CLINICOPATHOLOGICAL FEATURES OF MALIGNANT MELANOMA OF THE SKIN AMONG PATIENTS SEEN AT KENYATTA NATIONAL HOSPITAL

BY

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UNIVERSITY OF NAIROBI

A Dissertation submitted in part fulfilment for the award of Degree of Master of Medicine in Plastic and Reconstructive Surgery of the University of Nairobi.

STUDENT'S DECLARATION

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

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ABBREVIATIONS/ACRONYMS

AJCC:	American Joint Committee on Cancer
AMS:	Atypical Mole Syndrome
ALM:	Acral Lentiginous Melanoma
BCG:	Bacillus Calmette-Guerin
BCNU:	Carmustine
CCNU:	Lomustine
CI:	Confidence Interval
CL:	Clark's Level
CMM:	Cutaneous Malignant Melanoma
CT:	Computed Tomography
CTLA-4:	Cytotoxic T-lymphocyte-associated protein 4
CXR:	Chest radiograph
DTIC:	Dacarbazine
FDA:	Food and Drug Administration
FDG:	Fluorodeoxyglucose
H&E:	Haematoxylin and Eosin
IFN-α:	Interferon alfa
IL-2:	Interleukin 2
KEMRI:	Kenya Medical Research Institute
KNH- UON ERC:	Kenyatta National Hospital- University of Nairobi Ethics and Research Committee
LDH:	Lactate dehydrogenase
LFT:	Liver function tests
MBChB:	Bachelor of Medicine, Bachelor of Surgery
MEK:	Mitogen-activated protein kinase enzyme
MM:	Malignant Melanoma
MRI:	Magnetic Resonance Imaging
NO:	Number
PCR:	Polymerase Chain Reaction
PD-1:	Programed cell death-1

PD-L1:	Programed cell death-1 ligand
PD-L2:	Programed cell death-2 ligand
PET:	Positron Emission Tomography
PET/CT:	Positron Emission Tomography–Computed Tomography
QOL:	Quality Of Life
SD:	Standard Deviation
SES:	Socio-Economic Status
SLNB:	Sentinel Lymph Node Biopsy
SOPs:	Standard Operating Procedures
SPSS:	Statistical Package for Social Sciences
T:	Tumour
TNM:	Tumour, Node, Metastasis
U/S:	Ultrasound
UV:	Ultraviolet
UVA:	Ultraviolet A (long-wave) rays
UVB:	Ultraviolet B (short-wave) rays

ABSTRACT

Background: Malignant melanoma (MM) originates in the pigment-producing melanocytes of the skin. Although once considered uncommon worldwide, the annual incidence has increased over the last few decades. It is curable when diagnosed in its early stages, but poses a major challenge to the physician in advanced stages and can be fatal. While it is not the most common of the skin cancers, it causes the most deaths. There is paucity of data regarding the clinical and pathological characteristics of MM in Kenya.

Objective: The aim of this study was to describe the clinical and pathological characteristics of MM of the skin among patients at the Kenyatta National Hospital (KNH).

Materials and methods: This was a cross-sectional descriptive study carried out over 6 months at Kenyatta National Hospital (KNH) surgical wards and histopathology laboratory. Patients with skin lesions confirmed on histology of incisional biopsy, to be MM were enrolled consecutively from the: Plastic Surgery Ward, General Surgery Wards, Surgical Out-Patient Clinic and Accident and Emergency Department. Data collected included gender, age at diagnosis, clinical examination findings, histopathologic subtype, stage of the disease clinically and pathologically, Serum Lactate Dehydrogenase (LDH) level and radiological tests.

Data collected was checked for completeness, entered into MS Excel, cleaned and analyzed by the use of Statistical Package for Social Science (SPSS) version 20. Demographic data was presented by use of frequencies and percentages, as well as means and standard deviations. Categorical variables were analyzed as proportions. Fisher-Freeman-Halton exact test was used to test associations. All results were considered significant at $p < 0.05$. The data was presented in form of tables, bar charts and pie charts.

Results: The results of this study show that the most common histopathologic subtype of MM in the Kenyan population presenting at the Kenyatta National Hospital for treatment is acral lentiginous melanoma (ALM) followed by nodular melanoma. The female population is affected to a larger degree than the male population, with a male: female ratio of 1:2.4. The mean age was 62 years, and the peak incidence was in the 6^{th} and 7^{th} decade of life. The commonest symptoms were swelling and ulceration. The anatomical location of 95.8% of the lesions, was in the lower limb especially on the foot, the left being more frequently affected than the right. Majority of the patients presented with stage II disease with a higher number of them being female, followed by stage III disease. In this study 58.3% of the patients presented with T4b (Tumour) disease with ulceration being prevalent across all T size stages. 70.8% of the study population had disease with a Breslow thickness greater than 4mm. 54.2% of the patients presented with symptoms of 1-3 years.

Conclusion:
This study has demonstrated that the most common molecular subtype of MM across all age groups is ALM, followed by nodular melanoma. Majority of the patients presented with late stage disease. The poor prognosis in black patients in Kenya is the result of delayed presentation with thick primary lesions and advanced disease.

1.0 CHAPTER ONE: INTRODUCTION

Malignant Melanoma results from malignant transformation of the melanocyte, the pigment-producing cell of the body derived from neural crest cells [1]. As such, it can occur anywhere melanocytes are present, including skin, eye, and the mucous membranes of the upper digestive tract, brain, sinuses, anus, and vagina. By far, the most common tissue in which melanomas arise is the skin.

From a clinical and public health point of view, the malignant melanomas are the most important group of skin cancers. Although less common than the familiar basal and squamous cell tumours of the skin, they are much more frequently fatal, due to intrinsic tendency to lymphatic and haematogenous metastasis [2].

The four major histopathologic subtypes of MM are: lentigo maligna melanoma, superficial spreading melanoma, nodular melanoma, and acral lentiginous melanoma. Rare subtypes include: desmoplastic, mucosal, nevoid and verrucous melanoma.

Local data on incidence, mortality and five year prevalence is limited [3, 4]. It is a deadly cancer with 5-year survival rates ranging from 15% to 97% [4] worldwide. Locally, there are no studies which have been carried out on the clinical and pathological characteristics of MM in Kenya. This study therefore hopes to improve on the local data and assist in planning on treatment and preventive strategies where possible.

1.1 LITERATURE REVIEW

1.1.1 Definition

MM is a potentially serious type of skin cancer. It is due to uncontrolled growth of melanocytes which grow out of control and form a tumor. Melanomas are often brown and black in colour but can show other shades. Normal melanocytes are found in the basal layer of the epidermis, producing melanin, which protects the skin by absorbing ultraviolet (UV) radiation. Melanocytes are found in equal numbers in black and in white skin, but the melanocytes in black skin produce much more melanin. People with dark brown or black skin are very much less likely to be damaged by UV radiation than those with white skin.

1.1.2 Epidemiology

Local data on incidence, mortality and five year prevalence is limited. In a three year registry study of Nairobi by Kenya Medical Research Institute (KEMRI), twenty four cases of MM were identified. Of whom nine were male and fifteen were female [3]. In a similar study over five years, forty two cases of MM were identified, with a male: female of 9:11[4].

In a five and a half years study of eighty five MM African patients by Kakande at KNH [5], the male: female was 3:4 with a mean age of 52.2 years. The peak incidence was in the seventh decade of life. Three women (6.1%) belonged to stage III as compared to ten men (27.8%), six males (16.7%) and fifteen females (30.6%) were in stage I.

Data from the Kenyatta National Hospital statistics department shows that fourteen patients were admitted with MM in the first half of 2015, thirty nine in 2014, and fifteen in 2013, eighteen in 2011, twenty five in 2010, nineteen in 2009, thirteen in 2008, twenty four in 2007, twenty five in 2006, twenty eight in 2005 and forty one in 2004 (Table 1). This data extrapolates an average annual number of MM patients seen at KNH to be twenty four. Unfortunately this may not reflect the current state of events resulting from underreporting, which may also be attributed to poor record keeping.

Table 1: Number of patients admitted with MM of the skin at KNH

Duration	Number of patients
2015, January-June	14
2014	39
2013	15
2010	25
2009	19
2008	13
2007	24
2006	25
2005	28
2004	41

The 5-year relative survival rate for patients with stage 0 MM is 97%, compared with 10% for patients with stage IV disease. MM predominantly affects adults, with a peak incidence in the fourth decade, with no sex prevalence. After diagnosis of the first melanoma, a patient's risk of developing a second primary melanoma is 3-5%. MM poses an increasingly difficult problem as more people are affected. The global incidence is estimated to be rising by almost 6% per year. Recognition of this disease is paramount so that patients may seek medical attention while the tumor is still in its early stages, preceding metastasis.

In the United States, the incidence of MM continues to increase, with the prevalence of trunk and extremity lesions rising relatively faster than that of head and neck lesions; however, survival rates are improving. An estimated 34,100 people developed MM in the United States in 1995, with 7,200 deaths [6]. This is an increase from the 27,600 new cases in 1990 and the 6,300 deaths [6]. Furthermore, approximately 44,200 new melanoma diagnoses were made in 1999, and approximately 7,300 deaths were reported [7]. Currently, in the United States, approximately 1 in 40 White people, 1 in 1,000 Black people, and 1 in 200 Hispanic people develops MM at some point in their lifetime [8].

Internationally, incidence varies worldwide. White populations in South Africa, southern United States, New Zealand and Australia have the highest rates, while Asian populations in Japan, China, Singapore, India and Hong Kong have the lowest rates. This suggests that white people who live in sunny areas are at significant risk. Studies done in different regions worldwide estimate the prevalence of MM to be 1.6% [9].

1.1.3 Risk factors/Aetiology

1. Family history – There is a positive family history in 5-10% of patients; with at least one affected relative, this translates to a 2.2-fold higher risk.

2. Personal characteristics - Blue eyes, fair and/or red hair and pale complexion. Fitzpatrick skin type classification which defines the risk for skin cancer as high for type 1 and 2, moderate for type 3 and 4 and mild for type 5 and 6. Refer to appendix II for detailed information; skin reaction to sunlight (easily sunburned); freckling; benign and/or dysplastic melanocytic nevi (number has better correlation than size); immunosuppressive states (transplantation patients and hematologic malignancies).

3. Sun exposure over lifetime – High ultraviolet B (UVB) and ultraviolet A (UVA) radiation exposure (Recent evidence has shown that the risk of melanoma is higher in people who use sunscreen. This is because sunscreen mostly blocks UVB, people using sunscreen may be exposed to UVA more than the general public, provided those people are exposed to the sun more than the general public) [10]; low latitude; number of blistering sunburns and use of tanning beds [11].

4. Atypical mole syndrome (AMS), (formerly termed B-K mole syndrome, dysplastic nevus syndrome or familial atypical multiple mole melanoma) for over ten years, carries a 10.7% risk of melanoma (versus 0.62% of controls). There is a higher risk of melanoma depending on the number of family members affected (with nearly 100% risk if two or more relatives have dysplastic nevi and MM).

5. Socioeconomic status (SES) - Lower SES may be linked to more advanced disease at the time of diagnosis. One survey of newly-diagnosed patients, found that low SES-persons have decreased MM risk perception and knowledge of the disease [12].

1.1.4 Pathophysiology

The skin is composed of multiple layers. The epidermis is the most superficial layer, and it contains keratinocytes in various stages of development. Melanocytes are located in its deepest layer. A basement membrane separates the epidermis from the underlying dermis, which is divided into papillary and reticular dermis. Subcutaneous tissue is deep to the reticular dermis.

In 1874, Sappey performed an anatomic study of cutaneous lymphatic drainage. This and follow up research concluded that an extensive overlap of basins drain the head, neck, shoulders, and trunk. In addition a specific basin cannot be predicted based on cutaneous location. Hence performing lymphoscintigraphy, to define the exact lymphatic drainage for each patient is necessary [13].

Researchers have suggested that benign melanocytic nevi are markers of MM risk rather than direct precursors; however, dysplastic nevi are believed to degenerate into MM over time. Lentigo maligna is believed to be a pervasive precursor of lentigo maligna MM, and at least 5% progress to malignancy [14].

1.1.5 Signs and symptoms

The skin lesion physical characteristics suggestive of malignancy (known by the acronym ABCDE) include: A: Asymmetry, B: Irregular border, C: Colour variations: Especially white, red and blue tones in a black or brown lesion, D: Diameter greater than 6 mm and E: Elevated surface [1].

Lesions may itch, ulcerate, bleed, or develop satellites. Patients who present with metastatic disease or with primary sites other than the skin, have signs and symptoms related to the affected organ system(s) [1].

1.1.6 Diagnosis

Even though the ideal method is complete excisional biopsy [15], the location of the MM may require alternatives. Dermatoscopy of acral pigmented lesions is very difficult, but can be accomplished with diligent attention. Initial confirmation of the suspicion can be done with a small wedge or punch biopsy. [16] Once this confirmatory biopsy is done a second complete excisional skin biopsy can be performed with a narrow surgical margin (1 mm). This second biopsy will determine the depth and invasiveness of the MM [17], and will help to define what the final treatment will be.

The most important prognostic indicator for stage I and II tumours is thickness, so a full-thickness biopsy must be obtained for adequate pathologic interpretation. Biopsy results ultimately determine the margins of resection and which patients are candidates for Sentinel Lymph Node Biopsy (SLNB) and other adjuvant treatment. SLNB is conducted with the use of blue dye, radioisotope, or both, injected at the site of the primary MM, the first-echelon node can be identified within the regional lymph node basin. Pathologist analysis using routine stains, immunohistochemistry, and even polymerase chain reaction (PCR) follows. SLNB is the standard of care for tumours greater than 1 mm in depth.

1.1.7 Histopathologic subtypes

The four major types of MM, classified according to growth pattern are:

Acral lentiginous MM (ALM): Although rare in Caucasians and people with lighter skin types constituting 2-8% of MM in whites, it is the most common subtype in people with darker skins comprising 35-60% in dark-skinned people [18]; may appear on the palms and soles as flat, brown, or tan stains with irregular borders; subungual lesions can be black or brown, with ulcerations in later stages [19]. It occurs on non-hair-bearing surfaces of the body, which may or may not be exposed to sunlight. It is also found on mucous membranes [2].The average age at diagnosis internationally is between sixty and seventy years [20]. Cellular proliferation is present along the dermal-epidermal junction with microinvasion into the papillary dermis and desmoplasia [21]. The cells have increased melanin granule production, which fills their dendritic extensions. According to Scolyer et al [22] ALM is usually characterized in its earliest

recognisable form as single atypical melanocytes scattered along the junctional epidermal layer. No correlation with a worse prognosis is demonstrated for these lesions when tumor thickness is considered. It has a poorer prognosis rate, in comparison to Cutaneous Malignant Melanoma (CMM) [23]. If caught early, the cure rate is similar to other types of superficial spreading MM.

Superficial spreading MM: Constitutes approximately 70% of MM; usually flat but may become elevated and irregular in later stages; the lesions average 2 cm in diameter, with variegated colours, and peripheral notches, indentations, or both. Histologically, the characteristic cells can be present singly or in nests along the dermal-epidermal junction, but they also may migrate into the stratum granulosum or corneum. These cells may invade the papillary dermis with an inflammatory lymphocytic infiltrate. Clinically, they usually arise in a pre-existing dysplastic nevus [24]. Typically, this lesion changes slowly over time, several months to years.

Nodular MM: Accounts for approximately 15-30% of MM diagnoses; the tumors typically are blue-black but may lack pigment. Histology of nodular MM is characterized by extensive vertical growth into the dermis with a minimal radial component. It is known to arise without a preexisting lesion.

Lentigo maligna MM: Represents 4-10% of MM; the tumors are often larger than 3 cm, flat, and tan, with marked notching of the borders; they begin as small, freckle like lesions. Dermal and epidermal changes from sun exposure, must be present on a cellular level. Histologically it appears as irregularly shaped hyperchromatic cells that form spindle-shaped nests. The epidermis appears atrophic, while the dermis contains solar elastosis with chronic inflammatory infiltrates. They occur in sun-exposed areas (e.g., neck and face of older individuals). Lentigo maligna MM usually arises within a Hutchinson freckle. Prognosis for these melanomas is not believed to be worse than that for other subtypes, when tumor thickness and location are taken into consideration [25].

Desmoplastic MM is a less common subtype of MM that lacks pigment and may demonstrate perineural invasion, especially in the neck and head. They are fairly rare, accounting for

approximately 1% of MM cases. They have a propensity for higher local recurrence rates but lower regional metastasis rates.

1.1.8 Classification and staging

Two classification schemes have been developed, based on either the vertical thickness of the lesion in millimetres or the anatomic level of invasion of the layers of skin. The Breslow classification scheme is used almost exclusively now because it more accurately predicts future tumour behaviour. The Clark's level is now used only in the staging of thin (T1) MM. The TNM (tumour, node and metastasis) system is used for clinical staging as designated by the American Joint Committee on Cancer (AJCC) staging system [26].

Breslow classification

Thickness of 1mm or less

Thickness of 1.01-2 mm

Thickness of 2.01-4 mm

Thickness greater than 4 mm

Clark's Level (CL)

Level I - Involves only epidermis (in situ MM); no invasion

Level II - Invades papillary dermis but not papillary-reticular dermal interface

Level III - Invades and expands papillary dermis up to the interface with, but not into, reticular dermis

Level IV - Invades reticular dermis but not into subcutaneous tissue

Level V - Invades into subcutaneous tissue

TNM staging

Refer to appendix 1 for detailed information.

AJCC groupings [27, 28]

Refer to appendix 1 for detailed information.

Clinical staging includes microstaging of the primary MM and clinical/radiologic evaluation for metastases. MRI of the brain is indicated in a patient with known distant metastases to detect additional asymptomatic metastases. Especially for patients being considered for high-dose interleukin-2 treatment. Where there's no known metastatic disease, MRI of the brain should be reserved for those patients who are symptomatic [48].

Positron Emission Tomography (PET) scans are not indicated in stage I or II disease, but in staging patients with known nodal involvement or in-transit or satellite lesions. Studies have reported that PET scans have greater sensitivity than conventional radiographic studies for the detection of metastatic disease. One meta-analysis found PET CT scanning to be the best imaging study to utilize for finding other sites of metastasis [49]. In particular, Fluorodeoxyglucose (FDG) Positron emission tomography–computed tomography (PET/CT) scans are a valuable tool for detecting additional metastasis in patients with metastatic melanoma[50], and are superior to stand-alone PET[51, 52, 53, 54]. PET scans are useful in evaluating the response of metastatic disease to therapy.

By convention, clinical staging should be used after complete excision of the primary MM with clinical assessment for regional and distant metastases.

Pathologic staging includes microstaging of the primary MM and pathologic information about the regional lymph nodes after partial or complete lymphadenectomy. Pathologic Stage 0 or Stage IA patients are the exception; they do not require pathologic evaluation of their lymph nodes.

1.1.9 Management

Medical Therapy

Medical therapy is useful as adjuvant treatment in advanced stages of unresectable or metastatic MM. Recent Food and Drug Administration (FDA) approvals include trametinib (Mekinist), dabrafenib (Tafinlar), ipilimumab (Yervoy), vemurafenib (Zelboraf), pembrolizumab (Keytruda), and nivolumab (Opdivo). Trametinib is a mitogen-activated protein kinase enzyme (MEK) inhibitor indicated for MM with BRAF (human gene that makes a protein called B-Raf)

V600E or V600K mutations. Dabrafenib is a BRAF protein kinase inhibitor indicated for melanoma with BRAF V600E mutation. Ipilimumab is targeted T-cell antibody that binds to cytotoxic T-lymphocyte-associated protein 4 (CTLA-4). Vemurafenib is an inhibitor of some mutated forms of BRAF serine-threonine kinase, including BRAF V600E. Pembrolizumab and nivolumab are monoclonal antibodies to programed cell death-1 (PD-1) protein. They block the interaction between PD-1 and its ligands (i.e., PD-L1 and PD-L2) [29, 30].

Surgical Therapy

Surgical therapy for MM is based on the predicted risk of local recurrence and metastatic disease and the potential morbidity of the operation. It is potentially curable, if the lesion has not spread beyond the primary site.

Stage 0

Wide excision with a 0.5 to 1 cm margin then observation for nodal or recurrent disease is necessary.

Stage I

1 cm excision margins. 2 cm margins for lesions greater than 1 mm and primary closure, skin grafting or flap to achieve closure.

Stage II

2 cm excision margins. No recurrence or survival advantage is gained when 2 cm margins are compared with wider margins (4-6 cm), as confirmed in a 2011 European study [31]. In addition smaller resection decreases the need for skin grafting and inpatient hospital stay [32].

Patients with suspected lymph node metastases based on physical examination findings, undergo complete elective lymphadenectomy. It involves excision of all lymph nodes in the affected regional lymph node basin.

SLNB where clinically positive nodes are absent, if positive regional lymph node metastases is probable and a complete lymph node dissection is indicated. If negative, the chance is 99% that all others are negative.

Lymphoscintigraphy is an imaging technique used to identify the lymph drainage basin, determine the number of sentinel nodes, differentiate sentinel nodes from subsequent nodes, locate the sentinel node in an unexpected location, and mark the sentinel node over the skin for biopsy. It's very beneficial in stage I and II melanoma [33, 34, 35]. Tc 99m tilmanocept is also approved for intradermal or SC injection for melanoma mapping [36]. The Multicenter Selective Lymphadenectomy Trial concluded that sentinel node scanning is a low-morbidity procedure for evaluating the regional nodal basin in early melanoma and should become the standard of care [37].

The use of hyperthermic arterial limb perfusion with melphalan, for extremity MM as an adjuvant therapy, was found to be beneficial in one study. In that it produced higher response rates and overall survival rates than those for surgery alone. Other studies do not demonstrate benefit.

Also undergoing clinical evaluation is the use of adjuvant chemotherapy and/or biological therapy. One study demonstrated that high-dose interferon alfa-2b resulted in prolonged relapse-free survival and overall survival compared with no adjuvant therapy. A follow-up study by the same group demonstrated preliminary results indicating high-dose interferon achieved a relapse-free survival benefit over no adjuvant treatment but not over low-dose interferon. Neither high- nor low-dose interferon had a significant overall survival advantage compared with observation alone. High-dose interferon can be associated with significant toxic/adverse effects (i.e., liver toxicity), and some patients require dose reduction because it may not be well tolerated.

Stage III

2 cm excision margins and regional lymph node dissection. Wider resection margins have no survival advantage [31, 32, 38]. To close the defect, skin grafting or other tissue-transfer techniques

may be necessary. The treatment failure rate is higher with wide local excision alone in this group as in stage II disease, compared with stages 0 and I.

Stage IV

Advanced metastatic MM is usually refractory to standard therapy; thus, these patients are considered for clinical trials. Although usually short-lived, some treatments have yielded various objective responses. Dacarbazine (DTIC) and the nitrosoureas, carmustine (BCNU) and lomustine (CCNU), produced a 20% objective response rate. Response rates for interferon alfa (IFN-α) and interleukin 2 (IL-2) range from 8-22% and 10-20%, respectively. A study showed improved rates of overall and progression-free survival in patients with previously untreated MM with the BRAF V600E mutation who received vemurafenib versus standard DTIC [39]. Another trial showed improved survival for patients treated with ipilimumab and DTIC versus placebo and DTIC [40].

Hyperthermic isolated limb perfusion therapy is a more effective way of controlling disease than isolated limb infusion therapy, according to another study looking at treatment of advanced extremity MM showed that [41].

For palliation, surgical resection of isolated metastases in the gastrointestinal tract, brain, lungs, bone, or lymph nodes may be performed. Symptomatic relief for metastases to bone, brain, or viscera, may be provided through radiation. At a rate of 2-3%, in-transit metastases arise in the lymphatics or soft tissue between the primary lesion and the regional lymph node basin. It's probable that the most effective treatment for extremity lesions, in addition to wide surgical excision as for a primary lesion, is isolated hyperthermic limb perfusion. Intralesional BCG (Bacillus Calmette-Guerin) vaccine injections and radiation have had varied success.

Recurrent melanoma

MM is usually refractory to most standard systemic therapy; however, surgical excision offers the most efficacious results in sites where it can be accomplished.

2.0 CHAPTER TWO: STUDY JUSTIFICATION

MM is a relatively uncommon but not a rare neoplasm in Africans. In spite of the few patients presenting to the KNH annually, as evidenced by the data from the KNH statistics department no study has been carried out in Kenya with regard to the clinicopathological characteristics of MM.

There are well recognized racial and ethnic variations in prevalence of MM worldwide. Most of the studies have been carried out in Caucasian and Asian populations with none having been done in African populations. There is paucity of data on the clinicopathological characteristics of these tumors in Kenya.

This study therefore seeks to fill these gaps in the knowledge by providing baseline data on the clinical and pathological characteristics of MM. Thus form a basis for the further research on management protocols, resulting in a positive impact on their quality of life.

3.0 CHAPTER THREE: STUDY OBJECTIVES

3.1 Broad objective

To describe the clinicopathological characteristics of Malignant Melanoma of the skin as seen at the Kenyatta National Hospital.

3.2 Specific objectives

1. To describe the anatomical location and gross appearance of Malignant Melanoma of the skin at the KNH.
2. To describe the histological characteristics of Malignant Melanoma of the skin at the KNH.
3. To describe the clinical staging of patients presenting with Malignant Melanoma of the skin at the KNH.

4.0 CHAPTER FOUR: MATERIALS AND METHODS

4.1 Study design

This was a Cross-sectional descriptive study conducted over 6 months.

4.2 Study setting

Study was conducted at KNH Surgical Wards (Plastic Surgery Ward, General Surgery Wards), Surgical Out-Patient Clinic, Accident and Emergency Department and histopathology laboratory.

4.3 Study population

Patients with a histopathological diagnosis of MM of the skin.

4.4 Inclusion criteria

The following cases were considered eligible for inclusion in the study:

1. Patients with skin lesions confirmed on histology of incisional biopsy, to be malignant melanoma.
2. Patients who consent or provide accent to participate in the study.

Patients with skin lesions confirmed on histology of incisional biopsy, to be malignant melanoma were enrolled consecutively from the: Plastic Surgery Ward, General Surgery Wards, Surgical Out-Patient Clinic and Accident and Emergency Department; by the principal investigator assisted by a trained study assistant. For the purpose of this study, a trained study assistant was defined as a medical officer with a minimal qualification of Bachelor of Medicine, Bachelor of Surgery (MBChB). The assistant was well informed of what the study entails and information that needed to be collected to make the study a success.

4.5 Exclusion criteria

1. Patients who declined to participate in the study.
2. Patients who did not undergo an excisional biopsy.

4.6 Sampling method

Consecutive patients who met the inclusion criteria and consented to take part in the study were recruited.

Sample size was calculated using the formula;

$$n = \frac{Z^2 x\ P(1-P)}{d^2}$$

(L. Naing, T. Winn, B.N. Rusli: Practical Issues in Calculating the Sample Size for Prevalence Studies; Archives of Orofacial Sciences 2006; 1: 9-14)

Where:

n = Desired sample size

Z = Standard normal distribution corresponding to desired confidence level (Z=1.96 for 95% confidence interval (CI).

P = Expected true proportion (estimated at 0.016), studies done in different regions worldwide estimate the prevalence of MM to be 1.6% [9].

d = Desired precision (0.05)

$$n = \frac{1.96^2 x\ 0.016(1-0.016)}{0.05^2} = 24$$

4.7 Data collection

The study was based at KNH surgical wards and histopathology laboratory. It commenced once approved by the department of surgery and Ethical Research Committee (ERC) - KNH- UON. I the principal investigator was assisted by one research assistant who was at the level of medical officer with a minimal qualification of MBChB. The research assistant's role was to identify patients in the General Surgery Wards and Accident and Emergency department who had skin lesions confirmed on histology of incisional biopsy to be MM. I the principal investigator identified patients in the Plastic Surgery Ward and the Surgical Out-Patient Clinic.

Recruitment of participants who met the inclusion criteria was done, where the study participants were informed of the nature, purpose, confidentiality, potential benefits and harmful effects of the study. From those who agreed to participate in the study, informed written consent was obtained and subsequently enrolled in the study. I the principal investigator clerked and conducted a physical examination on all research participants. Information obtained included

gender, age at diagnosis, clinical examination findings, histopathologic subtype, stage of the disease clinically and pathologically, serum Lactate dehydrogenase (LDH) level and radiological tests. This data was entered in a pretested data entry sheet partially adapted from the Tumour Node Metastasis (TNM) staging from the American Joint Committee on Cancer (AJCC) Staging Manual, Seventh Edition (2009) on diagnosis of MM of the skin (Appendix III).

The patients underwent excision or amputation of the site affected by the MM lesion depending on their clinical staging. The surgery was carried out in the KNH operating room, by surgeons in KNH Plastic Surgery Ward and General Surgery Wards. These surgeons were assisted by residents in their units. The histology specimens were handled no different than others in KNH. In the histopathology laboratory all excision and amputation specimens were evaluated by a dermatopathologist. Sensitization of the surgeons, residents and the pathologist was done through presentation at the Plastic Surgery tutorials, Plastic Surgery Clinic, Tumour Board and surgical conferences.

4.8 Laboratory procedures

Following gross examination and collection of tissues for evaluation, the specimen was preserved for at least six hours in 10% neutral buffered formal saline then processed for up to eight hours to dehydrate the tissues to prevent tissue degradation. The tissue was then filled with warm wax and transferred to a stainless steel mould where the molten paraffin wax was allowed to set to give the tissue support and shape, and allow for sectioning. The wax impregnated tissue was then allowed to cool and solidify.

It was then sectioned using a microtome to produce thin slices of tissue about one cell thick (about 3-4 micrometers). The thin sections were then floated on warm water so that they can be easily maneuvered and transferred to glass slides. The tissue section was then stained with Haematoxylin and Eosin (H&E) stain and the slide covered with a thin layer of glass. The slides were then evaluated microscopically by the dermatopathologist. Pathological analysis for tumour subtype, ulceration status, neurovascular invasion, Breslow thickness (maximum diameter of the invasive tumour) and mitotic activity was done.

4.9 Quality assurance

Only I the principal investigator, clerked and conducted a physical examination on all research participants. All reagents were prepared in accordance with Standard Operating Procedures (SOPs) and with the manufacturer's instructions. The fixation was made immediately using 10% neutral buffered formal saline and tissue processed using standard histology preparation protocols. All the stained sections were reported by an experienced consultant dematopathologist. All sections were randomly picked and re-examined by an independent pathologist. The pathologists then deliberated on their independent findings, to establish a consensus if discordance was noted in the tissue examination.

4.10 Data analysis

Data collected was checked for completeness, entered into MS Excel, cleaned and analyzed by the use of Statistical Package for Social Science (SPSS) version 20. Demographic data was analyzed by use of frequencies and percentages, as well as means and standard deviations. Categorical variables were analyzed as proportions. Fisher-Freeman-Halton exact test was used to test associations. All results were considered significant at $p < 0.05$. The data was presented in form of tables, bar charts and pie charts.

4.11 Study limitation

1. The main drawback of this study was the small sample size and challenging follow-up of patients, so that some of our outpatients were lost to follow-up.
2. We couldn't assess for metastasis on all our study subjects, as they couldn't afford the tests. These included serum LDH level and radiological tests (CXR, U/S, abdominal CT, chest CT).
3. We couldn't assess the lymph node stage of all patients as SLNB and elective lymph node dissection doesn't form part of the protocol of management of MM in KNH. This may have skewed our data on stage of disease.

4.12 Results dissemination

Results of this study will be submitted in part fulfillment of the degree of Master of Medicine in Plastic and Reconstructive Surgery, and will be disseminated to the Head of Plastic Surgery Unit

in the department of Specialized Surgical Services in KNH and to the overall head of Surgical Services in KNH. Copies will also been availed to the UON; Department of Surgery, College of Health Sciences library and to The Ethics and Research Committee of KNH- UON. The findings of this study will be disseminated in seminars, conferences and workshops. Manuscripts will be submitted for publication in peer reviewed journals.

4.13 Ethical Considerations

The study commenced after approval was obtained, from the Department of Surgery UON and the KNH- UON ERC. All tissue biopsy samples were carefully used to make tissue sections to avoid risks that can be caused by repeat of procedure.

Electronic data files generated were password protected, whereas hard copies were kept in a locker and secured. Access was controlled by the principal researcher and limited to the research assistant on authorization by the principal researcher and the principal researcher. At completion of the study, raw data in hard copy was destroyed. Patient privacy and confidentiality was strictly observed. All results of histology were communicated to the attending surgeon adding value to the management of the patient.

The patient received pre-consent counselling on the study after which informed consent was obtained from them. With a signed informed consent the patient was enrolled into the study.
Patients were not coerced to enroll as patients in the study. Non-participation did not affect such a patient's care in the hospital. Participation in this study did not attract extra cost to the medical care of the participants. Feedback of information; all participants were informed of the histology results and further care needed depending on their results.

5.0 CHAPTER FIVE: RESULTS

5.1 Characteristics of the study population:

Out of the twenty nine patients recruited, five patients did not undergo an excisional biopsy of their lesion. Of the twenty four analyzed, 70.8% were female and 29.2% were male. They ranged in age from 38-90 years with a mean age of 62 yearswith a standard deviation (SD) of 12.9 years. The male and female age distribution was a follows: 30-40 years; 1 and 0 respectively, 41-50 years; 2 and 1 respectively, 51-60 years; 3 and 4 respectively, 61-70 years; 0 and 7 respectively, 71-80 years; 1 and 4 respectively and 81-90 years; 0 and 1 respectively. Peak incidence was in the 6th and 7th decade of life (Figure 1).There was no statistically significant difference between age in years and gender as assessed by Fisher-Freeman-Halton exact test, (p = 0.170).

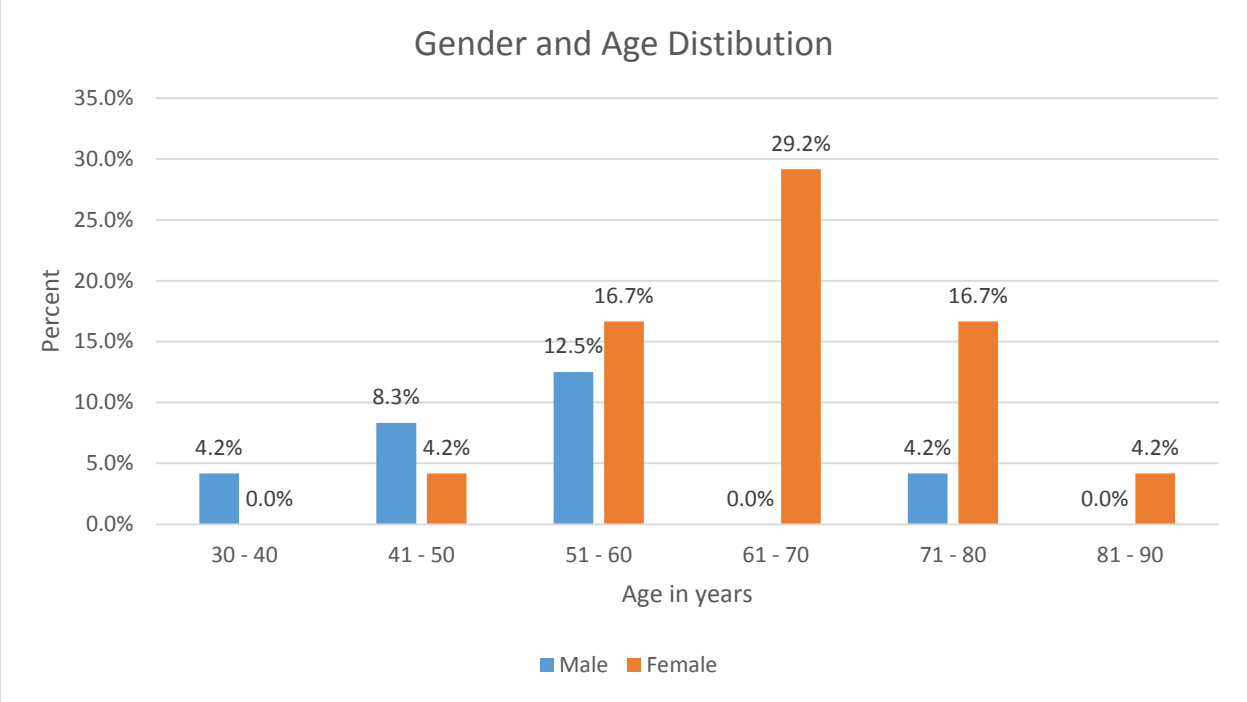

Figure 1: Gender and Age distribution

The distribution of sites of origin of melanoma was varied. A majority occurring on the foot, the left (13) being more frequently affected than the right (9) foot. One patient had melanomas arising from the eyelid, ear and lip (Table 2 and Figure 2). This patient had Fitzpatrick skin type 1, as he was an albino.

Table 2: Site of primary lesion

Primary site	Frequency (%)
Lower limb	23 (95.8)
Leg	1(4.2)
Foot	22 (91.7)
Left	13 (59)
Right	9 (40.9)
Head	1 (4.2)
Total	24 (100.0)

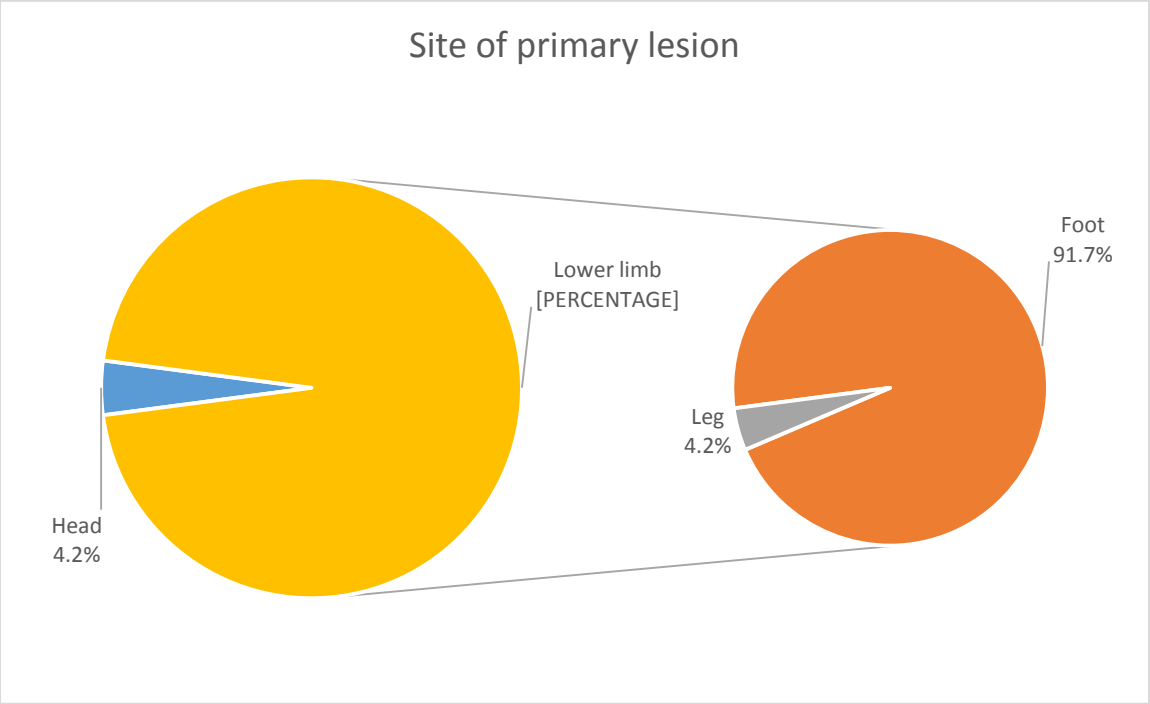

Figure 2: Site of primary lesion

There were only 4 patients with duration of symptoms of less than one year, at the time of presentation to the hospital. More than three quarters of the patients had had symptoms for over a year (85.7% men, 82.4% women). The male and female distribution of duration of symptoms was as follows: less than one year; 1 and 3 respectively, 1-2.9 years; 5 and 8 respectively, 3-4.9 years; 1 and 3 respectively, 5-6.9 years; 0 and 1 respectively and 9-10.9 years; 0 and 2 respectively (Figure 3). There was no statistically significant association between duration of symptoms in years and gender as assessed by Fisher-Freeman-Halton exact test, ($p = 0.934$).

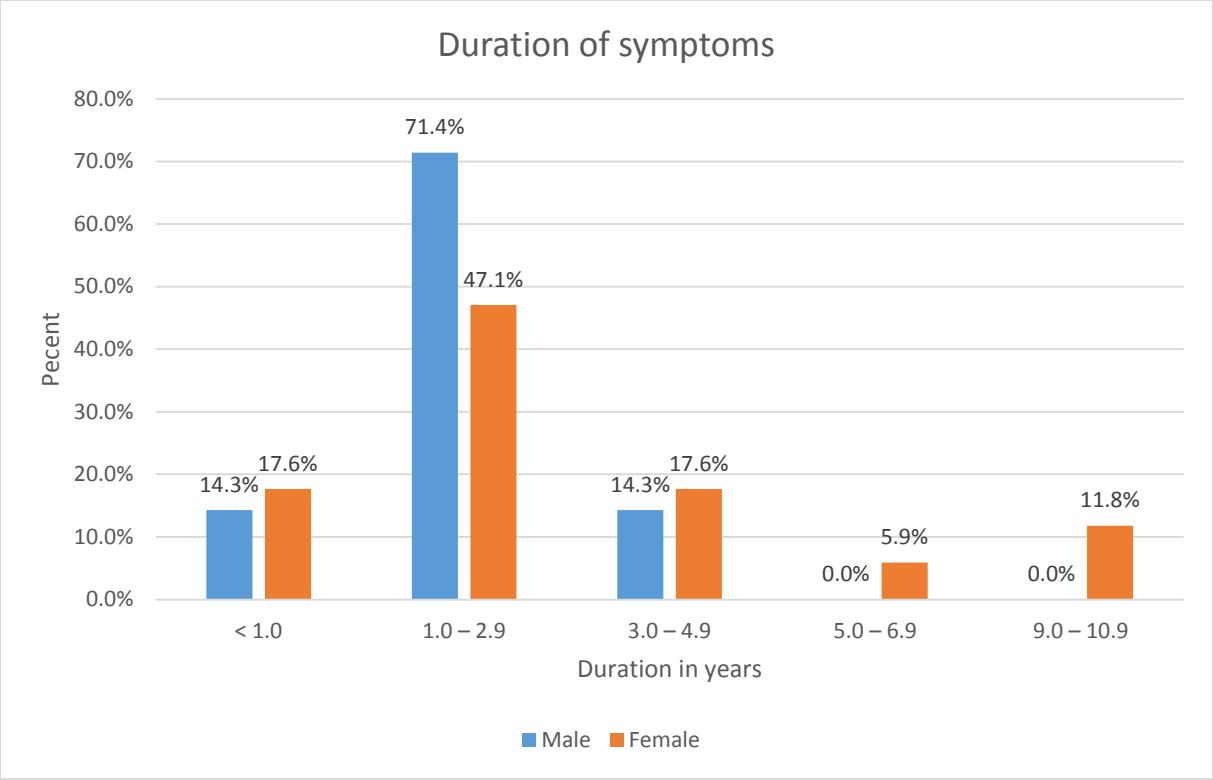

Figure 3: Duration of symptoms

Staging by the TNM system revealed that three patients presented with stage I disease, eleven with stage II, six with stage III, and four with disseminated metastatic disease. Three women (17.6%) had stage I as compared to no men (0%). An equal number of women (2, 11.8%) and men (2, 28.6%) had stage IV melanoma (Table 3). Majority of the female patients presented with stage I and II disease as compared the male patients. We couldn't assess for metastasis on all our study subjects, as they couldn't afford the tests. These included serum LDH level and radiological tests (CXR, U/S, abdominal CT, chest CT). We also couldn't assess the lymph node stage of all patients as SLNB and elective lymph node dissection doesn't form part of the protocol of management of MM in KNH. This may have skewed our data on stage of disease. The available test results were incorporated to derive the TNM stage of each research participant. There was no statistically significant association between stage of disease and gender as assessed by Fisher-Freeman-Halton exact test, ($p = 0.737$).

Table 3: Stage of disease

Stage	Male (n, %)	Female (n, %)	Total
I	0 (0.0)	3 (17.6)	3 (12.5)
II	3 (42.9)	8 (47.1)	11 (45.8)
III	2 (28.6)	4 (23.5)	6 (25.0)
IV	2 (28.6)	2 (11.8)	4 (16.7)
Total	7 (100.0)	17 (100.0)	24 (100.0)

Assessment of the tumour vertical thickness in millimetres showed that seventeen (70.8%) of the study population had a Breslow classification of greater than 4mm, while four (16.7%) had a Breslow classification of 0-1mm (Table 4).

Table 4: Breslow thickness (mm)

	Frequency	Percentage
0-1	4	16.7
2.01 – 4	3	12.5
>4	17	70.8
Total	24	100.0

The most common histopathologic subtype of MM in the Kenyan population presenting at the Kenyatta National Hospital for treatment is acral lentiginous M (70.8%), followed by nodular M (29.2). The male and female distribution of histopathologic subtypes was as follows: ALM; 4 and 13 respectively and nodular M; 3 and 4 respectively. There was no other subtype identified in the population (Figure 4).There was no statistically significant association between histological subtype and gender as assessed by Fisher-Freeman-Halton exact test, ($p = 0.374$).

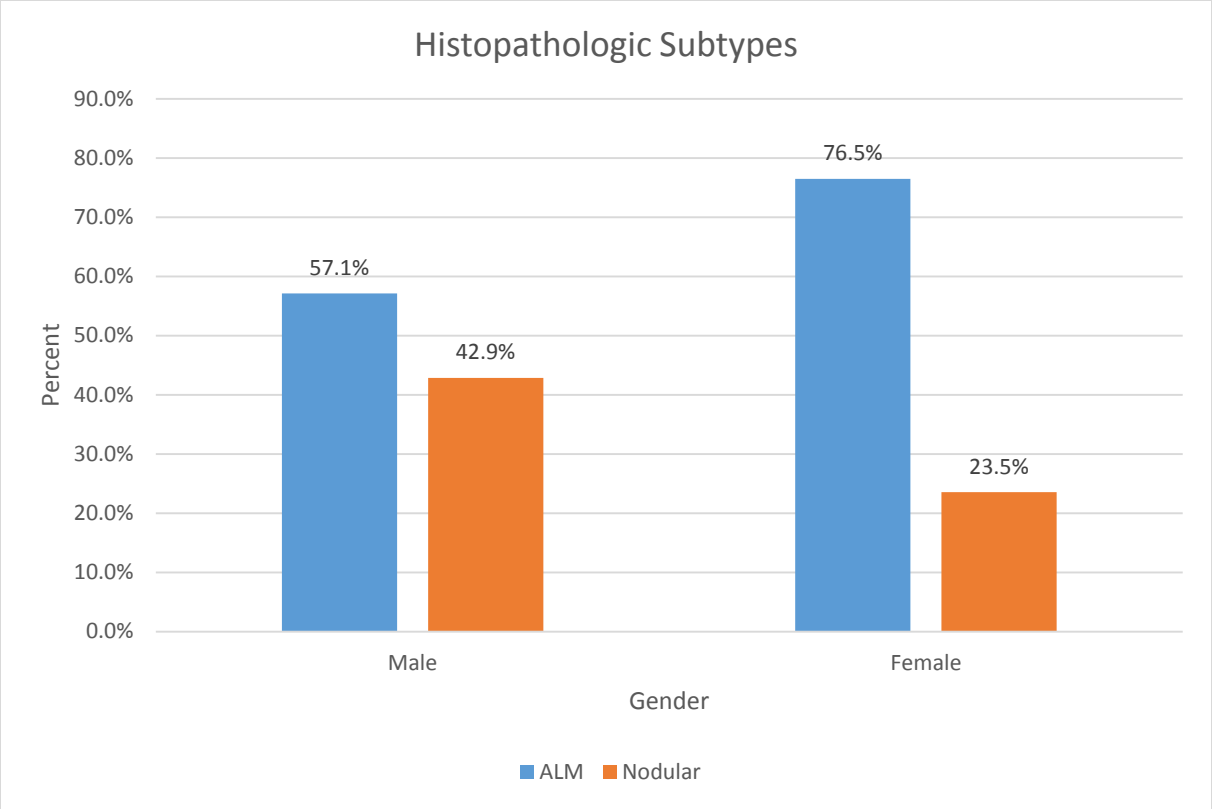

Figure 4: Histopathologic subtypes

6.0 CHAPTER SIX: DISCUSSION

6.1 Discussion

Melanoma is potentially the most dangerous form of skin tumour and causes 90% of skin cancer mortality [42]. It's increasingly an important global health problem as incidence rates of cutaneous melanoma continue to rise almost inexorably worldwide. Diagnosis of MM at an early stage is almost always curable and a large proportion of melanomas probably can be ascribed to a single (modifiable) risk factor; sun exposure [43]. Major initiatives in recent years have concentrated on education about sun avoidance, the importance of skin awareness and skin examination, and the screening of populations at high risk for melanoma.

Exposure of the skin to the sun results in short term effects including freckles, rashes and sunburn. Whereas the long term effects include accelerated skin ageing making it dry, wrinkled, loose and dull and pigment changes. It can also cause changes in the skin cells, which may lead to skin cancer. This exposure to UV radiation through sunlight, is a major etiologic factor associated with the incidence of melanoma across all Fitzpatrick skin types [10, 11, 43].

The results of this study show that the mean age was 62 years, range in age was from 38-90 years with a standard deviation (SD) of 12.9 years. Peak incidence was in the sixth and seventh decade of life. This is in keeping with findings by Hudson and krige in a South African population with a mean age of 60.5 years, range in age was from 30 to 85 years, and peak incidence was in the sixth decade [44]. Therefore sun avoidance education and screening should target all age groups, young and old.

Site of lesion in a majority of the patients with Fitzpatrick skin type 6, occurred on the foot; the left (13) being more frequently affected than the right (9) foot. This is in keeping with findings by Hudson and krige in South African study, the foot was also the commonest site of disease (45 patients of the 63 that were studied). Seven patients had subungual melanoma, seven had primary mucosal lesions, and in six, the primary lesion could not be found [44]. In a study conducted by Kakande the majority of the tumours occurred on the foot, the right being more frequently affected than the left which is in contrast to our findings. Whereas three patients had melanomas

arising from the eyelids, two had oral lesions, one had a tumour arising from the nose and one had tumour involving the vulva vagina and cervix [5]. Among these patients, only one is reported to have suffered from xeroderma pigmentosa, presenting with a left forehead tumour [5]. None of these patients were reported to have albinism, a known predisposing factor [45, 46, 47]. In our findings only one albino patient had melanomas arising from the eyelid, ear and lip. Melanin deficiency in people with oculocutaneous albinism predisposes them to the harmful effects of ultraviolet radiation exposure, resulting in photophobia, decreased visual acuity, extreme sun sensitivity, and cutaneous malignancies including melanoma [45, 46, 47].

Three (12.5%) patients presented with stage I disease, eleven (45.8%) with stage II, six (25%) with stage III, and four (16.7%) with disseminated metastatic disease in this study. Three women (17.6%) were affected by stage I disease while none of the men (0%) had stage I disease. An equal number of women (2, 11.8%) and men (2, 28.6%) had stage IV melanoma. Majority of the patients presented with stage II disease with a higher number of them being female, followed by stage III disease. For this reason we need to aggressively conduct SLNB on our patients, where clinically positive nodes are absent to guide our elective lymphadenectomy and stage our patients accordingly. This may dictate that we conduct more elective lymphadenectomies. The role of imaging in staging also can only be stressed.

In contrast the Hudson and krige study with sixty three patients, thirty (46.9%) patients presented with stage I disease, two (3.1%) with stage II, 23 (35.9%) with stage III, and nine (14.1%) with disseminated metastatic disease [44]. Early stage disease presents the advantage of a possibility of achieving cure in its management, which is less likely in our setting from the findings above.

Radiological investigations are valuable in staging disease, with any negative imaging study providing a baseline study for future comparison. Follow up imaging is useful in evaluating the response of metastatic disease to therapy. We couldn’t assess for metastasis on all our study subjects, as they couldn’t afford the tests. These included serum LDH level and radiological tests (CXR, U/S, abdominal CT, chest CT). Hence no MRI or PET scans were conducted. Chest radiography is indicated for stage III disease, in-transit disease, or local recurrence [48].

Chest CT scan is indicated for a patient with stage IV disease, to detect asymptomatic metastatic lesions. Whereas in patients with stage I, II, or III disease, it should be performed only if clinically indicated. Abdomen CT scan is indicated in stage III, locally recurrent, or in transit disease. Pelvis CT scan is indicated only if a patient has local regional recurrence below the waist, is symptomatic, or has known metastatic disease with a history of primary tumors below the waist [48].

The results of this study show that the most common histopathological subtype of MM in the Kenyan population who present at the Kenyatta National Hospital for treatment is ALM, followed by nodular MM. This data is supported by other studies that reported that the melanoma histological subtypes pattern in Kenyans mimics that of other Africans where ALM is the most common molecular subtype, followed by nodular MM [5, 44]. The Hudson and krige study also found superficial spreading melanoma [44]. Although rare in Caucasians and people with lighter skin types constituting 2-8% of MM in whites, it is the most common subtype in people with darker skins comprising 35-60% in dark-skinned people [18]. Whether this could be attributed to the reduced melanin pigment in the non-hair-bearing glabrous skin of the palms and soles remains to be confirmed.

The Breslow depth was greater than 4mm in 17 (70.8%) of the study population, an accurate predictor of the risk for lymph node metastasis, with deeper tumours being more likely to involve lymph nodes and therefore such patients bear advanced disease[55, 56].This was quite similar to the mean Breslow depth of 6.15 mm (range of 1 to 25 mm) as defined by Hudson and krige [44]. This indicates that in both studies patients presented with thick tumours, which indicated the risk that patients were likely to have advanced disease.

Patients with localized disease were treated by wide local excision and split skin graft, while patients with melanoma in the nail bed were treated by amputation of the involved digit. Patients who benefit from elective lymph node dissection are those with metastatic tumour in regional nodes but no viable tumour dissemination beyond the nodes. Thus, prophylactic dissection of regional nodes should interrupt the metastatic cascade and prevent the spread of melanoma. The

debate surrounding this has been whether this is a substantial percentage of the patients or an inconsequential fraction [57-58].

The major component of delayed presentation or advanced disease at first hospital contact in our patients is patient-related. Varying from financial difficulties experienced when accessing healthcare, to lack of community awareness on the importance of early reporting to hospital for early diagnosis and treatment.

According to this study, early presentation of our patients should be encouraged to improve outcome occasioned by early intervention. We need to embrace the practice of diagnostic microscopic nodal staging during management of primary disease, so that we can improve prognosis in our patients and reduce dissemination and recurrence of disease.

6.2 Conclusion

This study has demonstrated that the most common molecular subtype of MM across all age groups is ALM, followed by nodular melanoma. Majority of the patients presented with late stage disease. The poor prognosis in black patients in Kenya is the result of delayed presentation with thick primary lesions and advanced disease.

6.3 Recommendations

An active education program; involving education about sun avoidance, the importance of skin awareness and skin examination, and the screening of populations at high risk for melanoma, may reduce mortality by detecting the disease earlier.

A larger long-term multicentre study would help to elucidate whether the clinicopathological features are different in our cohort of patients from other population groups in Kenya.

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APPENDICES

Appendix I: TNM staging

Primary tumour (T)

TX - Primary tumour cannot be assessed (for example, curettage or severely regressed melanoma)

T0 - No evidence of primary tumour

Tis - Melanoma in situ; involves only epidermis (CL I)

T1 - Tumour 1 mm or less in thickness; invades papillary dermis (CL II) (or to papillary-reticular dermal interface (CL III) (pT1b can mean that either the melanoma is ≤ 1 mm with ulceration or is < 1 mm but is Clark's level IV or V with or without ulceration.)

T2 - Tumour 1.01-2 mm in thickness

T3 - Tumour 2.01-4 mm in thickness

T4 - Tumour greater than 4 mm in thickness and/or invades subcutaneous tissue (CL V) and/or satellite(s) within 2 cm of the primary tumour

T4a - Tumour greater than 4 mm in thickness with or without ulceration

Any Ta - Not ulcerated

Any Tb - Ulcerated

A and b subcategories of T are assigned based on ulceration and number of mitoses per mm^2.

Table 5: Primary tumour (T) staging

T classification	thickness (mm)	ulceration status/mitoses
T1	≤1.0	a: w/o ulceration and mitosis $<1/mm^2$ b: with ulceration or mitoses $\geq 1/mm^2$
T2	1.01–2.0	a: w/o ulceration b: with ulceration
T3	2.01–4.0	a: w/o ulceration b: with ulceration
T4	>4.0	a: w/o ulceration b: with ulceration

Regional lymph nodes (N)

NX - Regional lymph nodes cannot be assessed (for example, previously removed for another reason)

N0 - No regional lymph node metastasis

N1 - Metastasis in 1 lymph node

N2 - Metastasis in 2-3 lymph nodes or spread of melanoma in the skin toward a nearby lymph node area

N3 - Metastasis in 4 or more lymph nodes or spread of melanoma in the skin toward a lymph node area and into the lymph node(s)

Any Na - Melanoma only seen under the microscope

Any Nb - Melanoma in the lymph node visible to naked eye

1. Micrometastases are diagnosed after sentinel lymph node biopsy and completion lymphadenectomy (if performed).

2. Macrometastases are defined as clinically detectable nodal metastases confirmed by therapeutic lymphadenectomy or when nodal metastasis exhibits gross extracapsular extension.

Table 6: Regional lymph node (N)

N classification	No. of metastatic nodes	Nodal metastatic mass
N1	1 node	a: micrometastasis1 b: macrometastasis2
N2	2–3 nodes	a: micrometastasis1 b: macrometastasis2 c: in transit met(s)/satellite(s) without metastatic nodes
N3	4 or more metastatic nodes, or matted nodes, or in transit met(s)/satellite(s) with metastatic node(s)	

Distant metastasis (M)

MX - Distant metastasis cannot be assessed

M0 - No distant metastasis

M1 - Distant metastasis

M1a - Metastases to skin or subcutaneous (below the skin) tissue or distant lymph nodes

M1b - Metastases to lung

M1c - Metastases to all other visceral sites or distant metastases to any site combined with an elevated serum lactate dehydrogenase (LDH)

Table 7: Distant metastasis (M)

M classification	site	serum LDH
M1a	Distant skin, subcutaneous, or nodal metastasis	Normal
M1b	Lung metastases	Normal
M1c	All other visceral metastases Any distant metastasis	Normal Elevated

AJCC groupings [26, 27]

Stage 0 (pTis, N0, M0): The melanoma is in situ, meaning that it involves the epidermis but has not spread to the dermis.

Stage IA (pT1a, N0, M0): The melanoma is less than 1 mm in thickness and Clark's level II or III. It is not ulcerated, appears to be localized in the skin, and has not been found in lymph nodes or distant organs.

Stage IB (pT1b or pT2a, N0, M0): The melanoma is less than 1 mm in thickness and is ulcerated or Clark's level IV or V, or it is 1.01-2 mm and is not ulcerated. It appears to be localized in the skin and has not been found in lymph nodes or distant organs.

Stage IIA (pT2b or pT3a, N0, M0): The melanoma is 1.01-2 mm in thickness and is ulcerated, or it is 2.01-4 mm and is not ulcerated. It appears to be localized in the skin and has not been found in lymph nodes or distant organs.

Stage IIB (pT3b or pT4a, N0, M0): The melanoma is 2.01-4 mm in thickness and is ulcerated, or it is thicker than 4 mm and is not ulcerated. It appears to be localized in the skin and has not been found in lymph nodes or distant organs.

Stage IIC (pT4b, N0, M0): The melanoma is thicker than 4 mm and is ulcerated. It appears to be localized in the skin and has not been found in lymph nodes or distant organs.

Stage III (any pT, N1-3, M0): The melanoma has spread to lymph nodes near the affected skin area. No distant spread is present. The thickness of the melanoma is not a factor, although it is usually thick in people with stage III melanoma.

Stage IV (any pT, any N, any M1): The melanoma has spread beyond the original area of skin and nearby lymph nodes to other organs, such as the lungs, liver, or brain, or to distant areas of the skin or lymph nodes. Neither the lymph node status nor thickness is considered, but in general, the melanoma is thick and has spread to lymph nodes.

Table 8: AJCC groupings

ANATOMIC STAGE/PROGNOSTIC GROUPS							
Clinical Staging[3]				Pathologic Staging[4]			
Stage 0	Tis	N0	M0	0	Tis	N0	M0
Stage IA	T1a	N0	M0	IA	T1a	N0	M0
Stage IB	T1b	N0	M0	IB	T1b	N0	M0
	T2a	N0	M0		T2a	N0	M0
Stage IIA	T2b	N0	M0	IIA	T2b	N0	M0
	T3a	N0	M0		T3a	N0	M0
Stage IIB	T3b	N0	M0	IIB	T3b	N0	M0
	T4a	N0	M0		T4a	N0	M0
Stage IIC	T4b	N0	M0	IIC	T4b	N0	M0
Stage III	Any T	≥ N1	M0	IIIA	T1-4a	N1a	M0
					T1-4a	N2a	M0
				IIIB	T1-4b	N1a	M0
					T1-4b	N2a	M0
					T1-4a	N1b	M0
					T1-4a	N2b	M0
					T1-4a	N2c	M0
				IIIC	T1-4b	N1b	M0
					T1-4b	N2b	M0
					T1-4b	N2c	M0
					Any T	N3	M0
Stage IV	Any T	Any N	M1	IV	Any T	Any N	M1

Appendix II: Fitzpatrick skin type

SKIN TYPE	one 	two 	three 	four 	five 	six 
Hair	red, blonde	blonde, red, light brown	chestnut, dark blonde	brown, medium brown, dark brown	dark brown	black
Eyes	blue, grey, green	blue, grey, green, hazel	brown, blue, grey, green, hazel	hazel, brown	brown	brown
Skin	very pale white, pale white	pale white	white, light brown	medium brown, dark brown	dark brown	black
Tanning Ability	burns very easily, never tans	burns easily, rarely tans	sometimes burns, gradually tans	hardly ever burn, tans very easily	Rarely burns, tans easily and quickly darkens	Never burns, tans very dark

Appendix III: Data entry sheet

Patient numbers			
Date			
Telephone No			
Age and gender			
Presenting symptom(s)			
Duration of symptom(s)			
Anatomical site(s) affected			
physical exam: race	Negro	Caucasian	Asian
Skin type			
Nature of lesion: symmetry border colour diameter elevated surface ulceration status satellite lesion in-transit lesion			
Lymph node status	Number Matted yes ……. no…….		
Histopathology: Type of tumor Ulceration status Neurovascular invasion Breslow thickness			

Mitotic activity (/mm^2) Margins Regression features Special features	
Blood tests: LDH	
Radiological tests: Compulsory: CXR Abdominal U/S Optional: CT scan Chest Abdomen MRI Chest Abdomen	

Appendix IV: Histopathology report form

Sample collection date ……..

Reporting date ……..

Tumor subtype
- ☐ Acral lentiginous melanoma
- ☐ Superficial spreading melanoma
- ☐ Nodular melanoma
- ☐ Lentigo maligna melanoma
- ☐ Others:……

……

Ulceration status		☐ present	☐ absent
Neurovascular invasion		☐ present	☐ absent
Breslow thickness		☐ 0-1 mm	☐ 2.01-4 mm
		☐ 1.01-2 mm	☐ >4 mm
Mitotic activity (/mm^2)	……		
Margins	Deep	☐ positive	☐ negative
	Lateral	☐ positive	☐ negative
	Medial	☐ positive	☐ negative
	Superior	☐ positive	☐ negative
	Inferior	☐ positive	☐ negative
Regression features		☐ present	☐ absent

Special features……

Appendix V: General patient information and consent form

English version

This is an informed consent form for persons aged 18 years and above as well as those below the age of 18 whose guardians/next of kin/parents allow to be included in the study whose title is;

'Clinicopathological features of malignant melanoma of the skin among patients seen at Kenyatta national hospital.'

Principal investigator: Dr. Wanjiru Karanja.

Institution: School of Medicine, Department of Surgery, University of Nairobi.

Supervisors: Dr. Nang'ole Wanjala, Dr. Loise Kahoro, Dr. Daniel Zuriel.

This informed consent has three parts;

1. The Information sheet that seeks to give you details about the study.
2. The certificate of consent to append your signature if you agree to take part.
3. Statement by the principal researcher.

A copy of the consent form shall be availed to you in full.

Part 1: Information sheet

Background

My name is Dr. Wanjiru Karanja, a Postgraduate student at the School of Medicine, University of Nairobi. I am conducting a research study titled 'Clinicopathological features of malignant melanoma of the skin among patients with skin cancer seen at Kenyatta national hospital.'

Purpose of the study

Malignant melanoma is a skin cancer that affects any part of the body's skin. If melanoma is recognized and treated early, it is almost always curable, if not, the cancer can advance and spread to other parts of the body, where it becomes hard to treat and can be fatal. This study aims to evaluate skin lesion(s) at patient presentation, to determine the stage of the cancer.

Benefits

Using the information derived from this study, conclusions will be drawn which will influence treatment practices locally. I would like to invite you to take part in this study. Participation is

purely voluntary and you are allowed to consent either immediately after getting this information or after a period of consultation.

You are free to ask questions at any time regarding this study, or to seek any clarification from either myself or my research assistant. If you consent to participate in the study, some personal details as well as information concerning your condition will be sought. Participation in this study will be through a clinical interview and a clinical examination. At regular intervals information will be sought from you regarding the tests carried out and progression of illness.

Risks

There are no risks, discomfort or morbidity involved in participating in the study.

Confidentiality

You are guaranteed that all the information taken from you will be kept strictly confidential and will not be accessed by anyone other than the researchers and any other person authorised by the KNH- UON Ethics and research committee. This information will be coded with numbers such that only the researchers can identify you.

The right to withdraw

Withdrawal from this study can be done at any stage and will not affect your treatment at this hospital. This proposal has been reviewed and approved by the KNH- UON ERC which is a body that ensures the protection of persons like yourself that take part in research studies.

This approval has been granted after submission of the study proposal to the committee by the Chairman of the Department of Surgery, School of Medicine, University of Nairobi with the approval of a University supervisor.

Part 2: Consent certificate

I……..... freely give consent of myself/my proxy ....……. to take part in the research study carried out by **Dr. Wanjiru Karanja**, the nature of which she has explained to me. I understand that my participation in the study is purely voluntary and that I am free to withdraw this consent at any time. I also understand that withdrawing my consent will not affect the quality of care given to myself/my proxy at the Kenyatta National Hospital.

Signature of participant/Guardian/Next of kin……

Date……

I certify that the above consent has been freely given in my presence

Witness Name .....

Witness Signature .....

Date .....

Left thumbprint if participant is illiterate (witness to countersign)

In the event that you require any additional information or for any other purpose regarding this study, relevant contact details are listed below:

1. **Dr. Wanjiru Karanja**
   Department of Surgery
   School of Medicine
   University of Nairobi
   P.O. Box 19676-00202, KNH, Nairobi, Kenya
   Tel: 0720459798
2. **The Secretary**
   KNH- UON Ethics and Research Committee (ERC)
   Tel no: +2542726300-19 Ext.44102
   P O BOX 20723-00202, Nairobi, Kenya
   Email: uonknh_erc@uonbi.ac.ke

3. **Dr. Nang'ole Wanjala.**
   Department of Surgery
   School of Medicine,
   University of Nairobi
   Tel:020-2726300
4. **Dr. Loise Kahoro.**
   Department of Surgery
   Kenyatta National Hospital
   Tel: 020-2726300
5. **Dr. Daniel Zuriel.**
   Department Human Pathology
   School of Medicine,
   University of Nairobi
   Tel: 020-2726300

Part 3: Statement by the researcher

I confirm that the information relating to this study as contained in the information sheet has been accurately read to the participant. I confirm that I have ensured the understanding of its contents by the participant who understands that:

1. Declining to give consent or otherwise participate in this study will not affect the quality of care given at this institution.
2. All information provided by the participant will be kept strictly confidential.
3. The conclusions from this study may be used to influence clinical practice.

I further confirm that the participant has been allowed to seek clarification of all aspects of this study and that he/she has freely and willingly given consent. The participant has also been provided with a copy of the Informed consent form.

Name of researcher …….....

Signature .....

Date .....

Kiswahili version

Hii ni fomu ya ridhaa kwa watu wenye umri wa miaka 18 na kuendelea pamoja na wale chini ya miaka 18 ambao walezi/ya pili ya jamaa/wazazi wameruhusu kuhusishwa katika utafiti ambaye jina ni;

'Makala Clinicopathological ya malignant melanoma ya ngozi kati ya wagonjwa katika hospitali ya taifa Kenyatta.'

Mkuu wa uchunguzi: Dr. Wanjiru Karanja.

Taasisi: Shule ya Tiba, Idara ya upasuaji, Chuo Kikuu cha Nairobi.

Wasimamizi: Dr. Nang'ole Wanjala, Dr. Loise Kahoro, Dr. Daniel Zuriel.

Hii ridhaa ina sehemu tatu;

1. Karatasi taarifa kwamba inataka kutoa maelezo kuhusu utafiti.
2. Cheti cha ridhaa utakapotia saini yako kama wewe umekubali kuhusishwa katika utafiti.
3. Kauli ya mtafiti mkuu.

Nakala ya fomu ya ridhaa utapewa kikamilifu.

Sehemu ya kwanza: Maelezo

Usuli

Jina langu ni Daktari Wanjiru Karanja, mwanafunzi katika Kitivo cha masomo ya Udaktari, Chuo kikuu cha Nairobi. Ninafanya utafiti kuhusu;

“Makala clinicopathological ya melanoma malignant ya ngozi kati ya wagonjwa katika hospitali ya taifa Kenyatta.”

Lengo la utafiti

Malignant melanoma ni kansa ya ngozi ambayo huathiri sehemu yoyote ya ngozi mwilini. Kama melanoma itatambuliwa na kutibiwa mapema, ni karibu kila mara kutibika, kama sivyo, kansa inaweza enea katika sehemu nyingine za mwili, ambapo inakuwa vigumu kutibu na inaweza kuwa mbaya. Utafiti huu unalenga kutathmini vilema vya ngozi katika kuwasilisha mgonjwa, na kuamua hatua ya kansa.

Faida

Kutumia habari inayotokana na utafiti huu, hitimisho itakuwa inayotolewa ambayo kuwa na mvuto mazoea ya matibabu ndani ya nchi. Ningependa kukualika kujumuishwa kwenye utafiti huu. Kujumuishwa kwako ni kwa hiari na unayo haki kujiondoa kwenye utafiti huu wakati wowote. Idhini yako ya kujumuika unaweza kuipa maramoja baada ya kusoma nakala hii ama baada ya muda wa kufikiria.

Unao uhuru wa kuuliza maswali yoyote kuhusu utafiti huu kutoka kwangu. Kushiriki katika utafiti huu itakuwa kupitia mahojiano na uchunguzi wa mwili. Katika vipindi vya kawaida utaulizwa kuhusu vipimo vinavyo fanyika na maendeleo ya ugonjwa.

Hatari

Hakuna hatari, usumbufu au maradhi yatakayo kuathiri katika kushiriki katika utafiti.

Usiri

Unaweza kujitoa katika utafiti huu wakati wowote bila kuadhiri matibabu yako. Utapatiwa hakikisho ya kwamba maelezo yote utakayotoa yatawekwa siri wala hakuna atakayeyaona maelezo haya isipokuwa watafiti na watu waliokubaliwa na kamati ya uadilifu ya Hospitai kuu ya Kenyatta ikishirikiana na Chuo kikuu cha Nairobi. Nambari zitatumiwa badala ya majina ili kukinga maelezo yako. Maelezo yatachukuliwa kwa njia ya maswali.

Haki ya kujiondoa

Kujiondoa kwako hakutaadhiri kiwango cha matibabu utakayopatiwa katika hospitali hii.

Ruhusa ya kufanya utafiti huu umepatiwa kutoka Kamati ya Uadilifu wa Utafiti ya Hospitali kuu ya Kenyatta ikishirikiana na Chuo Kikuu cha Nairobi, kupitia Mwenyekiti wa Idara ya Upasuaji, Kitivo cha Masomo ya Udaktari, Chuo Kikuu cha Nairobi.

Sehemu ya pili: Idhini

Mimi…….nimekubali kwa hiari yangu/hiari ya mgonjwa niliyemsimamia…….....

…….kujumuishwa kwenye utafiti unaoendeshwa na Daktari Wanjiru Karanja, baada ya kupewa maelezo kamili na yeye. Ninaelewa kuwa kujumuika kwangu ni kwa hiari na nina

uhuru wa kujiondoa wakati wowote. Naelewa kwamba kujiondoa kwangu hakutaathiri kwa vyovyote kiwango cha huduma nitakayopokea katika Hospitali Kuu ya Kenyatta.

Sahihi ya mgonjwa/Msimamizi wa mgonjwa……

Tarehe……

Nimeshuhudia ya kwamba idhini ya mhusika imetolewa kwa hiari yake mwenyewe

Jina la shahidi……..

Sahihi ya shahidi .....

Tarehe .....

Alama ya Kushoto gumba kwa mshiriki asiyejua kusoma na kuandika (shahidi ili kukabiliana na ishara)

Ikiwa unahitaji maelezo zaidi kuhusu utafiti huu, tafadhali wasiliana na wafuatao:

1. **Daktari Wanjiru Karanja**
   Idara ya Upasuaji
   Shule ya Tiba
   Chuo Kikuu cha Nairobi
   Sanduku la Posta 19676-00202
   Hospitali ya Taifa ya Kenyatta, Nairobi, Kenya
   Namba ya simu: 0720459798
2. **Katibu**
   KNH- UON Maadili na Kamati ya Utafiti (ERC)
   Namba ya simu: +2542726300-19 ugani simu 44102
   Sanduku la Posta 20723-00202, Nairobi, Kenya
   Barua pepe: uonknh_erc@uonbi.ac.ke
3. **Daktari Nang'ole Wanjala.**
   Idara ya Upasuaji

Shule ya Tiba
Chuo Kikuu cha Nairobi
Namba ya simu: 020-2726300

4. **Daktari Loise Kahoro.**
   Idara ya Upasuaji
   Hospitali ya Taifa ya Kenyatta
   Namba ya simu: 020-2726300
5. **Daktari Daniel Zuriel.**
   Idara za Binadamu Pathology
   Shule ya Tiba,
   Chuo Kikuu cha Nairobi
   Namba ya simu: 020-2726300

Sehemu ya tatu: Idhibati ya mtafiti mkuu

Ninatoa idhibati ya kwamba maelezo kuhusu utafiti huu yametolewa kikamilifu kwa mhusika, na kwamba nimemsaidia kuelewa kwamba:

1. Kutotoa idhini ama kujiondoa kwenye utafiti huu hautaathiri kwa vyovyote kiwango cha matibabu atakayopata katika hospitali hii.
2. Maelezo yote yatakayotolewa yatawekwa siri.
3. Matokeo ya utafiti huu yanaweza kutumiwa katika kuchangia ujuzi wa kubaini ugonjwa unaochunguzwa.

Ninatoa idhibati pia ya kuwa mhusika amekubaliwa kuuliza maswali yoyote kuhusu utafiti huu na kwamba ametoa idhini kwa hiari bila kulazimishwa. Mhusika pia amepewa nakala ya stakabadhi ya idhini.

Jina la mtafiti ……

Sahihi .....

Tarehe .....