of a standard proforma resulted in reports containing all the mandatory clinical information (37).

3.0 STUDY JUSTIFICATION

Quality Assurance is a very important aspect of laboratory practice and it ensures that standards of quality are met. Audits are important tools in quality assurance. They are used to monitor introduction of new tests or changes in practice and also monitor adherence with best practices. Continuous audits are recommended for quality improvement in the laboratory.

Synoptic reporting has been introduced in various regions around the world including KNH with the aim of improving pathology reports. It involves the use of a standardized checklist from which various breast cancer parameters are reported. Narrated or dictated pathology reports are based on an individual pathologist's assessment of a breast cancer case and have often been considered incomplete as they do not provide all the relevant information needed by clinicians for management of patients.

Traditionally reporting of breast cancer histopathology at KNH was by narrated standard text reports. Since the introduction of synoptic reporting in 2016 no audit has been done to assess the effectiveness of using this method in the reporting of invasive breast cancer and whether the reports are now more complete as compared to standard text reports.

Some tumor characteristics infer prognostic implications and also determine the treatment modalities to be applied. It is therefore very important to ensure that surgeons, oncologists and physicians are given complete histopathology reports.

This study sought to highlight the effectiveness of using synoptic reporting in ensuring the completeness of breast cancer histopathology reports. It also sought to demonstrate the areas that require improvement and if there is need for training pathologists on the use of synoptic reports.

Structured reports provide an easier format from which information can be extracted for cancer registries.

Classification of invasive breast carcinomas according to their ER, PR and HER2 receptor status was to provide important data on hormonal receptor and HER2 receptor profiles seen at KNH. This data is important in the planning of treatment needs for the patients attending the breast cancer clinic at KNH.

3.1 Research Question

How effective is synoptic reporting in ensuring the completeness of invasive breast carcinoma histopathology reports at Kenyatta National Hospital?

What are the ER/PR/HER2 receptor profiles seen at Kenyatta National Hospital?

3.1.1 Broad Objective

To audit synoptic reports of invasive breast carcinomas from January 2016 to December 2018 and determine the completeness of histopathology reports and determine receptor profiles at Kenyatta National Hospital.

3.1.2 Specific Objectives

To review the completeness of histopathology reports using synoptic reporting at Kenyatta National Hospital against an adopted protocol.

To determine the estrogen, progesterone and HER/neu receptor profiles of the invasive breast carcinomas seen at Kenyatta National Hospital.

4.0 METHODOLOGY

4.1 Study Design

Laboratory based retrospective cross-sectional study

4.2 Study Setting

The study was carried out at the KNH/UON records department and the Kenyatta National Hospital (KNH) Histopathology laboratory.

4.3 Study Population

All invasive breast cancer mastectomy reports, immunohistochemistry reports and tissue blocks for mastectomy reports with no immunohistochemistry done from January 2016 to December 2018

4.3.1 Inclusion Criteria

Invasive breast carcinoma mastectomy synoptic reports and immunohistochemistry reports.

Tissue blocks for invasive breast cancer where no ER/PR/HER2 immunostains were done.

4.3.2 Exclusion Criteria

Invasive breast cancer reports with no immunohistochemistry reports whose blocks cannot be traced

4.4 Sample Size Determination

From the KNH/UON records department, approximately 60 invasive breast cancer mastectomy reports are filed every year. From this 180 mastectomy reports were estimated as the sample population from January 2016 to December 2018

The formula for finite population was used to calculate the sample size.

$$\underline{\hspace{4cm}}$$

Where

N = Population of invasive breast cancer reports available during the target (study) period

Z = Standard normal deviate for 95% level of confidence (Z = 1.96) d = desired level of precision (d = 0.05)

P = Proportion of complete breast cancer reports estimated at 49.75% based on median completion of breast cancer reports at KNH by Macharia (55)

$$\underline{\hspace{6cm}}$$

n = 123

4.5 Sampling Procedure

All consecutive invasive breast cancer mastectomy synoptic reports, immunohistochemistry reports from January 2016 to December 2018 that met the inclusion criteria were retrieved and all the information required was entered in a coded data sheet.

The histopathology reports were retrieved from the KNH/UON records department.

The reports were then audited against the audit tool. The parameters of interest in evaluation for completeness included:

Age

Surgical procedure done

Specimen laterality

Specimen integrity

Tumor size

 Lymph node sampling

Gross margins

Tumor site

Tumor Focality

Histologic type and grade

Ductal carcinoma in-situ; architectural pattern, necrosis, nuclear grade and extensive intraductal component

Lobular carcinoma in-situ

Gross and microscopic margins involved or uninvolved by invasive carcinoma and DCIS

Paget's disease

Lympho-vascular invasion

Lymph node status i.e. number of lymph nodes involved, number of lymph nodes sampled, Micrometastasis and extranodal extension

Skeletal muscle involvement

Skin involvement

Micro-calcifications

Treatment effect

Stage

The presence or absence of each parameter in the histology report was assessed individually against the adopted protocol and the results recorded.

For the immunohistochemistry reports, the receptor status was indicated as either positive or negative.

4.6 Sample retrieval and processing

Histopathology reports with no immunohistochemistry done were identified. Paraffin embedded tumour blocks as indicated in the trimming notes were retrieved from the KNH histology archives. A 4-micron section was cut from each block (Appendix II) and mounted on a slide and then stained with haematoxylin and eosin and examined to identify the appropriate block for immunohistochemistry. Once the tumor blocks were identified, 4-micron sections were cut from each block and mounted on slides. Positive controls were also mounted on each slide and stained for ER/PR/HER2 immunohistochemistry as per the Ventana analyser.

The immunohistochemistry slides were then reviewed by the principal investigator. For ER and PR, the staining intensity and proportion of stained cells was examined and recorded as per the Allred score. For HER2 the staining characteristics were examined and recorded as per the ASCO guidelines. The results were then confirmed by the supervising pathologists.

4.7 Quality Assurance

Pathology reports and specimen blocks were retrieved and labeled with a special laboratory number and the relevant clinical information was entered into the data collection tool. Reagents used were examined to ensure they were not expired and did not have turbidity or precipitates. The reagents were then prepared according to the standard operating procedures. Positive and negative controls were used to aid in correct interpretation of the immunohistochemistry slides.

4.8 Data Analysis

Data collected was entered, managed and analysed using SPSS version 20. Descriptive statistics; frequencies and proportions were used to summarize the microscopic findings. Level of completeness of each of the variables assessed was expressed as a percentage of all the reports analysed. ANOVA statistics was used to calculate for the association between age and tumor grade.Chi square tests were used to examine for the significant associations between receptor status and tumor grade.All statistical tests were conducted at 5% level of significance.

4.9 Ethical Approval

The study commenced after approval from the Kenyatta National Hospital and University of Nairobi Ethical and Research Committee.

Permission was also sought from the head of KNH and UON histopathology laboratories for retrieval of records and specimen and for processing and analysis.

5.0 RESULTS

5.1 Demographic characteristics

Age of the patients was documented in 100% of the reports. The mean age in the synoptic reports was 48.1 years (SD 11.5) with a range between 23 and 80 years. The most common (modal) age group was between 40 and 49 years with 49 (39.8%) (Figure1). Other reported age groups were 30 to 39 years 25(20.3%), 50 to 59 years 24(19.5%), 60 to 69 years 14(11.4%), 70 to 79 years 6 (5%), 20 to 29 years 3(2.4%) and 80 and above 2(1.6%).
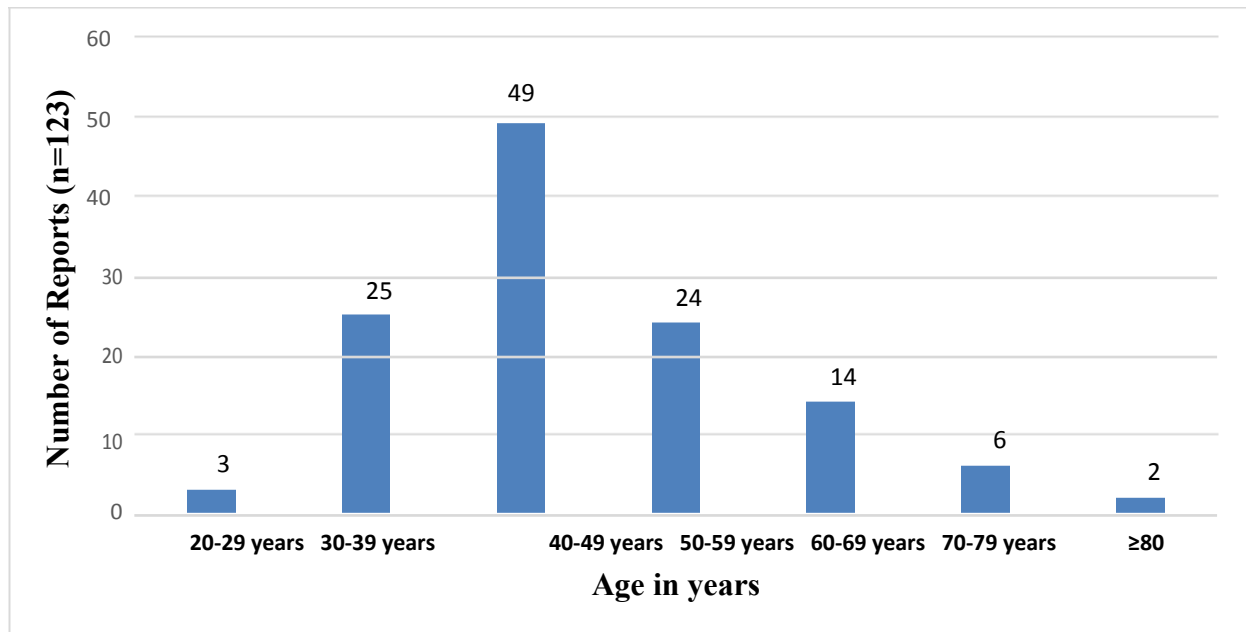
Figure 1: Age distribution in the reports

5.2 Surgical procedures

The type of surgical procedure conducted was documented in 119 (96.7%) and omitted in 4 (3.3%) reports. The type of procedure indicated was modified radical mastectomy (MRM) in all the reports.

Eight parameters were considered for assessment of completion i.e. specimen laterality, specimen integrity, tumor size, specimen gross description, gross margins, lymph node sampling, tumor site, and tumor Focality. Of the 123 reports examined, 94 (76.4%) had 100% completion of the eight parameters. Gross margins and lymph node sampling were documented in all the reports. Specimen laterality was documented in 118 reports (96%), Tumor size in 121 (98.4%) reports, specimen integrity in 110 (89.4%), specimen gross description in 94 reports (76.4%), tumor Focality in 113 (91.9%) and tumor site in 110 (89.4%) of reports as shown in Table 1.

Table 1: level of completion of macroscopic details

	Frequency (n)/123	Percent (%)
Specimen laterality		
Right	60	48.8
Left	58	47.2
Not specified	5	4
Specimen integrity specified	110	89.4
Tumor size specified	121	98.4
Specimen gross description	94	76.4
Gross margins	123	100
Lymph node sampling done	123	100
Tumor site reported	110	89.4
Tumor Focality indicated	113	91.9

5.3.1 Tumor site

Tumor site was indicated in 110 reports and omitted in 13 reports. The most commonly reported site was the upper outer quadrant in 42 reports (38.2%) . Other sites reported were upper inner quadrant in 18 reports(16.4%), lower inner quadrant in 14 reports (12.7%), lower outer quadrant in 12 reports (10.9%), central quadrant in 10 reports (9.1%) and in 14 reports (12.7%) more than one quadrant was involved. This is illustrated in Figure 2.
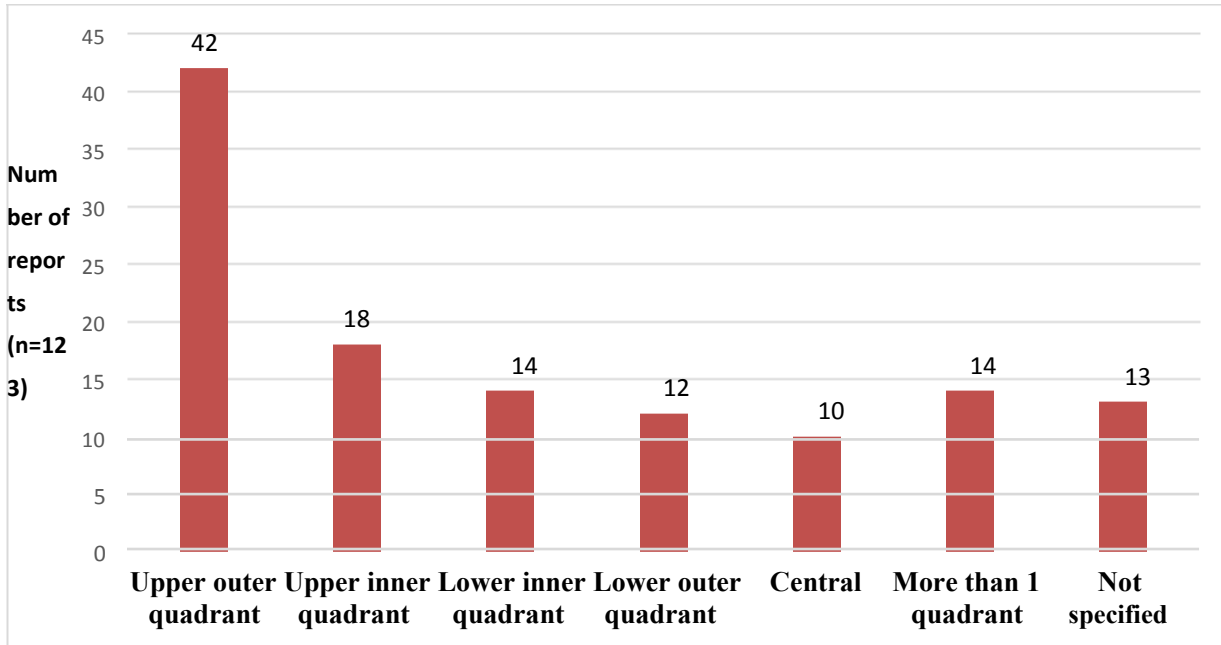
Figure 2: Tumor sites indicated

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5.4 Level of Completion of Microscopic Parameters

Histologic type, nuclear pleomorphism, mitotic activity, tubular formation and overall histologic grade was indicated in all the reports as shown in table 2

Table 2: Reporting of the histologic grade and type (n=123)

Microscopic findings	Whether microscopic findings are reported or not	Frequency (n)	Percent (%)
Histological type reported	Yes	123	100
	No	0	0
Nuclear pleomorphism indicated	Yes	123	100
	No	0	0
Mitotic activity indicated	Yes	123	100
	No	0	0
Degree of tubular formation indicated	Yes	123	100
	No	0	0
Grade reported	Yes	123	100
	No	0	0

5.4.1 Histologic types

Histologic type was indicated in 100% of the reports. Invasive ductal carcinoma of no special type was the most common histological type and it was reported in117 reports(95.1%) followed by lobular carcinoma in 3 reports (2.4%) mixed ductal and lobular carcinoma 2 reports(1.6%) and metaplastic carcinoma in 1 report (0.9%)as shown in figure 3

histologic types (n=123)

1
2
3

117

- invasive ductal carcinoma
- lobular carcinoma
- mixed ductal and lobular carcinoma
- metaplastic carcinoma
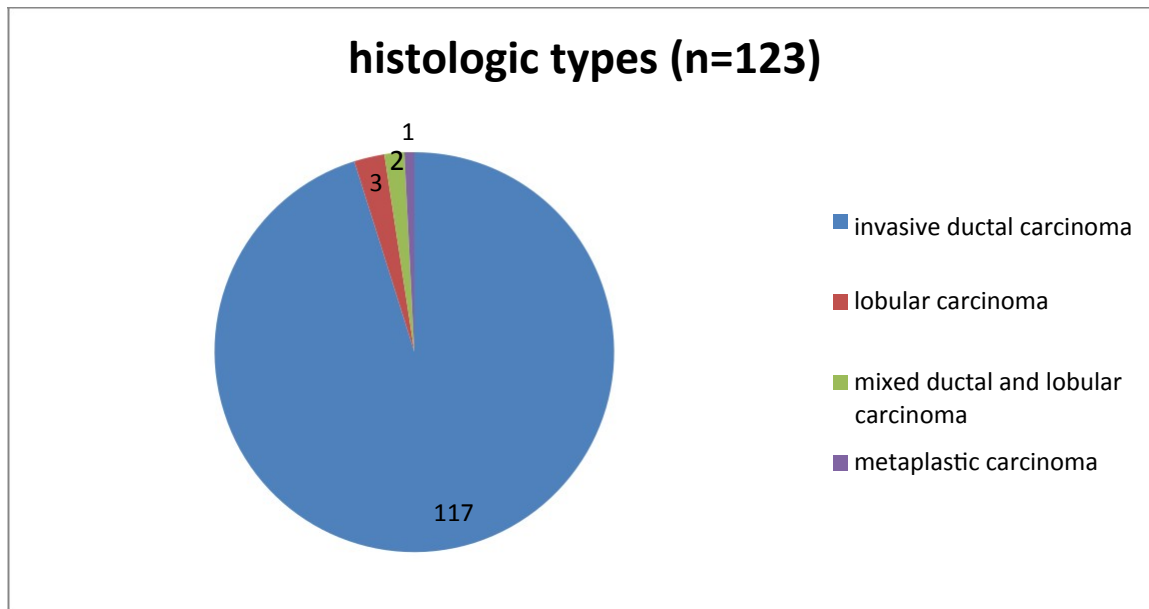
Figure 3: histologic types reported

5.5 Ductal Carcinoma in situ

The presence or absence of DCIS was documented in 120 reports (97.6%) and omitted in 3 reports. Of these 72 (60%) reports had DCIS. Extensive intraductal component was reported in 45.8%, architectural pattern in 69.4%, nuclear grade in 55.6% and necrosis in 47.2% of the reports as shown in table 3

Table 3: Reporting of DCIS (n=120)

Reporting of DCIS	Whether DCIS features are reported or not	Frequency (n)	Percent (%)
Presence or absence of DCIS reported(n=123)	Yes	120	97.6
	No	3	2.4
DCIS present (n=120)	Yes	72	60
	No	48	40
Extensive intraductal component reported (n=72)	Yes	33	45.8
	No	39	54.2
Architectural pattern reported(n=72)	Yes	50	69.4
	No	22	30.6
Nuclear grade reported (n=72)	Yes	40	55.6
	No	32	44.4
Necrosis reported (n=72)	Yes	34	47.2
	No	38	52.8

5.6 Lobular Carcinoma In-Situ

The presence or absence of LCIS was documented in 58 reports (47.2%) as illustrated in figure 4.

In all the documented reports LCIS was absent
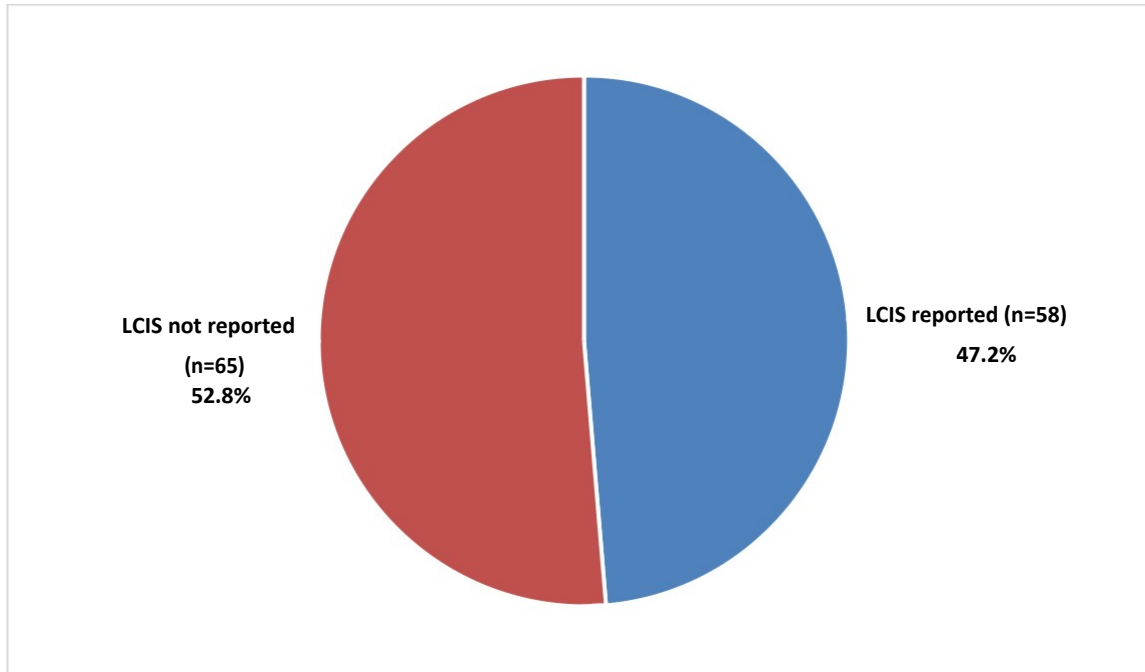
Figure 4: Reporting of presence or absence of Lobular carcinoma in situ (n=123)

5.7 Microscopic Margin Status

Margin status was reported in all the 123 reports. Margins were indicated as not involved in 98 reports (79.7%) and involved in 25 reports (20.3%). Where margins were involved by tumor all reports had the specific margin indicated.

In uninvolved margins only 68(69.4) reports had the margin and the distance closest to margin indicated as shown in table 4

Table 4: Reporting of microscopic margins

Reporting of margin involvement	Whether features of marginal involvement are reported on or not	Frequency (n)	Percent (%)
Are Margins involved (n=123)	Yes	25	20.3
	No	98	79.7
Is margin indicated if there is no marginal involvement (n=98)	Yes	68	69.4
	No	30	30.6
Distance from closest margin indicated (n=98)	Yes	68	69.4
	No	30	30.6
Margin involved by invasive OR DCIS indicated (n=25)	Yes	25	100
	No	0	0

5.8 Lymph Node Status

The number of lymph nodes involved out of all the lymph nodes sampled was indicated in all the reports. The presence or absence Micrometastasis was only documented in 32(26%) of the reports. The presence or absence of extranodal involvement was indicated in 90(73.1%). This is illustrated in table 5

Table 5: Reporting of lymph node status

Reporting of lymph node involvement	Presence or absence reported	Frequency (n)/123	Percent (%)
Lymph node number involved stated	Yes	123	100
	No	0	0
Micrometastasis	Yes	32	26
	No	91	74
Extranodal extension	Yes	90	73.1
	No	33	26.9

The number of lymph nodes sampled was indicated in each report. Majority of the reports, 61(49.6%) had 6-10 nodes sampled followed by 19(15.4%) reports which had 0 to 5 nodes sampled. 27 (22 %) reports had 11-15 nodes sampled, 11(9%) had 16 to 20 nodes and only 5(4%) reports had more than 20 nodes sampled. This is illustrated in table 6 and figure 5

Table 6: Number of lymph nodes sampled

Number of lymph nodes sampled	Frequency	Percent (%)
0-5	19	15.4
6-10	61	49.6
11-15	27	22
16-20	11	9
>20	5	4
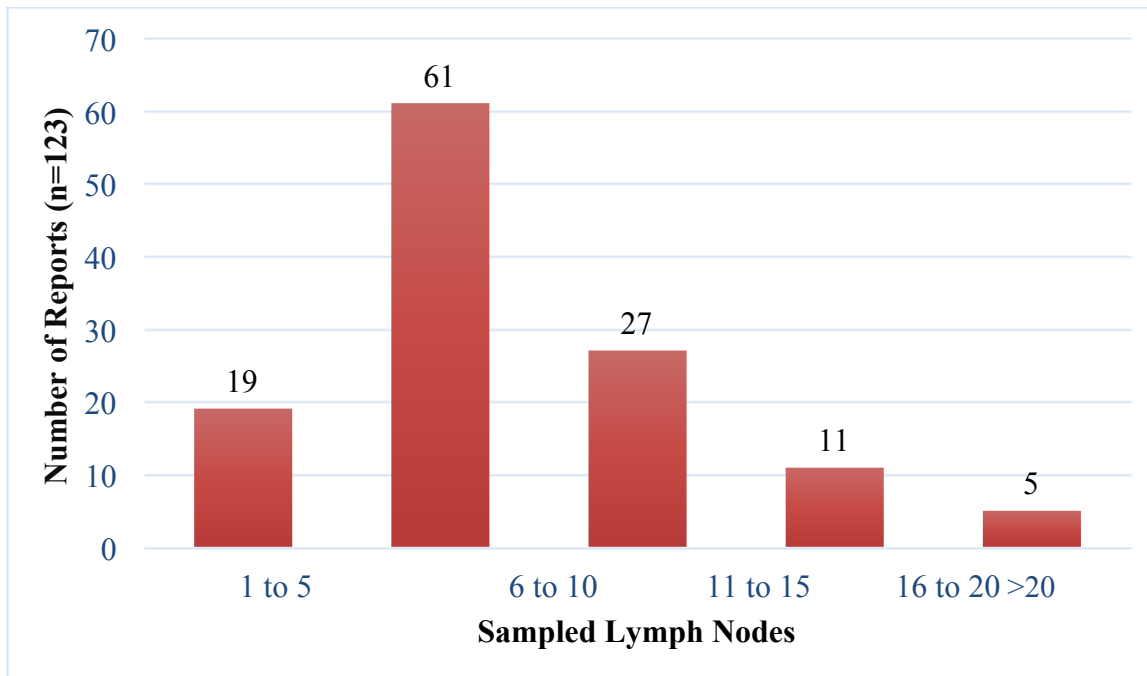
Figure 5: Number of lymph nodes sampled

5.9 Other Parameters Examined

The presence or absence of Paget's disease was reported in 113 reports(91.9%), lymphovascular invasion in 96.7%, skin involvement in 81.3%, micro-calcification in 88.6%, skeletal muscle involvement in 80.5%, treatment effect in 47.5% and staging 84.6% as shown in table 7

Table 7: Reporting of Paget's disease, lymphovascular invasion, skin and skeletal muscle involvement, microcalcifications, treatment effects and staging

Type of involvement	Whether features are reported or not	Frequency (n)	Percent (%)
Presence of Paget's disease indicated	Yes	113	91.9
	No	10	8.1
Presence of Lympho-vascular invasion reported	Yes	119	96.7
	No	4	3.3
Skin involvement reported	Yes	100	81.3
	No	23	18.7
Presence or absence of micro-calcification reported	Yes	109	88.6
	No	14	11.4
Presence or absence of skeletal muscle involvement reported	Yes	99	80.5
	No	24	19.5
Treatment effect indicated	Yes	58	47.5
	No	65	52.5
Stage indicated	Yes	104	84.6
	No	19	15.6

5.10 Overall Completeness

The overall completeness of the synoptic reports was based on documentation of 25 items in the reports. Documentation ranged from 16 to 25 items per report. This corresponds to a completion rate of 64% to 100%. The mean completion for the synoptic report was 82%. Only 6 reports had completion of the 25 items. Majority of the reports had 23 items reported. This is illustrated in table 8

Table 8: Parameters completed per report

Items reported/25	n/123	%	%level of completion
25	6	4.9	100
24	10	8.1	96
23	30	24.4	92
22	27	22	88
21	23	18.7	84
20	13	10.6	80
19	9	7.3	76
18	2	1.6	72
17	2	1.6	68
16	1	0.8	64

In summary the reporting of tumor size, gross margins, lymph node sampling, histologic type and grade, number of lymph node involved by tumor and margins involved by tumor was at 100%.

The reporting of extensive intraductal component, DCIS pattern, necrosis and nuclear grade, presence or absence of LCIS, margins uninvolved by tumor, micro metastasis and treatment effect showed low levels of completion.

5.11 Immunohistochemistry

ER positive tumors were 86 which constitutes 69.9%, PR positive tumors were 77(62.6%) while HER2 positive tumors were 23(18.7%). ER/PR positive and HER2 negative tumors represented the majority of the tumors with 74(60.2%). Triple positive tumors were 10(8.1%) while triple negative tumors were 23(18.7%) as shown in table 9.

Table 9: Receptor profiles

Receptor	Finding	n/123	%
ER	Positive	86	69.9
	Negative	37	30.1
	Equivocal	0	0
PR	Positive	77	62.6
	Negative	46	37.4
	Equivocal	0	0
HER	Positive	23	18.7
	Negative	97	78.9
	Equivocal	3	2.4
ER/PR positive & HER negative	ER/PR +VE and HER 2 negative cancers	74	60.2
	Other results	49	39.8
Triple negative	ER/PR/HER2 negative breast cancers	23	18.7
	Other results	100	81.3
Triple positive	ER/PR/HER2 positive cancers	10	8.1
	Other results	113	91.9

5.11.1 Association between age and cancer grade

There was a significant association between age and tumor grade (ANOVA F statistic = 3.48; d.f = 2, 110; p = 0.034). The mean age of patients with grade 1 tumors was 53.1 years (SD± 12.9) compared to 49.6 years (SD ±12.4) for grade 2 tumors and 44.8 years (SD± 9.2) for grade 3 tumors. As shown in table 10

Table 10: Association between age and grade

	N	Mean age	SD	P value
Overall grade				
1	11	53.1	12.9	0.034
2	57	49.6	12.4	
3	45	44.8	9.2	

5.11.2 Triple negative receptor status and tumor grade

There was a significant association between negative receptor status for all three receptors and tumor grade (p = 0.002). None of the grade 1 tumors had triple negative receptor status while 34% of grade 3 and 11.3% of grade 2 tumors had triple negative receptor status as shown in (Table 11).

Table 11: Association between Triple negative receptor status and tumor grade

	ER/PR/HER2			
	ER/PR/HER2 negative	Other results	Chi square	P
Overall grade				
1	0(0.0)	12(100.0)	12.1	0.002
2	7(11.3)	55(88.7)		
3	16(34.0)	31(66.0)		

5.11.3 Relationship between ER/PR positive HER negative tumors and tumor grade

There was a significant association between ER/PR positive HER negative tumors and tumor grade (p = 0.025) .The percentage of ER/PR positive HER negative tumors in the specific grades were: 91.7% for grade 1 tumors, 61.3% and 48.9% for grade 2 and 3, respectively as shown in table 12

Table 12: Relationship between ER/PR positive HER negative tumors and tumor grade

	ER/PR +VEand HER 2 -VE	Other results	Chi square	P
Overall grade				
1	11(91.7)	1(8.3)	7.2	0.025
2	38(61.3)	24(38.7)		
3	23(48.9)	24(51.1)		

6.0 DISCUSSION

Breast cancer is a growing concern worldwide and in Kenya it's the commonest cancer in women (1). Due to its significant morbidity and mortality a lot of research has been done with an aim of improving outcomes. Histological features and ER/PR/HER2 receptor status provide the basis upon which management of breast cancer is determined especially now in the era of targeted therapy. It is therefore critical that pathologists relay relevant histological information to clinicians. This is done by ensuring that pathology reports contain all the details on breast cancer characteristics that influence management. Several organizations e.g. the College of American Pathologists (CAP) and the Royal College of Pathologists have developed checklists for the management of breast specimens. These checklists provide guidance on the information required on a laboratory request form, handling of breast specimens, trimming, processing, the characteristics to report and assessment of receptors (5,6). The case for standardized reporting has been made by several studies that have demonstrated inadequacies of narrative reporting. Atanda et al in Nigeria (32) showed the reporting of tumor size was at 50%, histologic type at 92%, histologic grading at 40%, lymphovascular invasion at 12% and distance from resection margin at 62% when narrative reporting was used. Yesufe et al in Ethiopia (38) compared narrative reports with the breast health global initiative guidelines and demonstrated incompleteness in this reports. At KNH, a review and audit of mastectomy reports was done by Macharia et al (56) and it showed varying levels of completeness of various breast cancer characteristics highlighting a need for a more standardized approach in reporting of breast cancer.

In an effort to improve histopathology reporting of breast cancer, KNH introduced synoptic reporting adopted from the CAP guidelines. This being a new reporting format, an audit was important to assess its implementation. Various parameters were analyzed in the reports. It is important to note that certain information i.e. age, surgical procedure done, type of lymph node sampling done and laterality depend on the information provided by the surgeon.

The age demographic in this study was 23 to 80 years with a median age of 48.1 years. This age demographic was comparable to a study done by Sayed et al at AgaKhan University Hospital Nairobi that had an age range of 19-94 and a median age of 47.5 (31). This study also showed

that the commonest age group was 40-49 years which is comparable to a study done by Wasike et al which showed the highest proportion as 45-49years (39).

Age was documented in all the reports, surgical procedure done in 96.7% of the reports, laterality in 96% and lymph node sampling in 100%. This information is usually derived from the laboratory request form. When not present in the synoptic report it implies that either the surgeons omitted the information or it was not transcribed in the report. The reporting of these parameters was very good and was only missing in a few reports. To ensure 100% completeness of this information there Is need for a specific laboratory request form for breast cancer that guides the surgeon on the information required by the pathologist (40).

The specimen gross description was only documented in 76.4% of the reports. The presence of skin ulceration, edema (peau d' orange), and skin nodules are important in the staging of breast cancer. (41) If these characteristics are not documented and were present then there is likelihood that there was under staging of the cancer. Presence of lymph node sampling was documented in all the reports and was all axillary. Lymph node sampling enables the assessment of lymph node metastasis which is an important component in tumor staging. Tumor Focality was indicated in 91.9% of the reports. Focality has prognostic implications. Multifocal tumors have been found to have a high rate of recurrence and have a poor prognosis (42). Tumor location documentation was at 89.4%. Location has been shown to impact breast cancer survival where upper outer quadrant tumors have a favorable outcome (43). Majority of the tumors (38.2 %) in this study were located in the upper outer quadrant. Specimen laterality was documented in 96%, specimen integrity in 89.4% gross margins in 100% and tumor size in 100%. Only 94 (76.4%) of the 123 reports had all the macroscopic details documented.

Completeness of microscopic details ranged from 100% for histologic type to 45.8% for the reporting of extensive intraductal component for tumors with DCIS.

Lymph node status is very important in the evaluation of breast cancer and has prognostic implications. The number of lymph nodes positive for tumor determines the stage in the TNM classification. From this study reporting of lymph node status was at 100%. Of note was the number of lymph nodes examined. The number of axillary lymph nodes retrieved from a specimen depends partly on the extent of lymph node dissection done and also the pathologist's

retrieval of the nodes from the specimen. In the reports 15.4 % had 5 or less lymph nodes examined, 49.6% had 6 to 10 lymph nodes examined, 22% had 11 to 15 nodes, 9% had 16 to 20 nodes and 4% had more than 20 nodes examined. The number of positive and negative lymph nodes has been shown to influence overall disease free survival and recurrence (44–49). High negative lymph node counts have been associated with improved outcomes. When less than ten nodes are examined there may be under staging of the breast cancer (45). There is no agreed number of lymph nodes to be examined but it is recommended to examine a minimum of 10 nodes in order to reports the lymph node status with confidence (48,49).

A study done by Macharia B (56) that audited standard text reports showed reporting of histologic type at 100%, axillary node status at 89.3%, tumor margins at 75%, histologic grade at 66.3%, tubular formation at 5.7%, Paget's disease at 36.5%, DCIS 13.8% and vascular invasion at 25%. From this study there was marked improvement in reporting of these parameters with increased level of completeness. Histologic type reporting was maintained at 100%, axillary node status reporting improved from 89.3% to 100%. Histologic type of the tumor was reported in 100% of the reports as compared to 66.3% seen in standard text reports; tubular formation was also reported in 100% of the reports as compared to 5.7%. Presence or absence of DCIS reporting improved to 97.6% as compared 13.8% in text reports. Vascular invasion also improved from 25% to 96.7%. Reporting of Paget's disease also improved from 36.5% to 91.9%. Standard text report showed an average level of completeness of 49.75% compared to 82% in synoptic reports. This study therefore showed a marked improvement in reporting invasive breast cancer histology using synoptic reporting as compared to standard text reports.

The results of this study were also comparable to an audit done in Australia by Kricker et al (36) that focused on histological type and grading, tumor size, margins of excision, vessel invasion and DCIS. In this audit histological type was indicated in 99.6% of the reports compared to 100% in this study. Tumor size was stated in 94% of the reports compared to 100% in this study. Histologic type was documented in 99% compared to 100% in this study. Our study showed an increased reporting of the presence or absence of DCIS of 97.6% compared to the Australian audit which reported 79%. Reporting of various components of DCIS showed various levels of completeness in this study. Extensive intraductal component was reported in 45.8% compared to 39% in the Australian audit, architectural pattern in 69.4% compared to 95%, nuclear grade in

31

55.6% compared to 39% and necrosis 47.2 compared 41 %. Reporting of uninvolved margins was 69.4% compared to 62% in the Australian audit. These two studies have shown that reporting of DCIS and margins is still problematic.

A study done by Wilkinson *et al* (4) to examine conformity to the college of American pathologists reporting guidelines showed reporting of histologic type at 100% and compared to 100% in this study, reporting of tumor grade was at 90% and compared to 100% in this study. Microscopic margin status was reported in 94% compared to 100% in this study. Distance to closest margin reporting was similar in both studies at 69% compared to 69.4% in this study. These findings show that despite standardized reporting and presence of guidelines, compliance is not achieved fully. This was also seen in a study by Mathers et al that assessed the use of a standard proforma compared to narrative reports based on the National Health Service (NHS) guidelines (34) and a study by Idowu *et al* that analyzed lung, breast, colorectal and prostate reports from 86 institutions (50) which demonstrated that although there was marked improvement in reporting 100% completeness had not been achieved. These studies demonstrate that the use of standardized reporting improves reporting standards but does not guarantee the completeness of pathology reports. This emphasizes on the need for regular audits to assess compliance to set guidelines.

The receptor profiles in this study were comparable to a SEER study in the US in which Luminal A tumors were 72.7% compared to 60.2% in this study, triple negative tumors were 12.2% compared to 18.7% and Luminal B tumors were 10.3% compared to 8.1% (28).

A study by McCormack in Soweto South Africa showed ER positivity at 64.9% compared to 69.9% in this study, PR positivity was 53.1% compared to 62.6%, her2 positivity was 26% compared to 18.7% in this study. Luminal A tumors were 53.7% compared to 60.2%, luminal B tumors were 14.6% compared to 8.1% while triple negative tumors were 20.4% compared to 18.7% in this study (29).

In Uganda, a study by Indrojit *et al* found ER positive tumors were 60% compared to 69.9% in this study. Majority of the ER positive tumors were grade 2 while in this study the tumors were grade 1 or 2. HER2 overexpression was seen in 11% as compared to 18.7% in this study (30).

Hormonal receptor profiles in this study showed similarities with a study done by Sayed et al (31) at Aga Khan University Hospital Kenya. ER positive tumors constituted 69.9% in this study compared to 72.8%. PR positive tumors were 62.6% as compared to 64.8% and Her2 positive tumors were 18.7% as compared to 17.6%. Luminal A tumors were 60.2% compared to 61.2% , luminal B were 8.1% compared to 10.8% and triple negative tumors were 18.7% compared to 20.2%.

There was a significant association between ER/PR positive and HER2 negative tumors with tumor grade in this study as has been shown in other studies (51).

To achieve completeness of pathology reports there is need to include input from all the stakeholders of the lab. KNH introduced synoptic reporting based on standards from an external organization but the completeness of each report is based on the discretion of the pathologist. As thorough as the CAP guidelines are, we are in an era of evidence based medicine therefore all the parameters to be included in each report must have evidence of prognostic or predictive implication. As a result, individual pathologists may omit parameters which they deem as not important. The field of breast cancer is growing and as more studies are done more information about the disease is brought to light. It is paramount that all pathologists and trainee pathologists are kept abreast with all the new information. This will make full implementation of reporting guidelines easier.

The differences in how individual pathologists fill the information in the synoptic reports e.g. reporting the presence of DCIS without details on its characteristics could explain why 100% completion has not yet been achieved and why a few problematic areas in reporting have been identified in this study. These include DCIS details i.e. extensive intraductal component, architectural pattern, necrosis and nuclear grade, LCIS, microscopic margins. The reporting of presence or absence of DCIS is at 97.6% yet the specific details that define this parameter are often omitted. Nuclear grade, necrosis, architectural pattern and presence of extensive intraductal component have been shown to have prognostic implications. (15, 52, 53).This could mean that most pathologists assume that only the information on presence or absence is required and not the specific details. This highlights the need for continuous training in new developments in breast cancer.

Another problematic area was in the reporting of LCIS. LCIS and lobular carcinoma are rare but have been shown to sometimes coexist with DCIS or invasive ductal carcinoma and it has also been thought that they are clonal (17, 54). Due to the risk of developing contralateral breast cancer, it is an important factor to look for and document. In this study, its presence or absence was documented in only 47.2% of the reports. This puts to question on whether the presence of LCIS is looked for in the specimens and if so why it is not documented in the synoptic reports. Because it is rare it can be overlooked and only documented when it's present.

The reporting of gross margins and involvement of microscopic margins was at 100% but where margins were not involved only 69.4% of the reports specified the margin and distance from the margin. Both gross and microscopic margins provide better accuracy about margin status and thus should be used together (55).

This study highlights the importance of audits in the histopathology lab. Despite introduction of a standardized reporting format the completeness of reports has not yet reached 100%. Appleton et al (37) emphasized the need for continuous audits as guidelines and recommendations tend to be filed away and not implemented especially where there is a high turnover of junior staff. KNH is a teaching hospital and thus experiences a high turnover of junior staff and would therefore benefit from regular audits to ensure that reporting standards are maintained. Because knowledge on breast cancer keeps changing and improved upon there is need for continuous trainings for all pathologists to ensure that reporting standards reflect the current body of knowledge.

6.1 CONCLUSION

There has been an improvement in reporting of invasive breast cancer using synoptic reports as compared to standard text reports from 49.75% to 82%.

Despite introduction of synoptic reporting 100% completeness has not been achieved.

Problematic areas in reporting that have been identified in this study are the reporting of DCIS characteristics where reporting of extensive intraductal component was 45.8%, reporting of DCIS architectural pattern 69.4%, nuclear grade 55.6% and necrosis 47.2%. The reporting of presence or absence of LCIS was 47.2%. The reporting of distance from closest microscopic margins was 69.4% and reporting of treatment effect was 47.5%.

Receptor profiles seen at KNH are comparable with other studies in Kenya, Uganda, South Africa and the US

6.2 RECOMMENDATIONS

Need for interdepartmental consensus on comprehensive laboratory request forms to capture laterality, surgical procedure, pre-surgical interventions. This will aid in achieving complete reporting.

Sensitization of anatomic pathologists/registrars on clinical utility and need to report DCIS, LCIS, microscopic margins and treatment effect.

Based on observed incompleteness, periodic audits should be carried out with a target of achieving complete reports.

6.3 LIMITATIONS

There were poorly preserved paraffin embedded tissue blocks.

6.4 CONFLICT OF INTEREST

The author declares that there is no conflict of interest relevant to this study.

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APPENDICES

Appendix I: Audit Tool

SECTION A: laboratory information

		Lab No.	
1			
2		Age of patient (years)	
3		Study number	

SECTION B: Specimen Details

Procedure……………………………………….

Is the procedure stated   YES   NO ☐

Specimen laterality

Right

Left

Not specified

Specimen integrity

Specified   yes   No

Tumor size

Specified   yes   NO

Specimen gross description

Provided yes ☐ **Gross**   **NO** ☐

margins indicated?

Provided   yes   NO ☐

Lymph node sampling

Done   Yes   NO

Tumor site

Tumor site reported   yes   NO ☐

Tumor site ………………………………………………..

Tumor Focality

Indicated   Yes ☐   NO   ☐

Type …………………………………………………………..

SECTION C: Microscopic Findings

1**. Histologic type**……………………………………………………………

    Histologic type reported   YES ☐   NO ☐

Histological grade

Degree of tubular formation

Indicated YES ☐   NO ☐

Nuclear pleomorphism

Indicated YES   NO ☐

Mitotic activity

Indicated   YES   NO ☐

Grade reported   YES ☐ NO ☐

Overall grade……………………………..

3. **Ductal carcinoma in-situ**

Is Presence or Absence of DCIS reported

YES [ ] NO [ ]

Is DCIS present

YES [ ] NO [ ]

If present:

Is Extensive Intraductal component reported?

YES [ ] NO [ ]

YES [ ] NO [ ]

YES [ ] NO [ ]

Is the presence or absence necrosis reported?

YES [ ] NO [ ]

4. **LCIS**

Presence OR Absence Reported

YES [ ] NO [ ]

5. **Is Margins Involvement indicated?**

YES ☐   NO ☐

If no

Is the margin indicated?

YES ☐   **NO** ☐

Is the Distance from closest margin indicated?

YES ☐   NO ☐

If yes:

Margins involved by invasive carcinoma OR DCIS indicated?

ReportedYES ☐   NO ☐

6. Is Presence or Absence of Paget's disease indicated?

YES ☐   NO ☐

7. Is presence or absence of Lympho- vascular invasion reported?

YES ☐   NO ☐

8**. Lymph node involvement**

Is number of positive nodes reportedYES ☐ NO ☐

Total number of lymph nodes sampled …………………………………

Is the presence or absence of extra nodal extension reported   YES ☐   NO ☐

Is the presence or absence of micro metastasis indicated   YES ☐   NO ☐

9. Is the presence or absence of Skin involvement Reported

YES ☐   NO ☐

10**. Is presence or absence of Micro-calcifications reported?**

YES ☐   NO ☐

11. Is presence or Absence skeletal muscle involvement reported?

YES ☐   NO ☐

12. Is the presence or absence of treatment effect indicated?

YES ☐   NO ☐

13. Is the Stage Indicated?

YES ☐   NO ☐

Stage…………………………………..

IMMUNOHISTOCHEMISTRY

13. **HORMONAL RECEPTORS**

RECEPTOR	RESULT
ER	
PR	

14. **HER2**

RECEPTOR	SCORE	RESULT

Appendix II: Sectioning Of Tissue Blocks

Equipment and materials

1. Microtome
2. Tissue Floatation Water Bath
3. Microwave oven
4. Diamond pencil
5. Slides and slide holder

Release the brake and rotate the hand wheel on the microtome until the handle is at 1 o'clock position and re-apply the brake.

Push the quick release lever of the cassette clamp backward, insert the cassette clamp backward, insert the cassette, release the lever and check that the cassette is firmly clamped.

Use the vertical and horizontal tilt controls to orientate the specimen correctly with the knife edge and lock the orientation head.

Release the brake and turn the coarse advance knob clockwise and anticlockwise to bring the tissue block closer or away from the cutting edge.

Trim the block using the coarse advance knob until the full face is attained.

Set the section thickness with thickness control knob.

Turn the hand wheel to cut the sections.

Pick the sections and place them into the tissue floatation water bath to remove the creases.

Fish the sections and mount on clean microscope slides. Label the slides with a diamond pencil.

Put the slides in a hot air oven at 56 degrees Celsius for 1hour. Remove the slides and stain.

Appendix III: HEMATOXYLIN AND EOSIN STAINING PROCEDURE

Put the mounted slides in water.

Stain in Harris Hematoxylin for 5 minutes.

Rinse in tap water.

Differentiate in1% acid alcohol, 3 dips.

Rinse in tap water.

Blue in Scott tap water for 30 seconds or in running tap water for 10 minutes.

Counter stain in Eosin for 5 minutes.

Rinse in tap water excess eosin followed by 70% ethanol to obtain the desired shades of red and pink.

Dehydrate in 3 changes of absolute alcohol.

Clear in 3 changes of Xylene.

Mount with D.P.X.

Appendix IV: ER/PR/HER2 VENTANA IMMUNO-STAINING PROTOCOL

4 μm thickness paraffin sections are baked overnight at 50°c.

Standard antigen retrieval in Tris –EDTA buffer pH 7.8 at 95°c for 44

minutes Deparaffinization in EZ prep 75°c 8 minutes.

Cell conditioning (antigen unmasking) using standard conditioner at 95°c for 44 minutes.

Block with inhibitor at 37°c 4 minutes.

Apply 100μl of primary antibody and incubate at 37 for 60 minutes

Apply one drop of anti- rabbit horse radish peroxidase and incubate for 16min.

Apply one drop of DAB and one drop of hydrogen peroxide and incubate for 8 minutes

Apply one drop of copper and incubate for 5 minutes.

Counterstain in Hematoxylin, incubation time 8 minutes.

Bluing reagent, incubation 8 minutes.

Wash the slides in warm tap water with detergent and dehydrate in alcohol, clear in xylene and mount

Apply coverslip and examine.

Nucleus stain blue

Positive cells stain brown: ER/PR are nuclear stains, HER2 stains the cytoplasmic membrane

Appendix V: Grading of Breast Cancer (Modified Bloom Richardson Grading System)

This grading system is based on 3 morphologic features; degree of tubular formation, nuclear pleomorphism and tumor mitotic activity.

1

Tubules formation	score
>75% of tumor cells arranged in tubules	1
10-75% of tumor cell arranged in tubules	2
< 10% of tumor cells arranged in tubules	3

2

Nuclear pleomorphism (anaplastic area)	score		
Small, regular, uniform nuclei, uniform chromatin	1		
Moderate variability in size and shape, vesicular with visible nucleoli	2		
Marked variation, vesicular, often with multiple nucleoli	3		

3

Mitotic activity	score		
< 6 mitosis in 10 HPF	1		
>7 and < 13mitosis in 10 HPF	2		
>13 mitosis in 10 HPF	3		

3-5 points: GRADE I: Well differentiated

6-7 points: GRADE II: Moderately differentiated

8-9 points: GRADE III: Poorly differentiated

Appendix VI: Breast Cancer Staging

T: for primary tumor

TX: Primary tumor cannot be assessed

To: No evidence of primary tumor

Tis (DCIS): Ductal carcinoma in situ

Tis (Paget): Paget diseases of the nipple not associated with invasive carcinoma and/or DCIS in the underlying breast parenchyma.

T1: Tumor measuring   20mm in greatest dimension

T1mi: Tumor   1 mm in greatest dimension

T1a: Tumor   1mm but   5 mm in greatest dimension

T1b: Tumor   5mm but   10mm in greatest dimension

T1c: Tumor   10mm but   20 mm in greatest dimension

T2: Tumor   20mm but   50mm in greatest dimension

T3: Tumor   5 mm in greatest dimension

T4: Tumor of any size with direct extension to the chest wall and/or to the skin (ulceration or macroscopic nodules); invasion of the dermis alone does not qualify as T4

T4a: Tumor extension to the chest wall; invasion or adherence to pectoralis muscle in the absence of invasion of chest wall structures does not qualify as T4

T4b: Ulceration and/or ipsilateral macroscopic satellite nodules and/or edema (including peau d'orange) of the skin that does not meet the criteria for inflammatory carcinoma

T4c: both T4a and T4b are present

T4d: Inflammatory carcinomas

REGIONAL LYMPH NODE

pNx: Regional lymph nodes cannot be assessed

pN0: no regional lymph node metastasis identified

pN1: Micrometastases; or metastases in 1-3 axillary lymph nodes; and/or clinically negative internal mammary nodes with micrometastases or macrometastases by sentinel lymph node biopsy

pN2: Metastases in 4-9 axillary lymph nodes; or positive ipsilateral internal mammary lymph nodes by imaging in the absence of axillary lymph node metastases

pN3: Metastases in 10 or more axillary lymph nodes; or in infraclavicular (Level III axillary) lymph nodes; or positive ipsilateral internal mammary lymph nodes by imaging in the presence of one or more positive Level I,II axillary lymph nodes; or in more than three axillary lymph nodes and micrometastases or macrometastases by sentinel lymph node biopsy in clinically negative ipsilateral internal mammary lymph nodes.

METASTASIS

M0: No clinical or radiographic evidence of distant metastases evidence of distant metastasis

cM1: Distant metastasis detected by clinical and radiographic means

pM1: Any histologically proven metastases in distant organs; or if in non- regional nodes, metastases greater than 0.2mm

STAGES

Stage 0   Tis, N0, M0

Stage IA   T1, N0, M0

Stage 1B T0 Nimi M0 or T1, Nimi, M0

Stage IIA   T0, NI, M0 or T1,N1, M0 or T2,N0, M0

Stage IIB   T2, N1, M0 or T3,N0,M0

Stage IIIA   T0, N2, M0 or T1, N2, M0 or T2,N2, MO or T3, N1,M0 or T3, N2,M0

Stage IIIB   T4, N0, M0 or T4, N1, M0 or T4, N2, M0

Stage IIIC   T0-4, N3, M0

Stage IV   T0-4, N0-3, M1

Appendix VII: Anti-plagiarism Certificate

HISTOPATHOLOGY REPORTING AND BIOMARKER TESTING OF INVASIVE BREAST CANCER AT KENYATTA NATIONAL HOSPITAL: AN AUDIT OF THE SYNOPTIC REPORTSAND DETERMINATION OF ER/PR/HER2 RECEPTOR PROFILES

ORIGINALITY REPORT

12%	4%	8%	8%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

1	Submitted to Higher Education Commission Pakistan Student Paper	1%
2	Submitted to Mount Kenya University Student Paper	1%
3	"Abstracts", Journal of Thoracic Oncology, 2009 Publication	1%
4	Neal W Wilkinson, Azin Shahryarinejad, Janet S Winston, Nancy Watroba, Stephen B Edge. "Concordance with breast cancer pathology reporting practice guidelines", Journal of the American College of Surgeons, 2003 Publication	<1%
5	"Breast", Laboratory Investigation, 01/2009 Publication	<1%

"Breast Surgical Techniques and

Appendix VIII: KNH/UON –ERC Letter of Approval

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June 4, 2018

Ref: KNH-ERC/A/198

Dr. Priscilla Githinji
Reg. No.H58/80746/2015
Dept.of Human Pathology
School of Medicine
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University of Nairobi

Dear Dr. Githinji

RESEARCH PROPOSAL – HISTOPATHOLOGY REPORTING AND BIOMARKER TESTING OF INVASIVE BREAST CANCER AT KENYATTA NATIONAL HOSPITAL: AN AUDIT OF TH SYNOPTIC REPORTS AND DETERMINATION OF ER/PR/HER2 RECEPTOR PROFILES (P119/03/2018)

This is to inform you that the KNH- UoN Ethics & Research Committee (KNH- UoN ERC) has reviewed and **approved** your above research proposal. The approval period is from 4th June 2018 – 3rd June 2019.

This approval is subject to compliance with the following requirements:
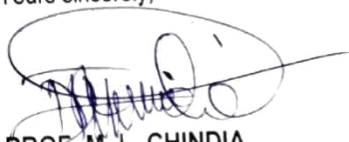
a) Only approved documents (informed consents, study instruments, advertising materials etc) will be used.
b) All changes (amendments, deviations, violations etc) are submitted for review and approval by KNH-UoN ERC before implementation.
c) Death and life threatening problems and serious adverse events (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) Clearance for export of biological specimens must be obtained from KNH- UoN ERC for each batch of shipment.
f) 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*).
g) Submission of an *executive summary* report within 90 days upon completion of the study.

Protect to discover

58

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 **http://www.erc.uonbi.ac.ke**

Yours sincerely,

PROF. M. L. CHINDIA
SECRETARY, KNH-UoN ERC

c.c.   The Principal, College of Health Sciences, UoN
          The Deputy Director, CS, KNH
          The Chairperson, KNH-UON ERC
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