A REVIEW OF CLINICO-PATHOLOGICAL CHARACTERISTICS, TREATMENT AND SURVIVAL, AMONG HIGH-RISK GTN PATIENTS MANAGED IN KENYATTA NATIONAL HOSPITAL BETWEEN 2013-2019

INVESTIGATOR:

DR. LAZARUS OMONDI KUMBA

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DECLARATION

This project dissertation is my original work and references have been made for work done by others.

DR LAZARUS OMONDI KUMBA (MBChB, M. Med)

Signature: ..... **Date** 18-11-2021

APPROVAL OF SUPERVISORS
This dissertation has been submitted with the approval of supervisors

PROF Shadrack B. O. OJWANG (MD, M. MED, OBS/GYN, DIP GYN.ONCOL)
Professor of Obstetrics and Gynecology,
Department of Obstetrics and Gynecology, University of Nairobi, Kenya.

Signature ..... **Date** 18/11/2021

DR ALFRED OSOTI (MBChB, M. Med, MPH, PhD)
Senior Lecturer,
Department of Obstetrics and Gynecology University of Nairobi, Kenya.
Affiliate Associate Professor,
Department of Global Health, University of Washington, Seattle, United States.

Signature: ..... **Date:** 18th Nov, 2021

DR ANN KIHARA (MBChB, M. Med)
SENIOR LECTURER
DEPARTMENT OF OBSTETRICS AND GYNECOLOGY
UNIVERSITY OF NAIROBI

Signature ..... **Date** 18/11/2021

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CERTIFICATE OF AUTHENTICITY

This is to certify that this project dissertation is the original work of Dr Lazarus Omondi Kumba, registration number H117/27884/2019, a Fellow of Gynecologic Oncology in the Department of Obstetrics and Gynecology, University of Nairobi.

This research was carried out in the Department of Obstetrics and Gynecology, School of Medicine, College of Health sciences, University of Nairobi. It has not been presented in any other University for award of a degree.

DEPARTMENT OF OBSTETRIC AND GYNAECOLOGY
P.O. Box 19676, NAIROBI
Date.....
COLLEGE OF HEALTH SCIENCES
UNIVERSITY OF NAIROBI

Signature..... **Date**..18/11/21

Professor Eunice J. Cheserem

Associate Professor of Obstetrics and Gynecology

Chairperson, Department of Obstetrics and Gynecology

University of Nairobi

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LIST OF ABBREVIATIONS

GTN	Gestational Trophoblastic Neoplasia
GTD	Gestational Trophoblastic Diseases
EMA-CO	Etoposide, Methotrexate, Actinomycin-D, Cyclophosphamide, Vincristine
FIGO	International Federation of Gynecology and Obstetrics
HIV	Human Immunodeficiency Virus
EMA-EP	Etoposide, Methotrexate, Actinomycin-D, Etoposide, Paclitaxel
EP	Etoposide, Paclitaxel
KNH	Kenyatta National Hospital
MRI	Magnetic Resonance Imaging
NHIF	National Health Insurance Fund
PSTT	Placental Site Trophoblastic Tumour
ETT	Epithelioid Trophoblastic Tumour
CM	Complete Mole
PM	Partial Mole
N.H.I.F	National Hospital Insurance Fund

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ABSTRACT

BACKGROUND

High risk Gestational Trophoblastic Neoplasia (GTN) is a common cause of morbidity and mortality all over the world. It contributes 2% of all reproductive tract malignancies in Kenya. The problem is grave in resource – poor third world countries where specialized GTN treatment centers do not exist, and poor referral systems is the norm compounded with lack of well-trained health workers to handle suspected cases. It is therefore useful to gather epidemiological data to guide in the routine diagnosis, treatment and follow-up of this malignancy

BROAD OBJECTIVES

A review of Clinico-pathological characteristics, treatment options, treatment outcomes among high-risk GTN patients managed in Kenyatta National Hospital, Kenya between 2013 – 2019.

METHODOLOGY

Study design

A descriptive retrospective cross-sectional study 2013-2019

Study site and setting

Oncology Unit, department of Obstetrics and Gynecology KNH, Nairobi, Kenya

Study population

Patients managed for High-risk GTN 2013-2019

Inclusion criteria

Patients managed for High-risk GTN at KNH between 2013 and 2019

Exclusion criteria

Missing files and files with incomplete data.

Sample size

Total calculated sample size was 73

Data collection

Descriptive variables, variables in management of High risk GTN, date and time of death were collected. Data was captured electronically into the REDcap software.

Data analysis

Data with descriptive statistics were summarized. Age was presented as means (SD), while categorical data was presented in proportions. Kaplan Meier curves were used to determine 2 and 5 year survivals for High-risk GTN patients. Patients who were still alive or lost to follow-up were censured in the survival analysis.

RESULTS

A total of 64 files were analyzed. The mean age of patients reviewed was 35 years. 92.2% had never done a pap smear before. Only 4.7% were H.I.V. Positive. The most frequently used imaging modality was pelvic ultrasound. Chemotherapy alone was the main mode of treatment. The 2-year survival was 18% while 5-year survival was 10%.

Conclusion

Most patients presented with per-vaginal bleeding. 50% of the patients died of haemorrhage. Chemotherapy is the main mode of treatment of High-Risk GTN in Kenyatta National Hospital.

INTRODUCTION AND LITERATURE REVIEW

Gestational Trophoblastic Diseases (GTD) describes a spectrum of neoplastic anomalies that affects the placenta.(2,5) Invasive mole, choriocarcinoma, placental site trophoblastic tumour (PSTT) and epithelioid trophoblastic tumour (ETT) are all histological diagnosis while Hydatidiform mole is diagnosed by correlating clinical, laboratory and ultrasound results. These malignancies are the most curable of all gynecological malignancies because there is a tumour marker which can be used for diagnosis and follow-up, and these cancers are vulnerable to multiple chemotherapeutic drugs and we may define risk factors and individualize care for patients by incorporating chemotherapy and surgery with or without radiotherapy(2,5).

The exceptional curability of GTN can be partly due to the immunological response of the host to paternal antigens expressed in trophoblastic cells (17,18) GTD etiology potentially includes genetic abnormalities during fertilization, defective differentiation and pronuclear cleavage, defective decidual implantation, defective myometrial invasion, and abnormal maternal cell-mediated immune response(8,20).

Oncogenes are genes that have the ability to transform a normal cell into a cancerous cell. It may result from a mutation that activates the cell permanently, it may be chromosomal rearrangements, or at high levels the genes are over expressed. This is significantly correlated with the production of post molar tumors, causing uncontrolled cell growth. P53, c-fms, c-myc, c-erbB2 and bcl-2 are the genes responsible for complete mole and choriocarcinoma. The extravillous trophoblast is also overexpressed by p21, Rb and MdM2 EGFR. P53, c-fms, c-myc, c-erbB2 and bcl-2 are the genes responsible for complete mole and choriocarcinoma. The extravillous trophoblast is also overexpressed by p21, Rb and MdM2 EGFR. Metalloproteinases (MMPs) are significant in cell-matrix interactions as well as the degradation of the basement membrane. These two processes re crucial for the metastasis the of cancer to other tissues.

Choriocarcinoma exhibits substantially greater matrix metalloprotein-1 and matrix metalloprotein-2 expression and reduced matrix metalloprotein-1 (TIMP-1) tissue inhibitor expression than complete and partial mole and normal placenta syncytiotrophoblast.

This is what contributes to the invasiveness of choriocarcinoma cells. Relaxation of parental imprinting is also seen in these patients. In the blood of patients with complete moles, circulating immune complexes are also found. Paternal HLA antigen is found in these immune complexes. The maternal host blood is sensitized to paternal HLA antigen in a complete mole. The maternal host is sensitized when the villous trophoblast layer is disrupted and HLA positive villous stromal cells are released into the circulation.

The occurrence of molar pregnancy varies across the globe. The incidence in southern Africa is around 1.2 per 1000. The incidence in Ireland is 1 per 1945 for complete moles. The risk is influenced by factors such as race/ethnicity, diet, socioeconomic status, age, and previous reproductive history. If we perform a study in tertiary hospital setting rather than population-based studies, the results would be skewed . (7,8,)

High incidences of molar pregnancy are associated with age; women under 15 years or more than 40 years according to the Duke study (11,16,17). Abnormal fertilizations occurs more frequently in ova from older women. Men of advanced age tend to get complete mole.(19,14) Increased risk of Hydatidiform mole was associated with populations with diets low in protein and vitamin-A.

Berkowitz and colleagues found that these patients lacked the dietary fat required for vitamin A absorption, resulting in an overall carotene-deficient state.

Previous molar pregnancy also raises the risk 10 fold for complete molar pregnancy.

It was found that patients with a history of previous use of oral contraceptives have a greater risk of developing choriocarcinoma. Hormonal variables therefore lead to choriocarcinoma.

Hydatidiform moles may be categorized as either complete mole or partial moles. In a normal fertilization, an ovum is fertilized by a sperm. The ovum usually has 23X chromosomes while the sperm has 23X chromosomes or 23Y chromosomes. The zygote will be either 46XX chromosomes or 46XYchromosomes. In a complete mole an empty ovum is fertilized by 2 sperms to give 46XX chromosomes or 46XY chromosomes. Sometimes an empty ovum is fertilized by one sperm with 23XX chromosomes which then duplicates its own chromosomes to form 46XX chromosomes or 46XY chromosomes. All the chromosomes are from the father .The complete mole will not have any embryonic or fetal tissues .The chorionic villi are oedematous with increased hyperplasia. There is cellular pleomorphism compared to normal trophoblast cells at implantation site. There are no 46YY moles. Mitochondrial DNA in complete moles are of maternal origin but the chromosomes are from the father.

The recent technological advancements like ultrasound and beta- hCG laboratory assay has enabled early diagnosis of Hydatidiform mole.

The following histological features characterize partial Hydatidiform mole.

Chorionic projections of different sizes with central oedema and increase in the number of the cells and tissues in the middle where the blastocyst attaches to the wall of the uterus at the start of pregnancy.

Centrally, in the middle section where the blastocyst connects to the wall of the uterus at the beginning of pregnancy, the cells appear mildly irregular in form and size and coloration.

Extensive indentations or erosions of the normally appearing smooth villi and strikingly intracellular inclusions in the cytoplasm of the supportive tissues of the trophoblast.

A fetus or embryonic tissue can be seen under the microscope.

To form a partial mole, 2 sperms fertilize one normal ovum. This means 23X chromosomes or 23Y chromosomes combining with 23X chromosomes to form 69XXY chromosomes or 69XXX chromosomes. So partial moles contain both the genes of the father and the mother.

The clinical presentation of hydatidiform moles is vaginal bleeding,the level of haemoglobin will fall. Expulsion of grape-like, vesicles occurs in the second trimester.

Excessive nausea and vomiting due to elevated levels of hCG and estrogen in combination with an exceptionally bulky uterus.

Symptoms of high blood pressure, proteinuria and edema during pregnancy. Eclampsia, however, is uncommon.

Symptoms of excessive thyroid stimulating hormone when hCG is very high. Thyroid storms can occur if this hyperthyroidism is not well regulated by Inderal or other beta-blockers.

Chest complications arise after the evacuation of molar tissues in theatre. The extravasation of molar tissues that join the blood vessels and are accumulated in the lungs is the cause . This induces low levels of oxygen in the blood and excess bicarbonate in the blood. Some patients may need mechanical ventilation support.

Bilateral cystic swelling of the ovaries due to hCG stimulation of the ovaries. They can experience torsion or rupture and may require laparoscopic aspiration. They range in size from 6cm and above.

Excessively enlarged uterus, not commensurate with the date of conception. It is caused by the retention of blood and chorionic tissue. This occurs in 28 percent of New England Trophoblastic Disease Center patients (8,11,17)

If the Hydatidiform mole is present in the oviduct, it will display the classical signs and symptoms of ectopic pregnancy with tubal rupture and internal bleeding.
The first 7 presentations only occur in complete molar pregnancy. In partial mole, the curretings must be submitted for histology to come up with a diagnosis. They usually present with signs and symptoms of missed abortion or incomplete abortion. Patients with partial mole do not present with hyperthyroidism, prominent theca-lutein cysts or excessive nausea and vomiting. Only 4% of them have pre-eclampsia. To make a diagnosis of Hydatidiform mole, we usually combine the characteristics of levels of hCG clinical history, physical examination and ultrasound findings of a snowstorm appearance.
In patial moles, the ultrasound features are as follows. The ratio of the transverse diameter of the gestational sac and the anteroposterior diameter is >1.5. Also ultrasound may see a conceptus with congenital anomalies with a placenta that is oedematous
When the diagnosis of GTD is made we should monitor the progress of the patient with serial hCG measurements in the laboratory. A chest X-ray should be taken before and after evacuation of the molar pregnancy. The following laboratory tests should be carried out. Full haemogram, Bleeding time, clotting time, APTT, coagulation factors and a full coagulation profile,Urea, creatinine and electrolytes,Bilirubin, total serum proteins, alkaline phosphatase, SGPT, SGOT enzymesBlood grouping and rhesus factor,hCG levels.Chest X-ray or Computerized tomographic-scan of the chest and Brain Magnetic resonance imaging Computerized Tomographic-scan or Magnetic resonance imaging of abdomen and pelvis Suction dilatation and evacuation should be done. This is followed by sharp curettage to remove the few remaining molar tissues. Rhesus negative patients should receive Anti-D immunoglobulins. Patients who already have desired family size may benefit from removal of the uterus. This removes the risk of local spread of the tumour.
Kim et al found that giving chemotherapy to patients with complete moles reduced the incidences of post molar GTN from 47% to 14%. This is only justified in patients whom we suspect will be lost to follow-up (20). Adequate contraception is indicated for next 1 year. Combined oral contraceptives are preferred. Copper-T and other intrauterine contraceptive devices are not recommended until levels of serum hCG become normal. The following categories of patients with complete moles are at high risk of developing malignant GTN. Those with very high levels of hCG and excessive uterine size, with theca lutein cysts and age above 40 years with repetitive molar pregnancy. (Barakat).
Complete moles in mothers more than 40 years old are more frequently having aneuploidy leading to an unbalanced chromosome complement, that is not an exact multiple of the haploid number which is 23X or 23Y.

The current FIGO requirements for making a diagnosis of post-molar GTN are as follows: If blood levels of βhCG, do not change by 10% above or below the previous value in 4 readings over 21 days. i.e. day one, day seven, day fourteen, and day twenty one; if levels of beta hCG rise by 10% or more, for three readings or more at least fourteen days: day one, day seven, day fourteen, pathologic report of ETT, PSTT, choriocarcinoma or invasive mole, prolonged positivity of beta hCG even after 180 days after molar evacuation, the presence of metastases and beta hCG levels are still high in a patient who is not gravid

Anatomical International Federation of Gynecology and Obstetrics Staging System For Gestational Trophoblastic Neoplasia 1980

Stage 1 = Tumour restricted to the corpus.
Stage 2 = Tumour outside corpus but limited to the reproductive structures-vagina and/or pelvis
Stage 3 = Tumour extends to the chest with or without known reproductive tract involvement
Stage 4 = Tumour has spread to other parts of the body like liver, brain, kidneys ,GIT.
This anatomical FIGO staging system is reported in Roman numbers as Stage 1V or Stage 111 or Stage 11 or Stage 1 and it is usually combined with the FIGO prognostic score.
The following is the revised WHO prognostic scoring system adapted by FIGO. It was developed so that we report both the stage of the disease and the score. For example we can say stage 1:4 meaning the cancer is limited to the corpus and the risk score is 4. Another example is stage 1V:8 meaning that the cancer has spread to distant parts of the body and the risk score is 8. This scoring system enables us to objectively compare data and treatment results. It relies on various parameters.

1. Age of the patient. For those below 40 years they score 0, If age is 40 and above they score 1
2. Interval from index pregnancy in months. If less than 4 months they score 0. If between 4months and 6 months they score 1. Those between 7 months and 12 months score 2. If above 13 months they score 3
3. Levels of beta hCG in mIU/mL before starting treatment. If less than 1000 they score 0. If between 1000 and 10,000 are given a score of 1. Those levels between 10,000 and 100,000 score 2. Those above 100,000 score 3
4. Largest tumour size including the uterus in centimetres. If between 3cm and 5 cm they score 1. Those more than 5 cm score 2.
5. Site of metastases. If in the Lung they score 0. If metastases are to spleen or kidney they score 1. If metastases are to GIT they score 2. If metastases are to brain or liver they score 3.
6. Number of metastases identified. If no metastases identified they score 0. If there are between 1 and 4 metastases identified they score 1. If between 5 and 8 metastases are identified we give a score of 2. Those with more than 8 metastases identified score 3
7. Previous failed chemotherapy. Those who have had single agent cytotoxic drug score 2. Those who have previously had more than 2 drugs cytotoxics are given a score of 3.

We obtain the total score for each patient by adding the individual cores for each prognostic factor. Total score 0 to 6 = low risk: Total score greater than 7 = high risk.

High-Risk Metastatic Gestational Trophoblastic Neoplasia

Following Hydatidiform molar progression of pregnancy may be a histologic pattern of invasive molar tissue, choriocarcinoma, Placental Site Trophoblastic Tumor or Epithelioid Trophoblastic Tumor. But after a non-molar pregnancy, progressive trophoblastic tumor may have histological features of choriocarcinoma. Pregnancy choriocarcinoma does not contain chorionic villi but is made up of your sheets of both anaplastic cyto and syncitiotrophoblast. The placental site trophoblastic tumor is made entirely of mononuclear intermediate trophoblast and does not contain chorionic villi. Since PSTT emits very small traces of hCH, it would mean that there is a huge tumor load for the hCG to be detectable.

CLINICAL PRESENTATION

15% of patients with complete mole develop GTN. They may present with intraperitoneal hemorrhage if the tumour erodes through the myometrium into the peritoneum and vaginal bleeding if the tumour erodes the uterine and vaginal submucosal vessels. The tumour may be infected when it is huge and the tissues are necrotic.

After evacuation of Hydatidiform moles, 4% proceed to develop metastatic GTN or choriocarcinoma. This cancer has the tendency for early vascular invasion with distant spread to other organs like the lungs , vagina , kidney, brain ,GIT and liver . The tumour bleeds because the vessels are easily ruptured or damaged. This causes the patients to cough blood if the lungs are involved, or acute neurologic deficits if they bleed into the brain.
GTN produces 4 radiologic patterns in the lungs: Pleural effusion, Alveolar or snowstorm pattern, Discreet rounded opacities, Embolic pattern caused by pulmonary arterial blockage. Pulmonary hypertension may develop. Chest symptoms include difficulty in breathing and coughing out blood with chest pain. The differential diagnosis includes pneumonia and tuberculosis. Mechanical ventilation support may be necessary. Metastases to the liver present with yellowness of the eyes, internal bleeding. Brain metastasis gives headache, slurred speech , convulsions and neurologic deficit due to raised intracranial pressure and intracerebral bleeding.. Vaginal metastasis presents with vaginal discharge and vaginal bleeding with a mass from the vaginal submucosal vessels on the fornices or suburethral vessels (7,9,11)

Patients with high risk GTN are treated using a combination of cytotoxic drugs. MAC – means Methotrexate and Actinomycin-D and Cyclophosphamide .EMA-CO is Etoposide, Methotrexate ,Actinomycin -D, Cyclophosphamide and Vincristine.
If we choose to start with MAC, we take the weight of the patient and height. We derive the surface area of the patient using the normogram for calculating the body surface area. We then calculate the dose of the drug to be given. For the first 5 days we give methotrexate daily 15mg intravenously, and Actinomycin- D daily at 500mcg intravenously. and Cyclophosphamide daily at a dose of 3mg/kg intravenously. The patient then rests for 10 days of drug free period. On day 15 we start again the next cycle only if the blood parameters haemogram, liver tests and kidney tests are okey. We again give the chemotherapy for 5 days and take a break for 10 days until levels of beta hCG become less than 5 mIU/ml. Once we achieve this normal value, we give 2 more cycles of chemotherapy.

If we choose to give EMA-CO, then we still get the weight of the patient and height then we derive the surface area of the patient from the normogram of adults. We then make sure all the blood parameters are within normal ie Haemogram, liver function tests, kidney function tests. On day 1 we give Etoposide at a dose of 100mg/m^2 intravenously, Methotrexate 100mg/m^2 intravenously as a bolus and 200mg/m^2 IV infusion over 12 hours and Actinomycin-D 350mcg/m^2 intravenously.

On day 2 we give Etoposide 100mg/m^2 intravenously, and Actinomycin-D 350mcg/m^2 intravenously, and Folinic acid 15mg orally or intramuscularly or intravenously every 12 hours for 4 doses beginning 24 hours after methotrexate bolus.
On day 8 we give cyclophosphamide 600mg/m^2 intravenously and Vincristine 1mg/m^2 intravenously. The patient then rests for 7 days without any medication. On day 15 we begin again the next cycle after checking that all the blood parameters are normal. ie Haemoglobin is above 10g/dl , Liver function tests are normal, and kidney function tests are normal. Every week when the patient finishes the cycle, we also measure the levels of serum beta hCG to be sure that there is a decline. When levels of beta hCG become less than 5 mIU/ml we consider this as a negative value. The patient is now given 2 more cycles of chemotherapy after achieving a negative value.

Surveillance for GTN during and after chemotherapy is done as follows:

1. Resistance means that the levels of beta hCG are rising by more than 10% of the previous value or they plateau in 2 cycles. In this situation we change the chemotherapy from EMACO to EMA-EP or from MAC to EMACO depending on the regimen currently in use. We also consider surgery to remove tumour that is not shrinking despite chemotherapy. Also the patient may be developing new sites of metastases despite chemotherapy being given.
2. Response means the levels of serum beta hCG are declining by more than 10% during one cycle. In this situation we just continue giving the same chemotherapy.
3. Plateau means that the levels of serum beta hCG do not change by more than 10% either upward or downwards. In this situation we change to a superior chemotherapy regimen. From MAC to EMA-CO or from EMA-CO to EMA-EP. We must always watch out for new metastases developing despite chemotherapy being administered.

After normal levels of beta hCG are obtained, we follow-up the patient by doing serum beta hCG every 14 days for 90 days, then every month for 12 months. We still follow-up the patients for life by doing physical examination every 6 months.

The mainstay of treatment of GTN is chemotherapy. Surgery can be done is few instances. Laparotomy to solve internal haemorrhage or abscess. Hysterectomy has the advantage of removing central disease and reducing the tumour burden.. Percutaneous angiographic embolization of sub-mucous vaginal or pelvic tumours can be done if they are bleeding. Craniotomy can be done to relieve increased intracranial pressure due to bleeding. Nephrectomy and thoracotomy may also be considered in rare situations but they must be combined with chemotherapy.(13,14,15).
Radiotherapy has a limited role in treatment of GTN. Whole brain irradiation in cerebral metastases is inferior to chemotherapy. Also following whole brain radiotherapy patients develop mental retardation.

Izildina Maesta et al (53) studied outcomes in the management of high-risk GTN in trophoblastic disease centres in developing countries of South America. The conducted a

retrospective cohort study assessing participants' demographic data, signs and symptoms, severity as per FIGO stage, prognostic risk scored based on World Health Organization's scale, and details related to patient management. The main outcome investigated was complete sustained remission or death 18 months after finishing treatment. After analyzing 147 patients, 87.1% had sustained remission, which included 68.4% of ultra-high risk GTN (prognostic score ≥12). Death with one month (considered as early death) from commencing the treatment showed statistical significant relation with ultra-high risk GTN and recorded a 13.8% proportion of the evaluated population. The most strongly associated factor to death after conducting regression analysis was included non-molar antecedent pregnancy, metastases to vital organs (brain, liver or kidney), FIGO stage and ultra-high risk prognostic score. Patients with high risk had a 90% survival probability while those with ultra-high risk had a 60% probability. This study has therefore a new cohort of patients called ultra-high risk that we have not studied in KNH. They have a problem of early deaths in South America. It would be reasonable to compare our survivals for high-risk and ultra-high-risk to see how we compare with South America.

Constantine Alifrangis, Roshan Agarwal et al (59) in their publication EMA-CO for high-risk GTN: good outcomes with induction Low-dose Etoposide-cisplatin and genetic analysis, found that we can reduce early deaths by giving low dose etoposide 100mg/m^2 and cisplatin 20mg/m^2 both D1 and D2 every 7 days in selected patients to reduce early deaths in high-risk GTN patients. They compared overall survival of two cohorts of patients. One group was studied between 1979-1995 and did not receive low-dose induction Etoposide – cisplatin. They had OS=85.4% and another group was studied between 1995-2010 and received low-dose induction Etoposide- Cisplatin. It had OS=94%. The cohort that received low- dose induction Etoposide-cisplatin had a better survival.

In a retrospective review of patients treated in a tertiary centre of comprehensive womens hospital in Tehran, Iran, Soheila Aminimoghaddam, Forough Nezhadisalami et al (54) evaluated the effectiveness of Etoposide, Methotrexate, Actinomycin-D, Etoposide and Cisplatin (EMA/EP) regimen in the treatment of high-risk GTN as well as patients outcome. They analysed 25 patients and found that if patients were given EMA/EP because single agent chemotherapy had failed, the complete remission rate was 100%. But if EMA/EP was given to those with primary high-risk GTN complete remission was 81% . The overall remission rate in high-risk GTN patients treated with EMA/EP regimen was 88%. Anaemia and leukopenia was the most common side effect of EMA/EP chemotherapy regimen. Acute myeloid leukemia and mortality as the most severe adverse effects of EMA/EP regimen were seen in only 1 patient. They recommend EMA/EP as the first-line therapy in patients with failure of single agent chemotherapy but we should watch out for hematological toxicity. Zhonghun Fu, Chan Ke Za Zhi in a Chinese study (56) evaluated EMA/CO chemotherapy on 20 patients with ultra-high-risk GTN (prognostic score ≥12) with liver, brain and extensive metastases. 67% showed complete remission while 33% showed drug resistance. The mode of treatment influence the remission rate gives 62.5% of those with full remission were treated with chemotherapy + surgery while the rest received EMA-CO regimen alone. For the 8 patients who showed drug resistant to EMA-CO, 5 of them received EMA/EP and 3 cases got remission. Side effects of Etoposide were anaemia, neutropenia, alopecia.. The incidence of anaemia was 96.4%.Neutropenia incidence was 21.6% and alopecia was 60.5%. They concluded that EMA-CO is an effective regimen with manageable toxicity for patients with ultra-high-risk GTN (56)

John R. Lurain, Bahareh Nejad et al (58) involved 26 patients on the efficacy of secondary chemotherapy following the failure of the initial high-risk GTN or relapsed from remission at the Brewer Trophoblastic Disease Centre. The distribution of the patient involved 10 patients receiving EMA-CO while 16 patients were treated with methotrexate/Actinomycin-D without Etoposide. Secondary chemotherapy consisted of EMA/EP, Bleomycin (BEP) or Ifosfamide (VIP, ICE). Adjuvant surgery and radiotherapy was used in selected patients. Clinical response and survival as well as factors affecting survival were analysed retrospectively. Overall survival was 61.5%. 10 patients failed primary treatment with EMA-CO but had complete clinical response with EMA-EP or BEP. 8 patients had hysterectomy out of the 26 while 5 patients had pulmonary resections and 1 had wedge resection of uterus. Survival depended on both level of hCG at the start of secondary therapy and sites of metastases. Methotrexate /Actinomycin-D based chemotherapy without Etoposide was administered to 16 patients where 10 patients had remissions after complete clinical responses to BEP (8) VIP(1) and ICE (1). BEP when given for more than 6 courses has high risk of lung fibrosis In another study (57) EMA-EP was found to be an effective option for the treatment of GTN patients resistant to EMACO regimen. Despite the promising outcome, the regime was not beneficial to all those who experienced a relapse following initial management with EMA-CO regimen with only 42.9% achieved complete remission. The main adverse effects of the EMA-EP is myelosuppression, hepatotoxicity and GIT problems. This limits the number of patients that can be treated with the planned dose intensity. Dose adjustments have to be done at one time or another. This study aims to find out the chemotherapy regimens that we use in K.N.H and survival.

A Chinese study (55) analysed BEP for treatment of high-risk GTN. They found that BEP alone without adjuvant treatment (surgery or radiotherapy) had 74% remission rate but when combined with radiotherapy or surgery, the remission rate was 88%. The side effects of BEP noted were bone marrow suppression, GIT side effects alopecia, peripheral neuritis abnormal liver function tests and anaphylaxis.

A retrospective case note review of patients with possible ectopic GTD between 1997-2010 at the Sheffield centre by Hassadia, Kew and Hancock looked at 6,708 patients. The review focused on themes such as signs& symptoms, management, histological review and outcome reported by ectopic GTD patients seeking care at Sheffield Centre(37). They found that ectopic GTD is rare. Also, presentation for ectopic GTD was the same as for conventional ectopic pregnancy with abdominal pain plus or minus vaginal bleeding being the commonest presentation at 67%. Ultrasound made a diagnosis of ectopic pregnancy in only 19% of patients. Laparoscopic removal of ectopic pregnancy was carried out in 50% of cases. The rest underwent laparotomy. Histology was done in 19 cases for whom there was clinical concern. 12 cases were confirmed histologically as ectopic GTD. 4 were choriocarcinomas, 5 were partial moles and 3 were complete moles. There was no evidence of metastases. 3 patients with ectopic choriocarcinoma required chemotherapy They concluded that histology should be reviewed in all cases where tissue is removed at surgery. They also found that conventional chemotherapy is effective and prognosis remains excellent.

Another retrospective study by Chu, Tse, and Ngan (2016) assessed clinical and pathological characteristics of patients diagnosed with placental site trophoblastic tumours who were treated between 1995 and 2012. The based on the data from medical records 10 patients with Placental Site Trophoblastic Tumour qualified where four had stage 1 tumor. The treatment for the four involved three people had hysterectomy only while the other person underwent

both hysterectomy and chemotherapy. All four patients experienced complete remission, but one of them had recurrence that was effectively managed with chemotherapy. Four patients had pretreatment serum beta hCG levels <1,000 IU/L and all of them had disease confined to the uterus. For patients with stage 3 and 4 disease, most of them had both hysterectomy and chemotherapy (41).

A case report by Schuman et al. (2010) reports Metastatic GTN in a 17 year old female complicated by Tumour Lysis Syndrome after the first cycle of EMA-CO failed to respond effectively to hydration and allopurinol progressing to having renal failure. Three days after taking a single dose of recombinant urate oxidase, rasburicase, uric acid level reduced below detectable levels while the renal failure was corrected. On restarting EMA-CO and administered three cycles, the patient developed congestive cardiac failure leading to a switch to single agent Actinomycin-D. The beta hCG was nullified after five cycles and ejection fraction normalized. This is a very rare occurrence because Tumour Lysis Syndrome is known to occur more commonly in lymphomas and other hematological malignancies and not in GTN.(40)
A systematic review of case reports by Mangla et al. (2017) analysed the unusual clinical presentations of gestational choriocarcinoma from 121 cases. The patients' aged ranged from from 17 to 67 years, and the duration between first pregnancy and development of choriocarcinoma ranging between one month and 25 years. Cardiopulmonary complaints were 20.66% followed by GIT at 18.43% and CNS 17.67%. The review also comes in handy in making early diagnosis by highlighting the most common clinical presentations, which would preserve their fertility.(42)

Dombrovsky et al (2020) detailed a case of metastatic brain choriocarcinoma in a 66 year old woman, which as uncommon given the disease is common among age-bearing women. The was seen at the Emergency Department complaining of abrupt onset of upper and lower extremity weakness. After assessment, she was diagnosed with brain tumor, which revealed it was choriocarcinoma. She was then initiated standard first line therapy of EMA-CO although she never sustained her subsequent follow-up. The case support the need to evaluate all women with tumors should have pregnancy tests to rule out choriocarcinoma to avoid missed diagnosis. (49)

In the Annals of Hepato-Biliary Pancreatic Surgery (2018) Aloysius et al describe splenic rupture from a metastatic choriocarcinoma(39). The authors presents a case of a 41 year old woman with complaints of acute abdomen and haemorrhagic shock. The clinical presentations were associated with splenic rupture following metastasis of choriocarcinoma, The case highlights the metastasis route for choriocarcinoma, which is haematogenously mainly presenting as bleeding from metastasis, even though splenic rupture is rare.
GTN is able to develop from previously normal trophoblasts as in cases of choriocarcinoma and PSTT following term delivery and abortion

In a study by Strohl and Lurain published in Gynecologic oncology (2016) they evaluated the effect of a clinicopathologic diagnosis of choriocarcinoma on clinical characteristics, extent of disease, and response to chemotherapy in Low Risk GTN(41). This was a retrospective study where 678 patients treated between 1962 and 2009 were analysed. Out of the 678 patients, 129 (19%) had a clinicopathologic diagnosis of choriocarcinoma. Patients with choriocarcinoma were likely to have higher parity, more pre-treatment beta hCG levels at >100,000Miu/ml, longer duration of disease and higher FIGO scores compared with those

with other histology. However, patients with choriocarcinoma and postmolar GTN presented with similar stage of disease. The result did not show it statistical difference on the survival rates between the two groups, although there was notable increase in resistance for line methotrexate chemotherapy in patients who had postmolar choriocarcinoma, those with pre-treatment beta hCG levels at >10,000Miu/ml and those with a higher FIGO score on multivariate analysis.
A case report by Breitbach G.P, Sklavounos P , Tempfer C shows that Etoposide given orally alone at a dose of 100mg day 1-day7 q28 days can be an alternative to EMA-CO in patients with oligometastatic choriocarcinoma. Side effects were grade 2 (WHO) alopecia and hot flushes

In a journal of Thoracic Disease Gvinianidze L, Panagiotopoulos N, Lawrence D have described the challenging management of lung choriocarcinoma. They conclude that choriocarcinoma of the lung is a clinical entity that should be considered in the differential diagnosis of lung lesions in women after pregnancy(51) This study aims to find out the clinico-pathologic characteristics, treatment options, chemotherapy regimens, 2 and 5 year survival and the correlation between clinico-pathologic characteristics and survival among patients managed in K.N.H between 2013 and 2019.

In South Africa a retrospective study was done by M. Moodley and T Marishane(60) . The aim of the study was to map out Demographic variables of GTD in KwaZulu Natal. They studied the pattern of referrals among diagnosed with GTD. They found that 51% of their GTD over a 5 year period were molar pregnancies. 46% were choriocarcinoma while 2% were PSTT. Most of the patients in the referral hospital came from other hospitals mainly regional hospitals 63.3% but almost a quarter (23.5%) of the cases was self-referrals. With regard to previous pregnancy 63.3% had term pregnancy, 13.3% had previous miscarriage, 2% had previous Ectopic pregnancy while 5.1% had molar pregnancy

Another study by Van Bogaert in South Africa looked at the clinico-pathological features of GTN in the Limpopo province, South Africa(61). Over a 3 year period he looked at 119 patients diagnosed with GTNs through biopsy showing that 70.6% of the cases were benign while 29.4% were malignant. The study established that 2.4% of all Hydatidiform moles were situated in the fallopian tubes while 6.5% of all choriocarcinomas originated in the tubes. In overall, 0.5% of the assessed 857 were associated ectopic pregnancies. There was no significant difference in the mean age of Hydatidiform mole and choriocarcinoma. 11.4% of the 35 choriocarcinomas were HIV positive.

In a retrospective study by Rim et al (66) at Salah Azaiez Institute data from medical records for women diagnosed with GTD from 1st January 1981 to 31st December 2012 was assessed for clinical characteristics, treatment and outcomes of GTD. The same involved was 109 patients with GTN, out of which 43% had metastases, and 30% of the metastasis involved the lungs, 13% involving the vagina. Low risk GTN were 51% while 19% had High-risk GTN, but 32 cases were exempted from the FIGO scoring. The cases were followed for a median period of 46 months, 21 patients had attrition. Out of those who were followed, mortality was recorded in 12 cases while 8 people had a relapse. A ten year follow-up had an 85% (OS) and PFS was 79%, which was mainly influenced by metastases. In another retrospective audit of 112 patients conducted at King Edward Hospital, Durban, South Africa (62), 70% were had Hydatidiform mole and 30% were choriocarcinoma.

Qureshi et al., 2013 (64) in their retrospective cohort study to describe the predictors of GTN chemotherapy outcomes at KNH between 2010 and 2015, they analysed 158 files of both Low Risk GTN and High-Risk GTN patients and found that all High-Risk GTN patients received either EMA-CO or EMA-EP and 14% also got Radiotherapy and 7% also required surgery. Also they found that the management of GTN in KNH did not conform strictly to the WHO/FIGO guidelines. The remission rate was below that of other similar tertiary institutions worldwide.

This study aims to find out the clinico-pathologic characteristics, treatment options, chemotherapy regimens, 2 and 5 year survival and the correlation between clinico-pathologic characteristics and the survival among patients managed in KNH between January 2013 and December 2019.

STUDY JUSTIFICATION

Patients with high risk Gestational Trophoblastic Neoplasia present late in Kenyatta National Hospital for diagnosis and treatment. Observational studies show a correlation between Clinico-pathological characteristics and survival. There are no studies that have been done locally to find out the clinico-pathological characteristics, treatment options, chemotherapy regimens, 2 and 5 year survival, and correlation between clinico-pathological characteristics and survival, among high risk GTN patients in KNH. We do not know how to gauge ourselves in Kenyatta National hospital and East Africa region. GTN is known to be highly curable when treatment is started early, with between 75%-100% remissions while preserving the fertility of the patients. This study will provide new knowledge and help us to gauge our performance in Kenya and Africa as a whole. It will guide local policy formulation that will also guide local management of GTN. This will result in improved outcomes of patients treated for high risk GTN in our local set-up. From this study the country may formulate policies which if implemented will improve outcomes of patients managed. This study will form baseline data for further studies on this topic. This study seeks to determine the clinico-pathological characteristics , treatment options, chemotherapy regimens, 2 and 5 year survival and the correlation between clinico-pathological characteristics and survival among high-risk GTN patients managed in KNH between 2013 and 2019.

STUDY QUESTION AND MAIN OBJECTIVE

STUDY QUESTION.

What are the clinico-pathological, management and survival among high risk GTN patients managed in KNH, between 2013 and 2019.

BROAD OBJECTIVE

To evaluate the clinico-pathological characteristics, management and survival of High-risk GTN patients managed in KNH, Kenya between 2013 and 2019.

SPECIFIC OBJECTIVES

Among women with high-risk GTN managed at KNH gynecological oncology unit between 2013 and 2019.

1. To describe the clinico-pathological characteristics
2. To describe the treatment options offered
3. To determine the 2 and 5 year survival
4. To determine the relationship between clinico-pathological characteristics and survival

METHODOLOGY

STUDY DESIGN

A retrospective descriptive cross-sectional study

STUDY SITE

Kenyatta National Hospital is in Nairobi which is the capital city of Kenya. It is an urban hospital about 4.5 kilometres south-west of the city centre. It was founded in 1901 and is affiliated to the University of Nairobi, college of Health sciences which is a learning institution. It is the oldest hospital in kenya. It is a public tertiary, referral hospital for the ministry of Health. The hospital has a capacity of 1800 beds and runs for 24 hours. It also serves the Naorobi metropolitan area with a population of over 9 million people. The hospital has several departments, of which department of obstetrics and gynecology is one of them. The gynecological oncology unit falls under this department of obstetrics and gynecology. The patients are admitted in ward 1D and ward 1B.

Other departments that actively manage these patients are the Pathology department, Interventional radiology and Radiotherapy Department. Examination under Anaesthesia for staging and biopsy is carried out for patients who have not been staged in KNH theatres. In the out-patient clinic, management plans for new patients are made and reviews for patients in care is carried out. Patients with acute conditions , those requiring chemotherapy or Salvage radiotherapy are admitted and managed in the wards. Acute conditions that require admission include renal failure, anaemia, deed venous thrombosis, acute infections and per vaginal bleeding. Radiotherapy for acute bleeding is provided in the radiotherapy department as an in-patient. This is usually external beam radiotherapy (EBRT). Once the bleeding stops the chemotherapy continues as an in-patient for 8 days then the patient is released to go home and come back for the next course of chemotherapy after 15 days. A multidisciplinary approach is employed in care. Other auxiliary services that form part of the Gyn Oncology unit include Departments of General Surgery, Plastic surgery, Urology, Nutrition, Palliative care and Psychosocial support.

Records Department is integral to the care of GTN patients. The KNH records department keeps a record of cancer patients admitted and managed as in-patients. Patients who are not admitted and are managed as outpatient, have their records kept manually in clinic registers. The ICD (International Classification of Deseases)—10 disease code is used. For GTN, segregation by FIGO stage is not done, all the stages are pooled into desease code C53,4(Cancer of the placenta). Patients who are not admitted, do not have their records captured in the Records Department. The Radiotherapy Department keeps an independent records system that is different from the rest of the hospital. The two records systems are not linked.

Upon discharge they are followed up in the oncology clinic which is in the out-patient department.

STUDY POPULATION

Patients managed for High-risk Gestational Trophoblastic Neoplasia at Kenyatta National Hospital, Gynecological Oncology units of ward 1B and ward 1D between 2013 and 2019.

INCLUSION CRITERIA

All patients with a documented World Health Organization Revised International Federation of Gynecology and Obstetrics 2000 scoring System for Gestational Trophoblastic Neoplasia (WHO, FIGO) score ≥ 7 (High risk GTN)

EXCLUSION CRITERIA

1. Patients whose files are missing
2. Patients whose files have incomplete data.

SAMPLE SIZE CALCULATION

To calculate a representative sample size for the study, Yamane, T (1967) statistics will be used as given in the equation below.

$$N = \frac{Z^2 * (p) * (1-p)}{C^2}$$

Where,
N= the required sample size
p = expected prevalence of the high risk GTN in the society (set at <5%)
The prevalence of cancers of the reproductive tract is very low in our population. High Risk GTN is a subset of cancers of reproductive tract. It is a very rare cancer. So its prevalence is even much lower. That is why Yamane, T (1967) formula applies.
C = Desired margin of error set at 5%
Z=Z value (e.g.1.96 for 95% confidence level.)
Substituting the values into the equation above, we get,
N= 72.99 = 73 patients.
All patients managed between January 2013 and December 2019 were included in the study.

SAMPLING PROCEDURE

Case records with diagnostic code for placental cancer were retrieved from records department of KNH. Using the KNH information management system, IP numbers were identified for all records meeting this diagnostic criteria for the period 2013-2019 for retrieval.
Retrieval of patient files started with screening all records that meet the eligibility criteria as described in study population. Based on the number of files that meet these criteria, a proportion of files were randomly selected until our estimated sample was arrived at. Only those whose FIGO prognostic score ≥7 were analysed.

CONCEPTUAL FRAMEWORK

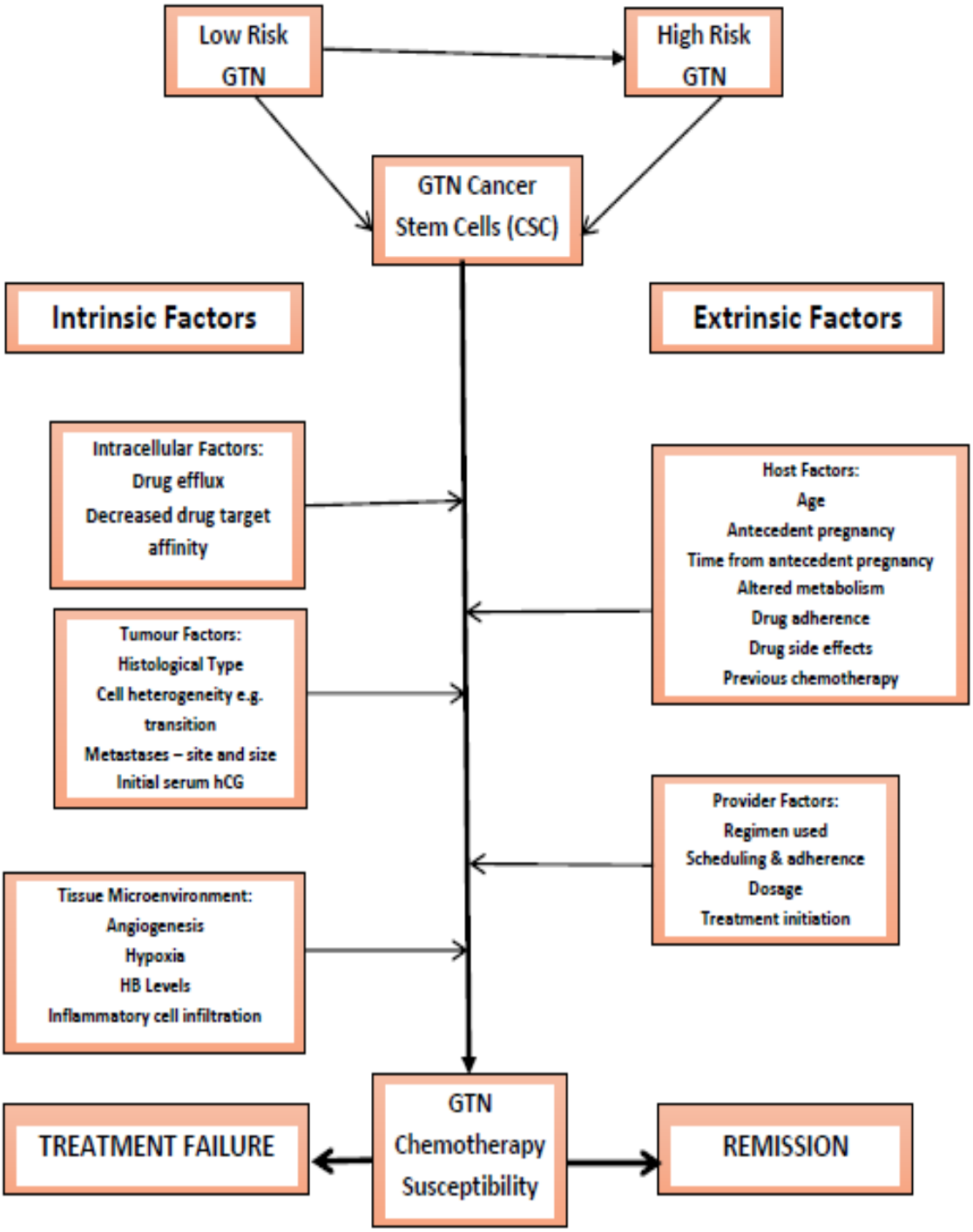
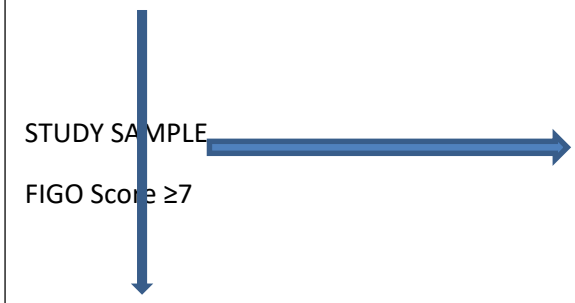


Figure 1 Conceptual Framework
Representative important determinants and concepts implicated in Gestational Trophoblastic Neoplasm

BOX 1 : PATIENT RECRUITMENT SCHEMA

All FIGO stages of Placenta cancer admitted in KNH, 2013 – 2019



EXCLUDE:

- Missing file
- Files with incomplete data

Study Sample

FIGO Score ≥ 7

DATA VARIABLES

Data variables			
	Specific Objectives	**Dependent variable**	**Sources of data**

1.	Descriptive variables	**Socio-demographic**
		• Age
		• Marital status (married, not married)
		• Religion
		• Occupation
		• Education level
		• NHIF registered
		Clinical
		• Parity
		• Family planning
		• Smoking
		• HIV status
		  ○ Lowest recorded CD4 count
		  ○ Lowest recorded viral load
		• Comorbidities
		  ○ Diabetes
		  ○ Hypertension
		  ○ DVT
		  ○ Anemia
		• Time to events
		• FIGO score
		• Histological type
		  ○ Choriocarcinoma
		  ○ Placental site Trophoblastic Tumour
		  ○ Epithelioid Trophoblastic Tumour
			Patient file record

2.	Determine the management of High-risk GTN	**Diagnosis of High-risk GTN**
		• Date of diagnosis of High-risk GTN
		• Mode of diagnosis
		  ○ Serum hCG
		  ○ Histology of endometrium
		  ○ Ultrasound scan
		  ○ MRI
		  ○ CT SCAN
		  ○ Chest X-RAY	

		Therapy modalities ○ Chemotherapy alone ○ Radiotherapy ○ Surgery ○ Chemotherapy+ Surgery ○ Chemotherapy +Radiotherapy • Chemotherapy given ○ EMA-CO ○ EMA-EP ○ High dose EMA-CO for CNS disease ○ EP for very sick pulmonary disease	
3.	Determine the 2 and 5-year survival of those with High-risk GTN	• Date of death • Time to death in months • Mean/median follow up time	
4.	-	• Date of last follow up at KNH • If dead, date of death	Phone call

DATA COLLECTION AND MANAGEMENT

A data abstraction tool was created using the variables in box 2. A soft version of the data abstraction tool was created using an electronic data capture software called Research Electronic Data Capture (REDcap). Research assistants were trained by the Principal Investigator on data abstraction from patient files.

To reduce missing data for survival, patients whose follow-up status was not known were called using the number provided to records department during the initial registration at Kenyatta National Hospital. Date of last follow-up at Kenyatta National Hospital and or dete of death are the only variables that were collected during the phone calls. Data was abstracted directly into the REDcap software. At the end of data collection, data was exported to an exel database.

QUALITY ASSURANCE

A research assistant were Post Graduate students in the Department of Obstetrics and Gynecology. They are qualified doctors who usually manage patients with High-risk GTN in the Department. They are all trained and certified in good clinical practice. Data abstraction tool was piloted together with the REDcap software which was used for electronic data capture. The REDcap software has inbuilt range and consistency checks were enforced in the database.

DATA ANALYSIS AND PRESENTATION

Data was exported from Excel database to Status software for analysis. Only de-identified data was analysed. Description of data analysis was per objective.

Descriptive characteristics: Data with descriptive statistics were summarized. Age was presented as means (SD), while categorical data was presented in proportions.

Determining histopathology of placental tissue and treatment modality offered; Data on histological types and High-risk GTN treatment offered was categorized and presented in proportions.

Determining the management of High-risk GTN. Data on mode of diagnosis , GTN risk score, chemotherapy regimen given, treatment given was categorized and presented in proportions.

Determining the 2 and 5 year survival: Kaplan Meier curves was used to determine 2-and 5-year survivals for FIGO SCORE≥ 7. Patients who were still alive or lost to follow up were censored in the survival analysis. To correlate characteristics with survival: survival was correlated with sociodemographic and clinical characteristics.

For the univariate and multivariate cox models, crude, and adjusted hazard ratios (HR) with accompanying 95% Cls corresponding P values were reported. Dummy tables in the appendix.

ETHICAL CONSIDERATIONS

Ethical approval was sought from KNH-UON ethical review committee. A letter of approval from KNH administration to collect data was sought.. De-identification of participants details was done.
Password protection of the collected data was done so that only the principal investigator and statistician had access to the data. The results obtained will be shared with KNH and UON to help improve planning for management of GTN patients. Due to the retrospective nature of the study, consent form was not needed. Telephone numbers of next of kin was used to trace those patients who were lost to follow-up.

STUDY LIMITATIONS AND RESULTS DISSEMINATION

LIMITATIONS

Missing data (these will be censored)

DISSEMINATION

Results will be presented to the Division, and study sites.
The Ethical review committee will be informed of the results
The results will be published
Policy brief will be done to the Ministry of health to inform clinicians who are involved in management of GTN.

STUDY TIMELINES

Timelines											
#	Activity	2020						2021			
		Jul	Aug	Sept	Oct	Nov	Dec	Jan	Feb	Mar	April
1.	Proposal Development										
2.	Development of Recap Software										
3.	Ethics Review and Approval										
4.	Prepare for data collection-training and tool testing										
5.	Data Collection										
6.	Data Analysis										
7.	Project write-up										
8.	Presentation to Department and Dissemination of Results										

BUDGET

Printing of data capture tools KSH 3000

Printing copies of proposal KSH 8000

Two Research assistants @2000 per day for 5 days KSH 20,000

Stationary KSH 500

Printing of Draft theses KSH 10,000

Printing of Final theses KSH 10,000

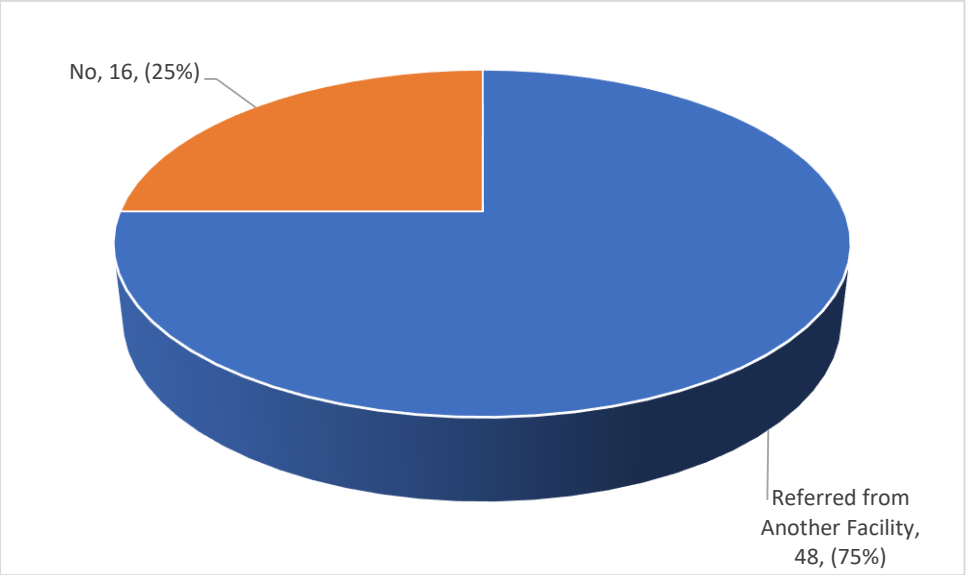
Contingency fund KSH 7,150

TOTAL KSH 78,000

RESULTS

A total of 64 files were retrieved from the records department against a target of 73 files. There was a challenge in finding files for patients who had died because there is no space for arranging those files properly in the records department.

Figure 1: Referred from another Facility



Among the patients seen in KNH, 75% are referred from all over the country while only 25% are walk-in from Nairobi and its environs. This is because KNH is a tertiary facility that handles referrals from all over the country.

Table 1: Socio-Demographic Factors (n=64)

Demographic Characteristics	Statistics	n	%
Age (in complete years)			
Mean	35.0		
Median	33.0		
Range [Min-Max]	20.0 – 58.0		
IQR [25-75%]	31.0-37.0		
< 20-29		23	35.9
30 -39		22	34.4
40 – 49		17	26.6
50 +		2	3.1
Marital Status			
Single		13	20.3
Married		48	75.0
Separated		2	3.1
Widowed		1	1.6
Religion			
Christian		61	95.3
None		2	3.1
Not Indicated		1	1.6
Employment			
Formally Employed		2	3.1
Not Employed		20	31.3
Casual		2	3.1
Self-Employed		30	46.9
Not Indicated		10	15.6
Education			
None		2	3.1
Primary		15	23.4
Secondary		29	45.3
College/University		8	12.5
Not Indicated		10	15.6

The mean age of patients in this study was 35 years. This differs from a similar study in South Africa whose mean age was 28 years.

Table 2: Clinical Characteristics (n=64)

Clinical Characteristics	Statistics	n	%
Parity			
Mean	2.0		
Median	2.0		
Range [Min-Max]	0-9		
IQR [25-75%]	2-3		
Null		10	15.6
1 -2		26	40.6
3 +		28	43.8
Family Planning			
None		9	14.1
Combined Contraceptive Pills		16	25.0
Depo Provera		19	29.7
Implant		2	3.1
ICUD - Copper T		2	3.1
Progesterone Pills		1	1.6
Other		2	3.1
Not Indicated		13	20.3
Pap Smear Results			
Normal		5	7.8
Not Done		59	92.2
Smoking			
No		48	75.0
Not Indicated		16	25.0
HIV Status			
HIV+		3	4.7
HIV-		22	34.4
No Results Found		39	60.9
Other Comorbidities			
None		3	4.7
Diabetes		2	3.2
Hypertension		8	12.6
Deep venous		4	6.3
Anemia		45	70.3
Other		9	14.1

The Mean Parity of patients was 2

Majority of patients, 92.2% had never done a Pap-smear

70.3% of patients had Anaemia

Table 3: Pathological Characteristics (n=64)

Pathological Characteristics	n	%
Pretreatment hCG levels		
<1,000	2	3.1
1,000 - 10,000	29	45.3
10,000 – 100,000	10	15.6
>100,000+	23	35.9
Histology Confirmed		
Choriocarcinoma	15	23.4
Invasive	-	
PSTT	-	
ETT	-	
No Histology	49	76.6
Deranged Kidney Fxn	3	4.7
Deranged Liver Fxn =γGT	34	53.1
Transfusions	8	12.5
Neupogen	19	29.7

The only Histology found was Choriocarcinoma. This Finding defers from Gitau et al, who found one Case of PSTT between 2010 and 2015.

53.1% of patients had elevated liver enzymes gamma glutaryl transferase.

12.5% of patients required blood transfusions during the course of treatment.

Table 4: INVESTIGATIONS

Investigation	Number	Percentage
H/gram	61	95%
U/E/Cr	60	93%
LFT	60	93%
CXR	58	90%
Pelvic Ultra Sound	60	93%
CT - Scan	6	9%
MRI	5	7.8%

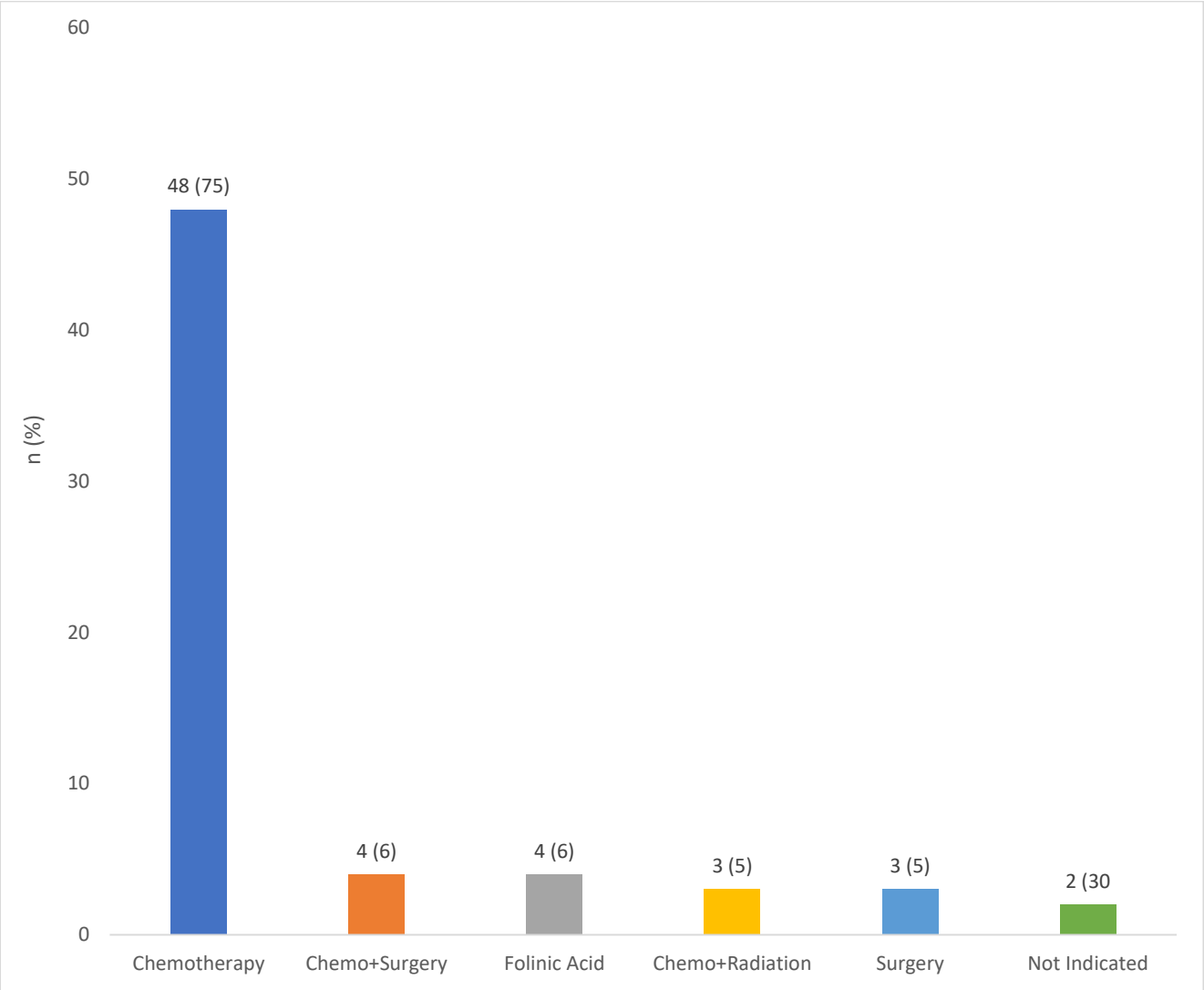
HB		
≥ 10	28	43.8
8 - < 10	23	35.9
< 8	13	20.3

Pelvic Ultrasound and Chest X-ray was the commonest imaging modality

43.8% of patients had hemoglobin above 10g/dl on admission

95% of patients had H/gram, LFTs, U/E/Cr done as basic investigations before they receive Chemotherapy.

Figure 2: TREATMENT GIVEN



Chemotherapy was the main modality of treatment for High Risk GTN patients.

6% also required surgery as adjuvant treatment

Table 5: Treatment offered both in KNH and from the primary referring facility.

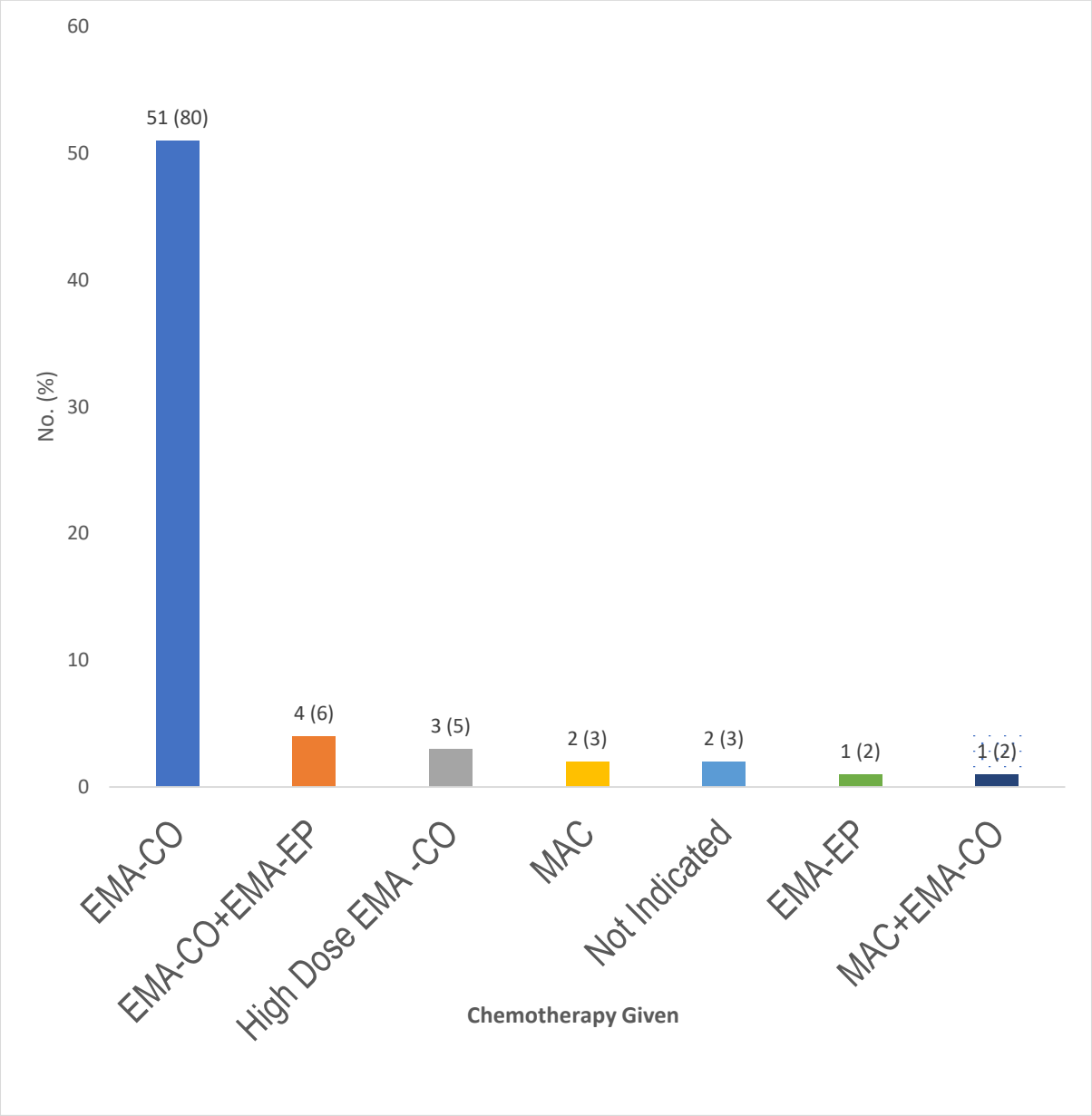
Treatment	n (%)
Cancer Treatment	
• Chemotherapy Alone	49 (76.6)
• Chemotherapy+Radiotheraphy	5 (7.8)
• Other Surgery= LAPAROSCOPY/ LAPAROTOMY + BIOPSY	2 (3.1)
• Surgery-Hysterectomy	6 (9.4)
• Not Indicated	2 (3.1)
Surgery Done	
• Hysterectomy	9 (14.1)
• Laparotomy	4 (6.3)
• No Surgery	51 (79.7)
Treatment Outcome	
• Clinical Response	43 (67.2)
• Death	21 (32.8)

Laparoscopy and LAPARATOMY was done in 3.1% of patients.

These patients presented in peripheral facilities with a pelvic tumor of unknown origin.

They were taken to theatre at the primary referral facility but found to be inoperable. Then they were referred to KNH for further management.

Figure 3: Chemotherapy Given



EMA-CO was the main chemotherapy for patients with High Risk GTN.

6% also got EMA-EP after failure of EMA-CO

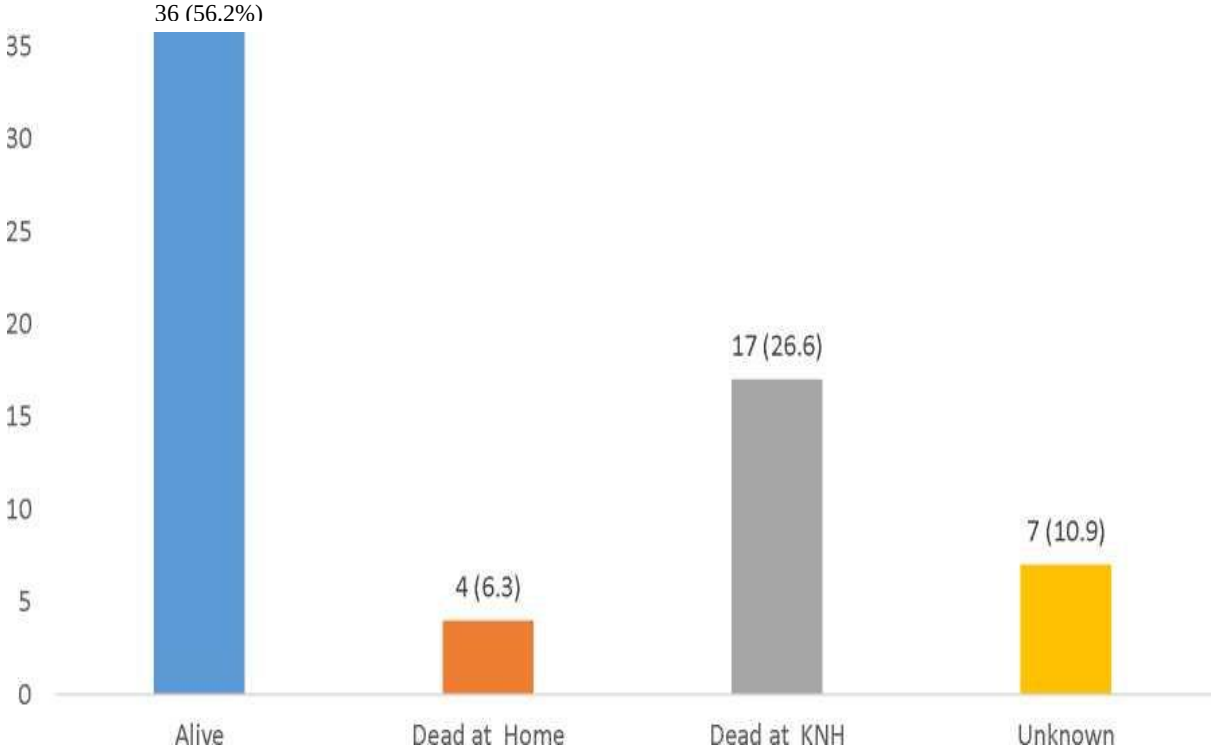
High Dose EMA-CO for CNS Disease was given in 5% of patients

EMA-CO= Etoposide,Methotrexate,Actinomycin-D, Cyclophosphamide, Vincristine

EMA-EP= Etoposide,Methotrexate,Actinomycin-D, Etoposide,Paclitaxel

MAC= Methotrexate,Actinomycin-D, Cyclophosphamide

Figure 4: Patient Status



Out of 64 Files analyzed, 21 patients have died while 43 patients are alive

Table 6: Causes of Death

Cause of Death	FIGO SCORING		
	< 10	10 - 15	15 +
Bacterial Infection	-	1	-
Haemorrhage	5	3	1
Chemo-toxicity	1	-	-
Pulmonary Embolism	-	2	-
CNS Metastasis	-	1	1
Chest Metastasis with Hemoptysis	1	2	-
Liver Failure	1	-	-
Others= administrative	2	-	-

Majority of patients died of Haemorrhage. 2 patients (9.5%) died of pulmonary embolism.

1(4.7%) died in ICU of pulmonary embolism, while another 1(4.7%) died at home after completing treatment. She had DVT in the ward, and was on Clexane, and was discharged on Warfarin.

1(4.7%) patients died of Chemo-toxicity thought to be related to Methotrexate. She developed severe profuse Gastroenteritis that lasted 2 days then she died.

3 patients(14%) died of Chest Metastasis with Hemoptysis causing respiratory failure.

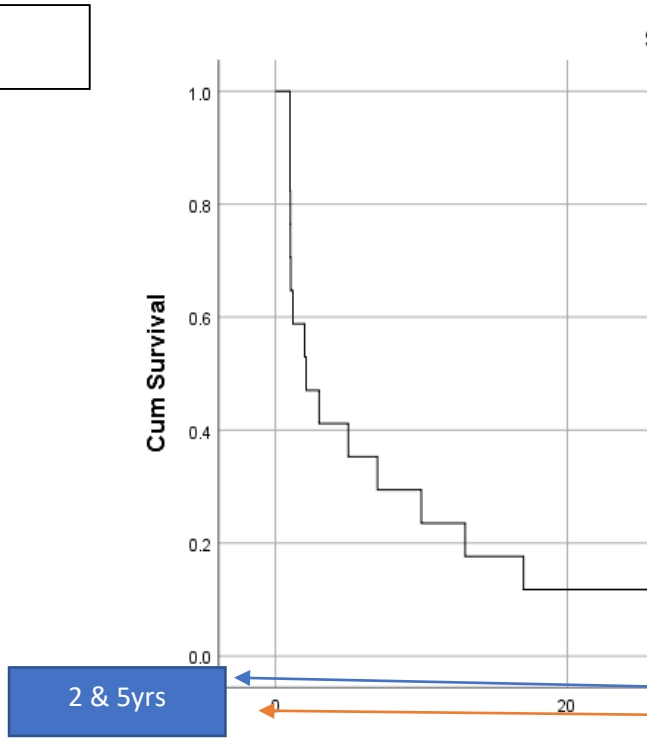
1 patient(4.7%) died of advanced cancer with Jaundice and liver failure

2 patients(9.5%) died of reasons linked to administrative failure.

Table 7: TREATMENT OUTCOMES

Remission	Change of Regimen	Loss of Follow-Up	Death	Total
43 after 8 courses=67%	24	6	21=33%	64

Figure 5: Survival Curves



2 years = 0.18

5 Years = 0.1

High-Risk GTN being a cancer, survival is dismal among patients treated in KNH. They continue to die even after completing their chemotherapy and hCG levels have become negative. The patients alive at 5 years are much less than at 2 years. Some patients are lost to follow-up. It is not clear whether they died or they changed their mobile numbers.

DISCUSSION

Kenyatta National Hospital is a tertiary institution that receives patients all over Kenya. 75% of the High-Risk GTN patients were referrals from other facilities. The mean age of the patients seen was 35 years. In a similar South African study the mean age was 28 years . Most of our patients in KNH were married and were Christians who had achieved secondary education and were self-employed.

92.2% of the patients had never done a pap smear. This was suprising because they presented with per-vaginal bleeding in 89.1% of the patients and the differential diagnosis of cervical cancer had to be ruled out on history of presenting illness. 15.6% of the patients were referred after undergoing a hysterectomy due to persistent per-vaginal bleeding and histology results made the diagnosis of choriocarcinoma. This now prompted the smaller facilities to refer the patients to KNH. 6.3% of the referred patients had CNS metastases presenting with neurological complications while 14.1% had chest metastases presenting with hemoptysis

The mean FIGO score for the patients who were treated and survived was 10 while the ones who died had a mean FIGO score of 11. This difference was not statistically significant.In KNH, 59% of the patients developed High-Risk GTN following a molar pregnancy. In south Africa, majority of their patients developed GTN following a term pregnancy.

Among the patients who were treated, 37.5% had their treatment revised from admission because either they started as Low-Risk and moved to High-Risk or they started with High-Risk on EMA-CO regimen and did not respond to treatment and had to be reviewed again and move to EMA-EP.

45% of the patients seen had their hCG levels between 1,000-1,0000. This may have been due to the laboratory machine used. There are some machines whose upper limit of hCG testing is 10,000 so that

even if the actual level of hCGis one million mIUml they would just read as 10,000mIU as the results.
The histological finding of choriocarcinoma was the only one. This does not mean that the other histological findings are not present. Hysterectomy was rarely done and this is why we could nor detect other histological findings. Between 2010 and 2015, only one PSTT was found by Dr Gitau, Prof Qureshi, Prof Kiarie et al (64).
Pelvic ultrasound and chest X-ray were the commonest imaging modalities while MRI and CT-scan was rarely used. This is because N.H.I.F coverage is poor and most patients do not have ready cash money to pay for MRI and CT-scan and they are expensive.
The basic routine investigations of blood tests before starting chemotherapy was done in all patients before starting EMA-CO. These were complete blood count, Liver function test, Urea, Creatinine and Electrolytes.
Out of the 64 files reviewed, 21 had died while 43 were still alive. Among the ones who died 4 died at home while on follow-up and 17 died in hospital while still on treatment
Majority 46.7% of GTN patients were treated using chemotherapy. Adjuvant treatment was either surgery or radiotherapy. The main chemotherapy given was EMA-CO (80%). A small number(4) received both EMA-CO and EMA-EP. The total number who received both EMA-CO and EMA-EP was 4. One died of chemoresistant dtumour while 3 survived.
A total of 11 patients moved from Low-Risk to High-Risk. 10 achieved complete remission while 1 died of chemoresistant tumour even after giving her EMA-CO, EMA-EP, Cisplatin + Paclitaxel, and even Etoposide+ Paclitaxel
One patient received EMA-CO = Radiotherapy + Total Abdominal Hysterectomy until hCGlevels were negative but died at home within 1 month of discharge from pulmonary embolism. She had DVT while in the ward and was on clexane and was discharged on warfarin.
The mean number of cycles of EMA-CO given to obtain a negative hCG level was 8. Eleven patients died after starting treatment with EMA-CO but 6 died after receiving treatment with EMA-CO until their hCG levels became negative.

8 patients got treatment failure with EMA-CO and had to switch to EMA-EP. 6 of them survived but 2 died even after Cisplatin + Paclitaxel in one of the 2. High-dose EMA-CO was given to 3 patients who had CNS disease.
The commonest causes of death was heamorrhage(9 patients)=48%. Two patients died of pulmonary embolism. One died of profuse gastroenteritis lastin 2 days suspected to be due to methotrexate. 2 died of CNS metastases due to advanced disease. 3 Died of advanced disease with chest metastases causing severe hemoptysis and respiratory failure. One died of jaundice with liver failure due to liver metastases in advanced disease with ascites and one died of bacterial infection revealed by post-mortem after she finished her chemotherapy and was discharged. She had low neutrophil count and was on Neupogen. 2 patients died of reasons that are purely administrative.
The remission rate for patients who received EMA-CO 8 courses was 67%
The Kaplan-Meir curves gave a 2 year survival of 18% and a 5 year survival of 10%.

CONCLUSION AND RECOMMENDATIONS

CONCLUSION

The mortality from High-Risk GTN is very high at almost 50%. Most patients present with per-vaginal bleeding and they die of haemorrhage before 2 years are over. Most High-Risk patients in KNH are treated with EMA-CO with good response. This is the standard chemotherapy modality. EMA-EP is superior to EMA-CO and was given to a few who did not respond to EMA-CO.

RECOMMENDATIONS

1. Availability of blood for transfusion in the blood bank should be improved. The National Blood Transfusion Services needs to be funded well. 50% of the patients who died were waiting for blood transfusion to bring their haemoglobin to 10g/dl before starting EMA-CO.
2. A high index of suspicion is required so that these patients are identified early in the wards.
3. Establishment of a National centre of excellence in management of Trophoblastic Diseases so that early refferals are made. This will save time so that treatment starts early
4. Administrative streamlining is required to avoid time wasting
5. Further research on this topic is required , both longitudinal study design and qualitative study design.

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CHAPTER 5: APPENDIXES

APPENDIX 1: DATA ABSTRACTION FORM

DATA ABSTRACTION FORM

CLINICO-PATHOLOGICAL CHARACTERISTICS AND TREATMENT OPTIONS, CHEMOTHERAPY REGIMENS AND TREATMENT OUTCOMES AMONG HIGH-RISK GTN PATIENTS MANAGED IN KENYATTA NATIONAL HOSPITAL, KENYA 2013-2019.

SECTION A: IDENTIFIERS

COUNTY OF BIRTH	**HOSPITAL REFERRED FROM**

SECTION A: ELIGIBILITY TO STUDY

1) **File available in the Records Department**
   ( ) Yes *(move to 2)*
   ( ) No *(exclude from study)*

2) **Confirmed diagnosis of high-risk GTN.**
   ( ) Yes *(move to number 3)*
   ( ) No

3) **The histopathology report of choriocarcinoma, Invasive mole, PSTT, ETT**
   ( ) Yes *(record date and move to 4)* __/__/__ (dd/mm/yy)
   ( ) No

4) **High-Risk GTN . The FIGO score>7**
   ( ) Yes
   ( ) No (exclude from the study)

Summary of eligibility criteria
All High-Risk GTN patients with FIGO score >7 admitted in KNH 2013 – 2019

SECTION B: SOCIO-DEMOGRAPHIC DATA

1) **RECEIVED EMACO HOW MANY CYCLES TO GET FIRST NEGATIVE?**

2) **Age in years _____**

3) **Marital status**
   ( ) Single
   ( ) Married
   ( ) Separated
   ( ) Widowed
   ( ) Other *(specify)* ----------
   ( ) Not indicated

4) **Religion**
   ( ) Muslim
   ( ) Christian
   ( ) Other *(specify)* ----------
   ( ) Not indicated

5) **Occupation**
   ( ) None
   ( ) Casual Laborer
   ( ) Self-employed
   ( ) Formal Employment
   ( ) Not indicated

6) **Education level**
   ( ) No formal education
   ( ) Primary Level
   ( ) Secondary level
   ( ) College/University
   ( ) Not indicated

7) **NHIF registered**
   ( ) Yes
   ( ) No
   ( ) Not indicated

8) Referral from another facility
   ( ) YES SPECIFY----------
   ( ) NO

SECTION C: CLINICAL CHARACTERISTICS

Past Medical History

9) Parity

Para ____ + _____ ( ) Not indicated

10) Family planning

( ) None
( ) IUCD- copper T
( ) IUCD- Mirena
( ) Depo provera
( ) Implant
( ) Progesterone pills
( ) Combined oral contraceptive pill
( ) Condoms
( ) Natural methods
( ) Other *(Specify)*…….
( ) Not indicated

11) Pap smear results

( ) NORMAL
( ) ABNORMAL
( ) NOT DONE

12) Smoking

( ) Yes
( ) No
( ) Not indicated

13) HIV status

( ) HIV positive

If positive:

Lowest recorded CD4 counts ……. ( ) Not indicated
Highest recorded viral load …… ( ) Not indicated

( ) HIV negative
( ) HIV status not indicated

14) Other comorbidities

( ) None
( ) Diabetes
( ) Hypertension
( ) Deep venous thrombosis
( ) Anemia
( ) Other *(Specify)*…….

15) Clinical characteristics at admission

( ) Per-vaginal bleeding
( ) Haemoptysis
( ) Neurological complication
( ) Surgery already done
( ) Chemotherapy already started
( ) Others (specify)----------

Time to events

16) Date of cancer diagnosis (date recorded in histopathology report)

( ) Yes (record date and move to 2) __/__/__ (dd/mm/yy)
( ) NO HISTOLOGY

17) Date of first clinic/hospital visit

( ) Yes (record the date) __/__/__ (dd/mm/yy)

( ) Not Indicated

18) Date of FIGO score> 7 diagnosis

__/__/__ (dd/mm/yy)

19) Date of first FIGO score (if it was less than 6 at some point)

__/__/__ (dd/mm/yy) (specify)…..…..

20) Patient alive or dead

( ) Alive

Date of last follow up clinic __/__/__ (dd/mm/yy)

( ) Dead

Date of death __/__/__ (dd/mm/yy)

Date of last follow up clinic __/__/__ (dd/mm/yy)

( ) Not clear *(indicate why)*……..

FIGO Scoring

21) Confirm this is FIGO score>7

( ) Yes, it is FIGO score >7

( ) No, it is not FIGO score >7 *(go back . exclude from study)*

22) How was FIGO scoring done ? *(Tick all that apply)*

( ) Examination without Anesthesia

( )Done in KNH

( )Done outside KN

( ) Previous failed chemotherapy

( ) Largest tumour size including uterus (cm)

( ) Site of metastases

( ) Number of metastases identified

( ) Antecedent pregnancy

( )Pretreatment hCG (mIU/mL

( ) Interval from index pregnancy(months)

( ) Age

23) FIGO score progressed from the admission FIGO score

( ) Not progressed

( ) Progressed

If progressed

Indicate progressed stage ……

Indicate date of progressed stage __/__/__ (dd/mm/yy)

How was diagnosis of progression made *(specify)*……

CLINICAL CHARACTERISTICS

24) Number of previous deliveries

25) Number of previous abortions

26) Number of previous molar pregnancies

27) HIV status

1= positive

2= negative

3= unknown

28) Hemoglobin level at admission in grams/dl----------
29) GTN followed
1= molar pregnancy
2= term pregnancy
3= ectopic pregnancy
4= abortion
30) Interval from index pregnancy in months
1= less than 4 months
2= 4-6 months
3= 7-12 months
4= 13 months and above

31) B.P----------
32) Pulse----------
33) Respiratory rate----------
34) Temperature----------
35) Weight----------
36) Height----------BMI= ---------- BSA= ----------
37) Symptoms
1. Vaginal bleeding
2. Pain
3. Bloating/ abdominal distension
4. Weight loss
5. Vaginal discharge
6. Decreased energy
7. Other----------

38) General exam
1. Pallor
2. Jaundice
3. Wasted
4. Convulsed
5. Confused mentally
6. None of above
7. OTHERS----------SPECIFY----------

39) Family history of cancer
1) None
2) Breast
3) Ovarian
4) Cervix
5) Colon

40) HIV Anti-retrovirals
1) yes
2) no

41) Pelvic exam
Uterine size _____
Uterus Involved
1) YES
2) NO

Vaginal involvement
1) yes
2) no

Ovary / Pelvic mass
1) YES
2) NO

Size of ovary on ultrasound……..

Para-metrial involvement
1) YES
2) NO

Liver involvement
1) YES
2) NO

Chest involvement
1) YES
2) NO

Brain involvement
1) YES
2) NO

Kidney involvement
1) YES
2) NO

Spleen involvement
1) Yes
2) No

PATHOLOGICAL CHARACTERISTICS

42) Pretreatment hCG levels
1) = <1,000
2) = 1,000-10,000
3) =10,000-100,000
4) =≥100,000

43) Histology confirms
1) Choriocarcinoma
2) Invasive mole
3) PSTT
4) ETT
5) NO HISTOLOGY

44) Deranged kidney functions
1) YES
2) NO

45) Deranged Liver functions
1) YES
2) NO

46) Age (years)
1) ≤39years
2) ≥ 40 years

47) Antecedent pregnancy
1) 0= H.Mole
2) 1 =abortion
3) = term pregnancy

48) Interval from index pregnancy (months)
   1) 0= <4 months
   2) 1= 4-6 months
   3) =7-12 months
   4) 3=≥13 months

49) Largest tumour size (cm) including uterus
   1) 1= 3-5 cm
   2) 2= >5cm

50) Site of metastases
   1) 0=less than 3 sites
   2) 1= spleen / kidney
   3) 2= GIT
   4) 3=Brain/ liver

51) Previous failed chemotherapy
   1) 0= nil
   2) 1=single drug
   3) 3= ≥ 2 drugs

52) Number of metastases identified
   1) 0 = nil metastases
   2) 1= 1-4 metastases
   3) =5 -8 metastases
   4) 3= > 8 metastases

53) Total WHO score……..

54) IMAGING FINDINGS
   1) Ultrasound----------
   2) Chest X-RAY----------
   3) MRI of PELVIS/ABDOMEN----------
   4) CT-SCAN of CHEST----------
   5) CT-SCAN of BRAIN----------
   6) CT-SCAN of ABDOMEN----------
   7) MRI CHEST, BRAIN, ABDOMEN----------

55) Treatment plan
   1) Surgery
   2) Chemotherapy
   3) Folinic acid
   4) Chemo + surgery
   5) Chemo + radiation
   6) Follow up
   7) NONE----DIED BEFORE TREATMENT COMMENCED/ DELAYED DIAGNOSIS

56) Received transfusions
   ( ) YES
   ( ) NO

57) Received Neupogen
   ( ) YES
   ( ) NO

58) For those who died
   1) Cycles of chemotherapy given
   2) Interval between admission and death
   3) Metastases identified
   4) WHO FIGO score
   5) Latest hCG levels

59) Multi-disciplinary team involved in management

1) Radiotherapy
2) Nutrition
3) Hospice care
4) Counseling
5) Psychosocial support
6) H.I.V clinic
7) Surgical
8) Medical hematologist, cardiologist

Histopathology

60) Histological type (check on histopathology report)

( ) Choriocarcinoma
( ) Invasive mole
( ) Placental Site Trophoblastic Tumour
( ) Epithelioid Trophoblastic tumour
( ) No Histology

SECTION D: MANAGEMENT OF HIGH-RISK GTN

61) **Date of diagnosis of High Risk GTN**

__/__/__ (dd/mm/yy)

62) Chemotherapy combination given

( ) MAC
( ) MAC + EMA-CO
( ) EMA-CO
( ) High dose EMA-CO (For CNS disease)
( ) EMA-EP
( ) EMA-CO + EMA-EP
( ) EP= Etoposide+cisplatin(Emergency for sick patients)
( ) GCP= Gemcitabine+Carboplatin+Paclitaxel
( ) PACE/ PAC-PLAT (for patients resistant to EMA-CO)
( ) NONE- PATIENT DIED BEFORE TREATMENT INITIATED

63) GTN developed following

) Abortion
) Term pregnancy
) Ectopic pregnancy
) Hydatidiform mole
) Premature delivery

64) Blood Tests done and abnormal

( ) Haemogram
( ) Liver function tests
( ) Renal functions
( ) None

SECTION E: GTN TREATMENT

65) Cancer treatment offered (Tick all that apply)

( ) Chemotherapy + radiotherapy (EBRT)
( ) Chemotherapy
( ) Surgery- Hysterectomy
( ) RADIOTHERAPY ALONE
( ) NONE---DIED BEFORE CHEMOTHERAPY STARTED

66) Surgery done

( ) Hysterectomy
( )Craniotomy
( ) Laparotomy
( ) LAPAROSCOPY
( ) No Surgery
( ) BIOPSY

67) Treatment outcome

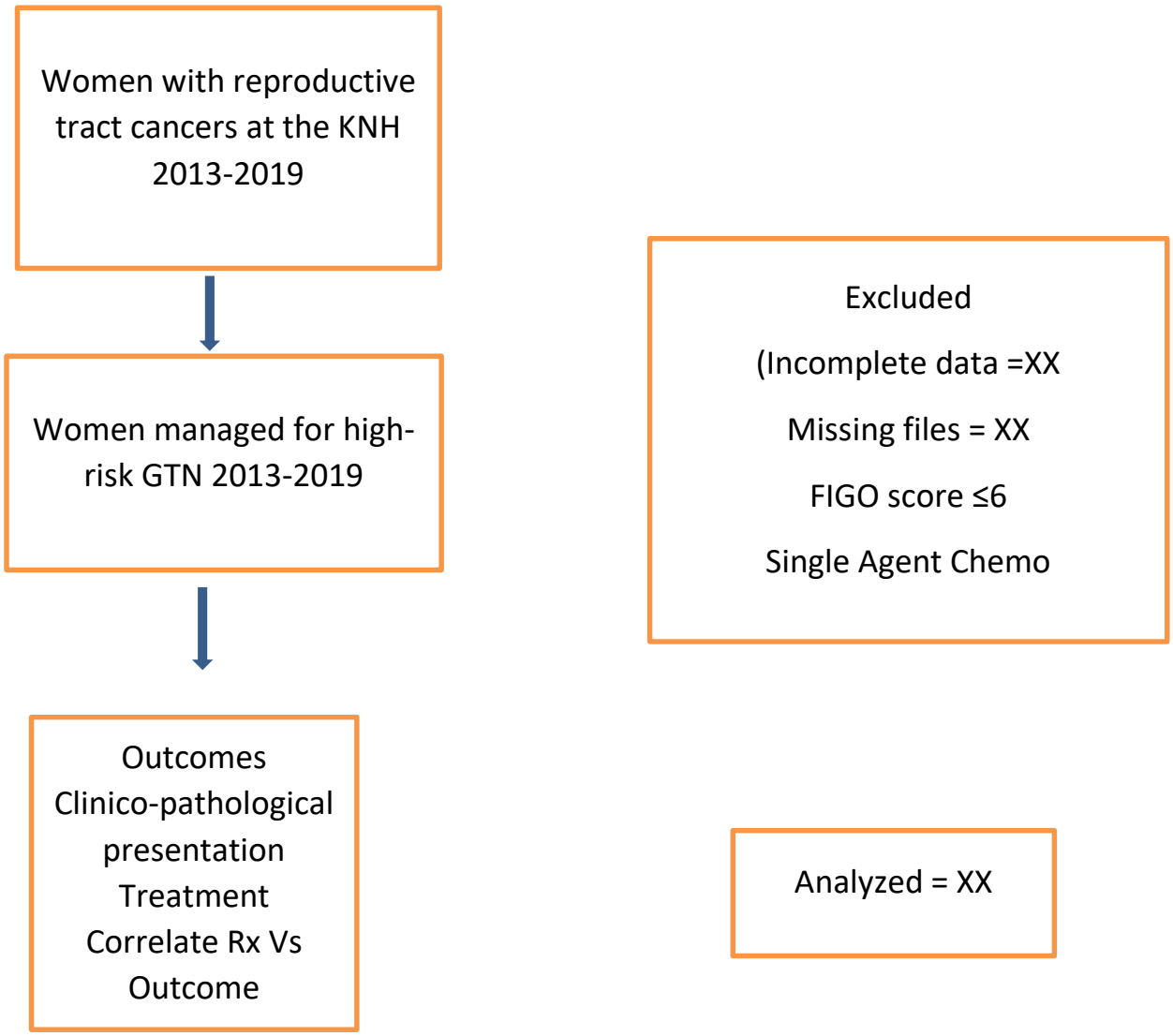
( ) Resistance to EMA-CO
( ) Recurrence
( ) Death
( ) Clinical response
( ) Drug Toxicity……(explain)

68) Cause of death

( ) Bleeding per vaginal
( ) CNS complications
( ) Chest complications
( ) Others……..(specify)

APPENDIX 2: DUMMY TABLES.

Enrolment flow chart



APPENDIX 3: VERBAL CONSENT

PHONE CALL VERBAL CONSENT-ENGLISH
CLINICO-PATHOLOGICAL CHARACTERISTICS, TREATMENT OPTIONS, CHEMOTHERAPY REGIMENS AND TREATMENT OUTCOMES AMONG HIGH-RISK GTN PATIENTS TREATED IN K.N.H 2013-2019
I am Dr Lazarus Omondi Kumba, the lead researcher in a review of clinico-pathological characteristics, treatment options, chemotherapy regimens, and treatment outcomes among High-risk GTN patients treated in Kenyatta National hospital. This study will evaluate 88 patients who have been in care since 2013, and you are one of them. Your phone number is listed in the file. I am calling because I need your assistance to clarify some of the information that is missing or unclear from your file. This information will help us complete the study and understand how to manage patients with High-risk GTN patients. This study has been approved by Kenyatta National Hospital/University of Nairobi Research and Ethics Committee. The ethics committee has granted access to your file. None of your identifying information will be collected. Information collected will be used only for purposes of this study. Your information will be kept confidential. Please note that the call may be recorded for reference purposes. The phone call will last a maximum of five minutes. Should you choose not to give any information or stop giving information at any point, it will not affect care given to you or your loved one at Kenyatta National Hospital. Do you have any questions/clarifications? I would be happy to answer the questions or clarify any concerns. Would you be willing to participate in the study and answer some questions on phone? ( ) Yes ( ) No

IDHINI YA MATAMSHI YA SIMU

USIMAMIZI NA UPONAJI WA SARATANI YA HIGH-RISK GTN KWA WALIOLAZWA HOSPITALI YA KITAIFA YA KENYATTA KIPINDI CHA 2013-2019

Mimi ni Dkt. Lazarus Omondi Kumba mtafiti mkuu anayeongoza uchunguzi unaoangazia usimamizi wa wagonjwa wa saratani katika hospitali ya kitaifa ya Kenyatta. Utafiti huu utawatathmini wagonjwa 88 waliokua chini ya uangalizi tangu mwaka 2013, na wewe ni mmoja wao. Namba yako ya simu imeorodheshwa katika faili. Nakupigia simu kwa sababu nahitaji msaada wako wa ufafanuzi zaidi wa habari ambayo haipo au haifahamiki wazi kutoka kwenye faili yako. Taarifa hio itatusaidia kuumaliza utafiti na kuelewa namna ya kuwasimamia wagonjwa walio na saratani vyema. Utafiti huu umeitishwa na kamati ya kitaifa ya hospitali ya kitaifa ya Kenyatta/kituo cha utafiti na maadili cha Chuo kikuu cha Nairobi. Kamati ya maadili imepeana ruhusa kutumiwa faili yako. Hakuna taarifa ya utambulisho wako itakayokusanywa. Habari iliyokusanywa itatumika tu kwa madhumuni ya utafiti huu. Taarifa zako zitawekwa siri. Tafadhali fahamu kuwa mazungumzo ya simu yanaweza kurekodiwa kwa sababu ya kumbukumbu. Mazungumzo hayo ya simu yatadumu kwa dakika tano. Iwapo utachagua kutotoa habari yeyote au kuacha kutoa habari wakati wowote, hakutoathiri huduma uliyopewa au kwa jamaa yako mpendwa katika hospitali ya kitaifa ya Kenyatta. Je, una swali lolote au ufafanuzi? Nitafurahi kuyajibu maswali yako au kufafanua wasiwasi wowote. Je, ungependa kushiriki katika utafiti na kujibu maswali kadhaa kupitia simu? ( ) Ndio ( ) La