REVIEW OF CLINICO-PATHOLOGICAL CHARACTERISTICS, MANAGEMENT AND OUTCOMES IN PATIENTS MANAGED FOR SEROUS CARCINOMA OF THE OVARY AT KENYATTA NATIONAL HOSPITAL FOR THE PERIOD 2012—2017.

INVESTIGATOR

DR ALFRED MOGAKA MOKOMBA

H117/27759/2019

DEPARTMENT OF OBSTETRICS AND GYNAECOLOGY

A PROJECT DISSERTATION SUBMITTED TO THE UNIVERSITY OF NAIROBI DEPARTMENT OF OBSTETRICS AND GYNAECOLOGY

IN FULFILMENTOF FELLOWSHIP IN GYNAECOLOGIC ONCOLOGY

2021

DECLARATION

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

DR ALFRED MOKOMBA

MBChB, Mmed(OBS/GYN),

SIGN---------- DATE 15/11/2021

This dissertation has been submitted with the approval of my supervisors

1.PROF. OJWANG S B O. MD,M.med ,Higher diploma in gynaecology oncology oncology(karlolinska institute), Consultant obstetrician gynaecologist, consultant gynaecologic oncologist

Professor, school of medicine, university of Nairobi

SIGN---------- DATE----15/11/2021-

2 .DR. DIANA ONDIEKI, MBChB, Mmed (OBS/GYN), Msc.

Epidemiology(LSHTM), Consultant Obstetrician Gynaecologist.

Lecturer Obstetrics and Gynaecology university of Nairobi

15/11/2021

SIGN---------- DATE----------

3.DR KIREKI OMANWA , MD,PhD,

Consultant Obstetrician Gynaecologist, Fertility specialist Lecturer Obstetrics and Gynaecology , University of Nairobi SIGN----------

DATE----15/11/21

CERTIFICATIFCATION OF AUTHENTICITY

This is to certify that this project dissertation is the original work of Dr Alfred mokomba, Reg no. H117/27759/2019, a fellow in gynaecologic oncology, in the department of obstetrics and gynaecology, University ofNairobi.

The research was carried out in the department of obstetrics and gynaecology, Faculty of medicine, University of Nairobi.. It has not been presented in any other university for award of a degree

signature---------- Date 15/11/21

Professor Eunice Cheserem

Associate professor of obstetrics and gynaecology

University of Nairobi

TABLE OF CONTENTS.

3. LIST OF ABBREVIATIONS

BRCA----BRCA genes

EOC----Epithelial ovarian cancer

EORTEC—European ovarian research and treatment centre

CDK—cytokine dependent kinase

CK7—cytokeratin 7

GOG-gynaecology oncology group

HOXA9—HOMEOBOX 9

HRSC—high risk serous carcinoma

IARC—Interagency research for cancer

IDS—interval debulking surgery

LRSC—low risk serous carcinoma

NACT—neoadjuvant chemotherapy

OS—overall survival

PDS—primary debulking surgery

PFS—progression free survival

PDS---Primary debulking surgery

NACT—neoadjuvant chemotherapy

KNH—Kenyatta national hospital

KRAS—KRAS proto-oncogene GTPase

PARP-Poly (ADP-ribose) polypase

SEER-surveillance, epidemiology and end results survey

WHO—world health organization

4. TABLES AND FIGURES

1. .Conceptual framework table
2. FIGO staging for cancer ovary
1. Table of variables
2. Timelines table
3. Budget table
3. 4.sociodemographic table
4. age table
5. history of cancer
6. clinical presentation dummy table
7. tumor markers and imaging
8. histology and grade
9. neoadjuvant chemotherapy
10. outcome table
11. 2 year survival
12. 5 year survival

EXPLANATION OF TERMS

1. Adjuvant chemotherapy---the chemotherapy given after surgery

2. Neoadjuvant chemotherapy---chemotherapy given before surgery

3. Primary cytoreduction –the first surgery done for surgical staging and cytoreduction

5.interval cytoreduction--- surgery done after 3 cycles of chemotherapy

6. second look surgery—surgery done after adjuvant chemotherapy to survey for any remnant of tumor

ACKNOWLEDGEMENT

Special gratitude to my family, wife Eddy, children, Teresa, Faith and Emmanuel for support and understanding

Special gratitude to Prof S.B.O OJWANG, for guiding us through the training, Dr. Diana Ondieki, Dr Kireki for their guidance in the research project

The chair and faculty members department of Obstetrics and Gynaecology for the enabling environment, advice and guidance

The pioneer group of gynaeoncology fellowship for the teamwork and advice throughout.

ABSTRACT

BACKGROUND

Ovarian malignancies account for 4% of malignancies but accounts for 8% of deaths from malignancies overall. Ovarian cancer accounts for 4 % of cancer in women, but accounts for more deaths because it is diagnosed at late stages. In most cases it is diagnosed when the disease is at advanced stage III -IV FIGO stage.. The WHO estimates about 222500 cases of ovarian cancer annually and 140200 deaths every year from cancer of the ovary. Ovarian cancer is not a single disease , but consists of 5 subtypes of malignancies of which epithelial malignancies are the commonest. Of the epithelial malignancies serous carcinoma is the commonest at 42-47%. in our institution ovarian cancer is the second commonest gynaecological malignancy after cancer of the cervix. There are no local or regional studies on serous carcinoma of the ovary.

THE RESEARCH QUESTION

What are the clinic-pathologic characteristics, management and treatment outcomes in patients managed for serous carcinoma of the ovary cancer in KNH for the period 2012 to 2017?

BROAD OBJECTIVE;

To evaluate the clinico-pathological characteristics, management and treatment outcome of patients managed for serous carcinoma of the ovary at KNH between 2012-2017

METHODLOGY

This was a cross sectional retrospective study design. Records of eligible patients with histology of serous carcinoma of the ovary were analyzed for data extraction at the medical records and information office at the Kenyatta National hospital. The data extraction was done using a structured questionnaire. The extracted data was then fed into SPSS, 24.0 VERSION for analysis.

STUDY SITE

The medical records and information department, filing unit at the Kenyatta national hospital.

RESULTS

The median age for patients with serous carcinoma in this study was 50 years. Most had no family history of cancer.60 % of the patients had a parity of over 3. The commonest symptoms were abdominal pain and distension in 80% of patients reviewed. 72 % had non specific gastrointestinal symptoms like constipation ,dyspepsia and early satiety. On physical examination 70 5 of patients had an abdominal mass and 55% had ascites.

60.1 % of patients presented in advanced stages III to IV ovarian malignancy. 55% had surgery and1st line chemotherapy in a third of cases. The commonest surgeries were total abdominal hysterectomy and bilateral salpingoophorectomy and omentectomy.

At 2 years the survival rate was 74 % and at 5 years 45%., 11.7 had recurrence by two years, tumor persistence at 19 %. The survival duration for those who were deceased was about 13 months

.6 .INTRODUCTION AND LITERATURE REVIEW

INTRODUCTION

Ovarian cancer is the fifth most common cancer in females and constitutes 22% of gynaecological cancers[1]. Ovarian cancers are the cause of most deaths among the female genital tract cancers and accounts for 5 % of all causes of death among cancers in women [1].The incidence is highest in north America ,Europe and lowest in Africa and Asia. The lifetime risk of developing ovarian cancer in a woman's lifetime is estimated to be 1-2%[1]. About 85% of ovarian cancer cases occur after age of 50 years, with peak in 6 th and 7 th decades but they can occur at all ages from childhood to adulthood[2]. The WHO estimates that there are about 222500 new cases of ovarian cancer annually and 140200 deaths attributable to cancer of the ovary. In Kenya there were reported 971 cases in 2018, constituting 2 % of cancers, and 13th commonest cause of cancer. Ovarian cancer consists of 22% of all gynaecological cancers, but contributes 47% of deaths attributable to gynaecologic malignancies because of it presents in late stages of disease[3]. In the US cancer of the ovary develops in 14 out of every 1000 women above 40 years [4]Ovarian malignancies constitute the second most common gynaecological malignancy after cancer of the cervix as per the KNH hospital information registry data. A study by Prof Cheserem on the general outcome of ovarian malignancies in general found 86 % of ovarian malignancies to be the epithelial type, out of which 45.7 % were of the serous carcinoma type.

. There is no reliable screening test or examination for cancer of the ovary that has high specificity and sensitivity for use in the general population. The use of tumor markers is non specific and is value in those with at risk gene mutations or strong familial history of ovarian cancer. Ovarian tumors are classified according to the ovarian cell of origin. Those from from coelomic epithelium (epithelial tumors), germ cells (germ cell tumors), mesenchyme (sex cord stromal tumors) and metastatic tumors (krukenberg). [3.]

. Out of all ovarian tumors, Epithelial type of ovarian tumors constitute the majority constituting about 85%-90% of all ovarian tumors [3]Serous carcinomas constitute the majority of epithelial tumors . The serous tumor are graded into low grade and high grade serous carcinomas of the ovary. The low grade serous malignancies arise from ovarian coelomic lining whereas the high

grade serous malignancies arise from both coelomic epithelium and the fallopian tube endothelial lining. There is poor overall survival with serous malignancies due to late stage presentation, residue tumor after surgery for cytoreduction since its most times not possible for optimum cytoreduction. The gold standard for management is optimal primary surgery followed by appropriate chemotherapy. The patients are then put on a lifelong follow in the oncology clinics to assess disease resolution, progression or recurrence and assess for any complications for timely interventions

.

LITERATURE REVIEW

Cancer is a complex disease that arises because of genetic and epigenetic alterations that disrupt cellular proliferation, senescence and death [5].This mutations causes loss of DNA repair mechanisms. that are essential in genetic editing to minimize errors during cell division. 10 % of ovarian cancers arise in women who carry germ line mutations in cancer susceptibility genes BRCA1 and BRCA 2[5].The vast majority of ovarian cancers are sporadic and arise because of acquired genetic damage[5].Acquired genetic alteration occurs when there is cellular proliferation and oxidative stress with free radical formation and inflammation that occurs during ovulation, endometriosis, or infections involving the ovary.[6] Reproductive events that decrease ovulatory cycle s are protective against ovarian cancer e.g. 5 year oral contraceptive use confers a 50%risk reduction [5].The other causes are carcinogenic substances in food and talc powder. It is thought that the repeated inflammation due to ovulation, infections or endometriosis leads to defects that result in cancer of the ovary. This is why it is thought that factors that limit ovulation like contraceptive use and pregnancy result in reduction in the risk of ovarian malignancy, whereas those that lead to more ovulation increase the risk e.g. nulliparity,early menarche and late menopause. The environmental factors that increase the risk are things like, talc, consumption of galactose, radiation, and smoking among others.

Epithelial ovarian tumors constitute most of the ovarian malignancies. Epithelial ovarian tumors are heterogenous with respect to behavior and histologic type. Low grade tumors are stable and are associated with mutations in genes K –RAS,, BRAF,PTEN and B-catenin. High

grade tumors are have genetic instability and are associated with mutations that cause inactivation of TP 53, BRCA1 and BRCA 2 and other genes in the DNA repair pathway. [7],[8]. BRCA is a group genes that encode proteins involved in repair of DNA double stranded breaks. Mutations in BRCA genes involve deletions and insertions encoding truncated protein products that are dysfunctional .[8]. BRCA are tumor suppressor genes,. BRCA gene defects account for 9 % of ovarian cancer [9].Others are associated with the other familial gene defects e .g the lynch syndrome (HNPCC) resulting from inherited mismatch repair genes (MSH2, MLH1, PMSI, PMS2)[9]

The other familial ovarian cancer include the lynch syndrome or HNPCC that involve colorectal, endometrial and ovarian cancers, inherited breast -ovarian cancer syndrome[3]. Breast and ovarian cancer syndrome involves germline mutations in BRCA 1and BRCA 2 genes which is associated with mutations in DNA mismatch repair genes [10] .

85-90 % of all ovarian cancers are epithelial ovarian cancers [3] . Among the epithelial tumors, serous carcinomas are the most common constituting 42% of epithelial cancers. [4]. The distribution of epithelial tumors is as follows;-

1. Serous ----42%
2. Mucinous ---12%
3. Endometroid---15%
4. Mesonephroid/clear cell—6 %
5. Undifferentiated –

The malignant tumors are further classified as low grade or high grade tumors [11,12] .

Low grade tumors are generally indolent or (type 1 ovarian epithelial cancers) and characterized by gene mutations in signaling pathways KRAS, BRAF, PIK3, CTNBB1, ARID1A, PPP2RIA [3]. Type 2 are more common, aggressive high grade tumors (high grade serous carcinomas), they have mutations in p53 gene and BRCA 1 AND BRCA 2 [4]

SEROUS CARCINOMA OF THE OVARY

The epithelial ovarian cancers type constitutes 85-90 % of ovarian tumors[3]. Serous carcinomas constitute 42-45 % of epithelial malignancies he serous cancers are divided into low grade and

high grade malignancies. High grade serous carcinomas of the ovary are thought to arise from the fallopian tube fimbriae and [3,4—11] .These tumors have histology that resemble tubal mucosa lining , have p53 mutations , and develop rapidly. The low grade serous carcinomas of the ovary originate from ovarian surface epithelium and mullerian inclusions .The mutations leading to the high grade types of epithelial tumors involve a multistep pathway and accounts for high grade endometrioid, clear cell and mucinous ovarian cancers [3].Serous carcinomas are characterized on histology by papillary, glandular, solid and transitional patterns. The diagnosis is confirmed by presence of psammoma bodies on the histological picture. There are glands that are slit like rather than smooth/round, with prominent cellular budding and polymorphic nuclei [13]. Serous tumors are graded as well differentiated (low grade), moderately differentiated, and poorly differentiated (both moderate and poorly differentiated are taken as high grade tumors [14]

The use of immunohistochemistry is used to make an accurate diagnosis. Low grade and high grade tumors stain for wilms tumor stain, estrogen and progesterone receptor positive. Immune histochemical stains for p16,Ki 67 and p53 are positive for high grade serous whereas low grade stains fo r p16 and low ki67[14,15,16,17] .

Peritoneal serous carcinomas arise from mullerian remnants in the coelomic epithelium or tubal fimbriae.[18] High grade serous carcinoma spreads by direct extension to the adjacent organs within the peritoneal cavity or through the detachment of cells from the primary tumor (. The tumor spreads through the peritoneal cavity, peritoneal fluid. The cells then implant and seed on distant organs with cancer cells which develop into secondary tumors[11]. The cells have predilection for the omentum, this is due to cellular metabolic requirement for fatty acid catabolism. The tumor only affects the surface of affected organs not the lumen [28]. Haematogenous route of spread is not common.

Patients in late stage develop malignant ascites, this happens due to blockage of lymphatic drainage or secretion of vasoactive and angiogenic factors which will promote vascular permeability [28]

Undifferentiated carcinoma denotes the presence of undifferentiated carcinoma. The tumors have discohesive, monotonous cells resembling lymphoma.[19]

Clear cell type comprises about 10 % of epithelial carcinomas. They are rarely bilateral [21] . It doesn't respond well to chemotherapy and has a bad prognosis if in advanced stage.

Mucinous tumors presents with a big unilateral mass, but when metastatic from elsewhere presents as multidodular ovaries. Metastasis can be from the appendix, colon and pancreas.[23] There are two major types mucinous borderline tumor, intestinal and endocervical .There also squamous cells clear cells and signet ring for metastasis from gut[25].Immunohistochemical stains help to distinguish the primary origin of the tumor. Primary ovarian tumors stain positive for CK7PAX8 OR DPC4 whereas gut tumors stain positive for CK20 [3,27] .Transitional cell tumors comprise 1-2 % of ovarian tumors, they are benign, borderline or malignant brenner and transitional cell tumors[26].

CLINICAL PRESENTATION, DIAGNOSIS AND SURGICAL STAGING

Most Serous carcinomas are diagnosed late at stages 3 and 4 [1]. Only 13 % of serous carcinoma of the ovary are diagnosed at stage 1 [29]. Most cases are diagnosed after they have metastasized or have grown to cause distension or ascites. The symptoms are non specific and involve the gastrointestinal system, the genitor- urinary system and. The symptoms include abdominal pain bloating, anorexia, urine frequency abnormal vaginal bleeding, and respiratory symptoms in late stages. The symptoms are significant when they present for less than a year and lasts longer than 12 days a month. The patient may have abdominal distension due to a large pelvic mass or ascites[29] .The most important sign is the presence of a pelvic mass on physical examination, with or without ascites. Pleural effusion maybe present in advanced cases.

DIAGNOSIS

The definitive diagnosis is made by histological evaluation of the ovarian tumor or a specimen. A history of the symptoms and physical examinations are done. The common laboratory investigations include tumor markers, ca 125, ca 119, CEA, Alpha fetoprotein. The imaging studies including abdominal pelvic ultrasound, CT scan MRI, and PET scan where available[23].An abdominopelvic Ultrasound is usually the first imaging to be done and suggestive

features include, a large lesion more than 5 cm,multiloculation,solid papillary projections , irregular septations and ascites [50,23]

TREATMENT OF SEROUS OVARIAN CARCINOMA

PRIMARY CYTOREDUCTION AND STAGING

The FIGO surgical Staging is done based on findings at primary cytoreductive surgery. Ovarian cancers spread by exfoliation of cells into the peritoneal cavity, lymphatic spread and rarely haematogenous spread.

Ascitic fluid is collected for cytology or in absence a saline wash of the peritoneal cavity with 50mls .-100mls is done.[46] Then a systematic exploration of intra-abdominal surface is done clockwise from the caecum ,cephalad, paracolic gutter, ascending colon, right kidney, liver and gallbladder, right hemidiapragm, and down the left gutter ,descending colon and sigmoid colon .Any suspicious lesions should be biopsied, sample diaphragm. The retroperitoneal spaces should be dissected and evaluated for pelvic lymph nodes and para -aortic node invovlement.[46]

Total abdominal hysterectomy, bilateral salpingo-oophorectomy, infracolic omentectomy and pelvic and aortic node sampling are done.[47]. A large tumor bulk contains areas that are poorly oxygenated due to poor perfusion therefore will respond poorly to chemotherapy. Large tumor cells contain a high proportion of cells that are not dividing which are resistant to chemotherapy hence the rationale for cytoreduction .[47]

The goal of primary cytoreductive surgery is therefore the removal of all primary cancer and metastasis; if not feasible resect the tumor to maximum effort. Griffiths proposed reduction of tumor to < 1cm in diameter[43]. Patients with complete resection have best prognosis (LION TRIAL)[43,44] .The bladder and colon are usually not invaded, hence resection can be avoided.

The Omentum is usually invaded to form an omental cake (an omental tumor). This may adhere to the peritoneum or anterior abdominal wall. The anterior abdominal wall the omentum is lifted cranially exposing the infracolic omentum, to the transverse colon. The mesenteric vessels are

ligated, then the omentum from the greater curvature of the stomach to the transverse colon is resected and the gastroepiploic and short gastric arteries are ligated[43.]

The disease may involve the small or large intestine and resection should be performed if it facilitates optimal cytoreduction. A phase 3 study showed no benefit of complete pelvic lymph node dissection only enlarged or visible nodes are dissected [18,19]

CHEMOTHERAPY

(a)Neoadjuvant chemotherapy

This is chemotherapy given three cycles before primary interval cytoreduction (EOTRC 1995). In EORTC -NCIC study the overall survival was similar between those who had primary cytoreductive surgery and those who had interval cytoreductive surgery after neoadjuvant chemotherapy. The survival in both groups was progression free survival of 12 months. Primary cytoreductive surgery is the standard of care, however NACT followed by interval surgery is reserved for stage 3 disease with poor performance status.[32,33,34,46]. The CHORUS and EORTIC studies showed no difference in overall survival between those who received NACT and interval cytoreduction and those who had primary cytoreduction surgery.[6] Neoadjuvant chemotherapy is mostly given to those in stage III and IV to reduce tumor size and create margins before interval cytoreduction.[32]

(B) ADJUVANT CHEMOTHERAPY

The Standard primary therapy for serous ovarian carcinoma involves the combination of maximal cytoreductive surgery and chemotherapy [2, 3,40,41.] The standard regime used for serous ovarian carcinoma is a combination of platinum compound (either cisplatin or carboplatin)and paclitaxel. [2, 48,49.] The duration of multiple agent chemotherapy is six cycles, as demonstrated in GOG 157 study[42]. The earliest agents used for treatment of ovarian cancer were alkylating agents, melphalan, cyclophosphamide and chlorambucil with poor response rates of 20%. The introduction of platinum compounds improved the response rate to 50%-80% range. In the 1990 s the introduction of paclitaxel which has increased the response rates. Other new introductions include topotecan, pegylated liposomal doxorubicin and gemcitabine (GOG182/ICON-5 clinical

trials[42]. The combination of paclitaxel and cisplatin is the standard first line chemotherapy for the treatment of ovarian carcinoma[42].

The prognostic indicators for serous carcinoma of the ovary include age, performance status of the patient, FIGO stage, Histologic grade, residual disease after cytoreduction surgery, and response to chemotherapy. Wright et al found out that delays in initiation of chemotherapy after surgery especially beyond 12 weeks increased the risk of death [35]. Tewari in GOG TRIAL 218 found that risk of death increased after 25 days post- surgery if chemotherapy has not been initiated [31]. Any further delay in chemotherapy decreased survival in order of 4.0 to 2.5years [36, 37]

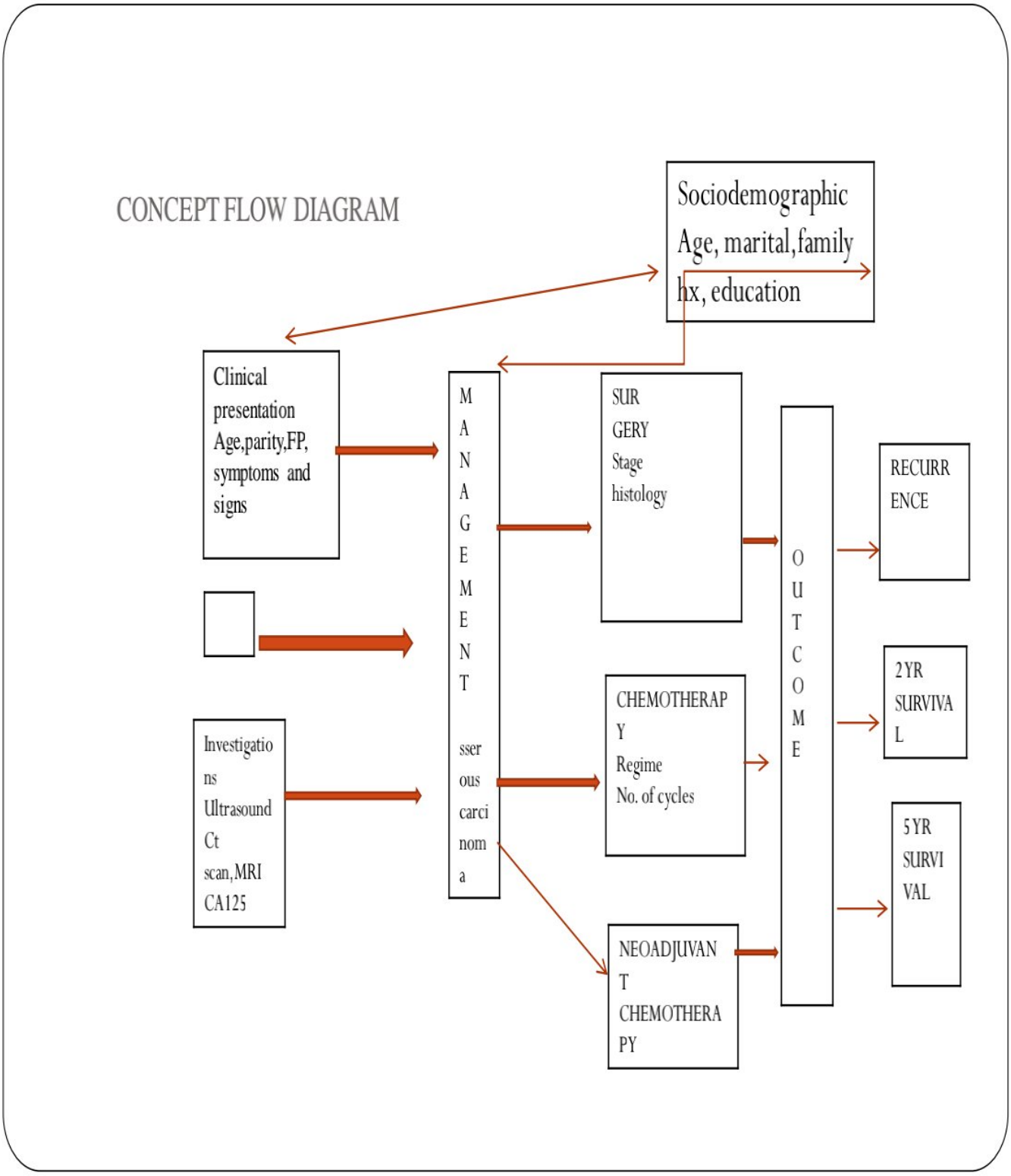
Platinum based standard chemotherapy regimens improves survival of patients with ovarian cancer but the five year survival remains at less than 50 % even with chemotherapy [38]. Bevacuzimab a monoclonal antibody targeted therapy agent delays disease progression for newly diagnosed and recurrent ovarian cancer.[38].However in gynaeoncology group 218 trial a combination of bevacuzimab a monoclonal antibody and a PARP inhibitor drug, veliparib or olaparip showed longer PFS.[40],[50]In platinum sensitive relapsed ovarian cancer pegylated liposomal doxorubicin in combination with carboplatin or as a single chemotherapy agent is used as a second line treatment .[39]

MANAGEMENT FLOW OF PATIENTS WITH CANCER OF THE OVARY AT KNH.

The standard of care at the gynaeoncology unit is for patients suspected with cancer of the ovary to have a thorough history and physical examination ,be investigated with laboratory tests, tumor markers especially the glycoprotein ca -125 ,imaging with ultrasound ,and CT scan or MRI.This is done at the gynaeoncology clinic 18. The Patients are then admitted through the gynaecological oncology clinic 18, after review of examination and investigations. The patients are then admitted to ward 1 B where planning for either surgery or chemotherapy is done during the major ward rounds and multidisciplinary discussions are done. Those selected for surgery are then prepared for primary or interval cytoreductive surgery. The patient is then next managed with chemotherapy regimens specific for the histologic type of ovarian tumor. After the recommended cycles of chemotherapy the patient is followed up in the gynaeoncology clinic for life to monitor for any sideffects, disease resistance or recurrence. The patients are seen in the

gynaeoncology clinic after every 3 months for two years for progress review, then 6 months for the next 3 years, and finally once every year for the rest of their life. During the visits history, physical examination, ca 125 levels and imaging as appropriate are done. The Files are stored in the health information department main filing section 19 of the hospital. This is where the files will be retrieved from for analysis

CONCEPTUAL FRAMEWORK



CONCEPTUAL FRAMEWORK NARRATIVE

Patients managed at Kenyatta national hospital between 2012-2017 with a diagnosis of serous carcinoma of the ovary will be identified from the hospital records information. All the data capturing their sociodemographic, gynaecological history, clinical, presentation , investigations and details of surgery will be documented. Further the adjuvant chemotherapy given including duration from surgery to initiation of chemotherapy and number of cycles will be documented. The outcome of treatment will be evaluated, ie resolution, resistance recurrence, and survival in 2 and 5 year periods will be analysed

STUDY JUSTIFICATION

The prevalence of gynaecological malignancies is rising, with high mortalities attributed to ovarian malignancies .Cancer of the ovary is the second most common gynaecological malignancy in Kenyatta national hospital. Patients with ovarian cancer present in late in advanced stages, therefore, it is important to determine the presentation and audit the treatment modalities offered at KNH. .There has not been a study done to determine the outcomes and survival for patients with serous ovarian carcinoma in KNH. Ovarian cancers are second to cancer of the cervix among gynaecological malignancies with poor survival.

The KNH records data base only records cases of ovarian cancer in general but does not separate the cases into the various histological types. As a multiple disease entity requiring different treatment approaches I seek to study serous ovarian cancers being the most prevalent subtype of ovarian cancer. There is no study on serous ovarian cancer in the institution or locally, therefore it is important to determine the characteristics, management and outcomes of this malignancy. This will form a baseline for ovarian cancer histologic specific studies.

.There is need to evaluate the survival among patients managed for serous carcinoma in KNH in order to assess areas of improvement to maximize on better management and improve on patient survival.

RESEARCH QUESTION

What are the clinico--pathologic characteristics, management and treatment outcomes in patients managed for serous carcinoma of the ovary cancer in KNH for the period 2012 to 2017?

- **BROAD OBJECTIVE**;
- To evaluate the clinico-pathological characteristics, management and outcomes of patients managed for serous carcinoma of the ovary at KNH between 2012-2017

To evaluate the clinico-pathological characteristics, management and treatment outcomes of patients managed for serous carcinoma of the ovary at Kenyatta national hospital

Between 2012-2017.

Specific objectives

Among patients managed for serous carcinoma of the ovary at Kenyatta national hospital between 2012-2017 to -:

1. Describe the clinico-pathological characteristics

2. Describe the treatment modalities.

3 Determine treatment outcomes

4. Determine the overall survival rate at 2 and 5 years

8. METHODOLOGY

i)STUDY DESIGN

The study is a retrospective cross sectional study on patients managed for serous carcinoma of the ovary at the Kenyatta national hospital.

.

ii) STUDY SITE AND SETTING

The study was done at the Kenyatta national hospital medical records and information filing unit. Kenyatta national hospital is the biggest referral and teaching hospital for the University of Nairobi and the Kenya medical training college. The hospital has a bed capacity of 2000 beds with a bed occupancy of 150% most of the time. The hospital receives referrals from the whole country and the east African region. The gynaecology oncology unit is domiciled in ward 1 B for elective procedure patients and 1D for emergency cases and those who require optimization before either surgery or chemotherapy. The gynaecology oncology Clinic is run on Fridays. Elective gynaecology oncology surgeries are done on Wednesdays and Thursdays. Daycare surgeries are done on Fridays including examination under anaesthesia, staging and biopsies.

The hospital has a radiotherapy department for those who require radiotherapy domiciled at the cancer treatment centre. There are two cobalt radiotherapy machines and one Linac radiotherapy machine.

iii) STUDY POPULATION

The patients managed for serous carcinoma of the ovary at Kenyatta national hospital for the study period 2012-2017.

INCLUSION

The patients with confirmed histology of serous carcinoma of the ovary cancer during the study period 2012-2017.

EXCLUSION

3.Patients with other histological types of ovarian cancer

2. Patients with incomplete details in their records

3. Patients lost to follow up.

STUDY LIMITATIONS

The information department only records cases of ovarian malignancy as one ovarian cancer disease in general without a break down of the various subtypes of ovarian malignancy. In addition a good number of patients drop out of the follow up programme after a while due to various challenges. The identified files had poor clerkship with most details missing like family history of cancer, contraceptive use and surgical stage on surgery

To overcome the limitations all the files marked for ovarian malignancy, then isolated those with the diagnosis of serous ovarian malignancy. This then had a detailed analysis. A phone call was made to the families of those lost to follow and a phone consent obtained to inquire about the progress and fate of their patient

iv. SAMPLE SIZE

SAMPLE SIZE CALCULATION

- To calculate a representative sample size for the study, Yamane, T (statistics will be used as given in equation below
- $n_o =$
- $Z^2 * (p) * (1-p)$
- c^2
- . Where,
- n – the required sample size, p – expected prevalence of the serious carcinoma of ovary (estimated at 42%), c 2 - confidence interval set at 5%, expressed as decimal, Z = Z value (e.g. 1.96 for 95% confidence level).
- Substituting the values into the equation above we get;-
- n = 374.3 ≈ 375 patients.
- Since in this case we have finite population (N is known), we further use the equation below to adjust the sample of the finite populations,
- This give us,
- = 237.8
- **≈ 238 patients.)**

.

v)SAMPLING PROCEDURE

The study used a two - stage multiple sampling procedure. Stage one involved the selection of files of patients with cancer of the ovary and stage two will be the sampling of files of patients with histological diagnosis of serous carcinoma of the ovary. A list of all files with cancer of the ovary will be obtained .The cases with histological diagnosis of serous carcinoma of the ovary will be selected for further evaluation. Only cases for the study period will be included in the study. Since the sample size and the definite number are close, all eligible files will be analyzed, considering missing files and files with incomplete data.

DATA COLLECTION

Data collection was done by well trained research assistants using a coded research questionnaire. The research assistants were resident doctors in obstetrics and gynaecology department. There was a dry run training on the collection tool before data collection is started. Patient files with a diagnosis of cancer of the ovary were be retrieved from medical information department data base , then files with histological diagnosis of serious carcinoma will be selected for analysis. Every file was selected for analysis of sociodemographic characteristics , clinical presentations features, investigations done, surgical staging at initial surgery and the histological diagnosis. Chemotherapy regimens used after surgery were obtained. The patients follow up status at 2 years and 5 year survival was be assessed. In particular whether the patient is alive or dead, disease resolution, recurrence or persistence as per the information on visits captured in the gynaeoncology clinic. For the patients who have dropped out of the follow up visits, a phone call was made and a phone consult was obtained. Those who consent to the phone call were be asked for information on patient's current status. For those who are deceased the date of demise was ascertained.

v).DATA ANALYSIS

The data was entered into a structured access database and later entered into Statistical Package for Social Sciences (SPSS) version 24.0 for analysis. Frequency listing was done to describe categorical variables while mean and standard deviation will be used to analyse continuous variables e.g age. 2 and 5 year survival will be generated using Kaplan Meir method.

VI). QUALITY ASSURANCE

Research assistants were trained on the data collection tool and taken through a dry run by the principal investigator. The research assistants were resident doctors in the obstetrics and gynaecology masters programme. There was be a dry run on use of the data collection tool before the actual data collection is initiated.

The list of patient files with a diagnosis of cancer of ovary were identified, and then those with histology of serous carcinoma will be selected for analysis.

The data collected was cleaned by the principal investigator to correct any errors before being used for data analysis

vii) DATA VARIABLES TABLES

SPECIFIC OBJECTIVES	INDEPENDENT VARIABLES	DEPENDENT VARIABLES
1.CLINICOPATHOLOGICALCHARACETERISTICS	1. SOCIODEMOGRAPHIC	Age,marital status,education level, employment status,history of cancer in family Contraceptive use
	2CLINICAL PRESENTATION	Abdominal pain Abdominal distension Per vaginal bleeding, constipation , hyperacidity
	3.INVESTIGATIONS DONE	Tumor markers –ca 125, Abdominal ultrasound CT scan, MRI
2.Management modalities	PRIMARY SURGERY	surgical stage1,2,3,4, complete cytoreduction, incomplete surgery

	HISTOLOGY	Histology Grade
	CHEMOTHERAPY	Adjuvant chemotherapy Neoadjuvant chemotherapy 2 nd line chemotherapy No.of cycles
3.outcomes	OUTCOMES	Remission Recurrence Persistent disease
4.survival	SURVIVAL	2 year-alive 2yr dead 5 yr alive 5 year dead

ETHICAL CONSIDERATIONS

Approval for the study was sought and obtained from the KNH /University of Nairobi ethics and research committee ref no.----------. Data collection was be done after research and ethics committee approval. The approval of KNH department of obstetrics and gynaecology was be obtained before data collection can be started. All data collected was treated with confidentiality. The data collection tool did not have names or any patient identifier. A study number was used instead. Only the investigator and statistician will had access to the data collected.

The results obtained will be shared with the Kenyatta national hospital and the University of Nairobi to help improve planning and care of patients with serous carcinoma of the ovary. The findings will be published in a peer reviewed journal.

x) STUDY LIMITATIONS

The filing system is manual making it tedious to collect data. All cases of ovarian malignancy were lumped into one diagnosis of ovarian cancer in general without breakdown into specific

histological types. Records for 2013 were lost in server crush. The data is only filed with broad disease classification as cancer of ovary in general without break down into the subtypes

To minimize these limitations involved a dry run training of research assistants. Further phone calls will be made to families of patients who have been lost to follow up to inquire on their progress to enable filling in incomplete information.

RESULTS PRESENTATION

A total of 180 files with a histological diagnosis of serous carcinoma of the ovary were abstracted for analysis

Socio-demographics.

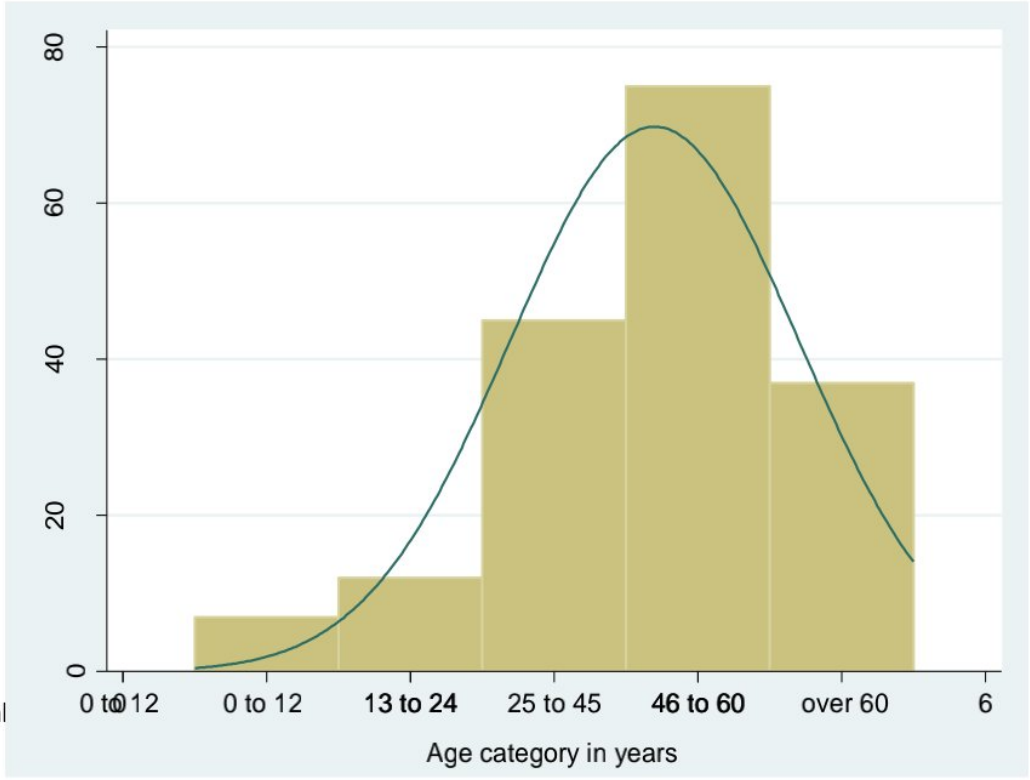
The median age of diagnosis was 50 years though it ranged from as low as 5 years to 98 years, with a majority above 45 years. Majority of the patients were married and over three quarters had at least some primary education. The history of cancer in the family was poorly documented in the files (44% missing) and where available, a majority reported no cancer

TABLE 2

Age category	Freq.	Percent %	Cum.
5 to 12 years	7	4	
13 to 24 years	12	7	
25 to 45 years	45	26	
45 to 60 years	75	43	
Over 60 years	37	21	

Total	**176**	100

TABLE 2



. See tal

Table 3: Description of the social, demographic and clinical characteristics

CHARACTERISTIC	VALUE	FREQUENCY
Age in years median (range)	Diagnosis (n=176)	50 (5-98)
	Menarche (n=36)	14.5 (12-20)
	Menopause (n=32)	47 (41-65)
Marital status	Married	89 (49.4)
	Separated	5 (2.8)
	Single	46 (25.6)
	Widowed	32 (17.8)
	Missing	8 (4.4)
Education level	None	15 (8.3)
	Primary	74 (41.1)
	Secondary	44 (24.4)
	Tertiary	16 (8.9)
	Missing	31 (17.2)
Employment status	Formal employed	14 (7.8)

	Self-employed	61 (33.9)
	Unemployed	77 (42.8)
	Missing	28 (15.6)
Family history of cancer	Yes	12 (6.7)
	No	88 (48.9)
	Missing	80 (44.4)
Parity	Missing value	14 (7.8)
	None	24 (13.3)
	1 to 2	40 (22.2)
	3 to 4	53 (29.4)
	More than 4	49 (27.2)
History of contraceptives use	Yes	54 (30.0)
	No	68 (37.8)
	Missing values	58 (32.2)

Clinical presentation.

Abdominal pain and abdominal distension were the commonest symptoms reported in over 80% of the patients, with less than ten percent having a vaginal bleeding; few had estrogenic or androgenic features. Others were nonspecific clinical presentations as shown in table 2 below.

Table 4: Clinical presentations

Characteristic	**Value**	**Freq. (%)**
Abdominal pain	Yes	161 (89.4)
	No	15 (8.3)
	Missing	4 (2.3)
Abdominal distension	Yes	168 (93.3)
	No	8 (4.4)
	Missing	4 (2.3)
Vaginal bleeding	Yes	13 (7.1)
	No	163 (90.6)
	Missing	4 (2.3)
Estrogenic features	No	175 (97.2)
	Yes	1 (0.6)
	Missing	4 (2.2)
Androgenic features	No	175 (97.2)
	Missing	5 (2.8)
Other general signs	Weight loss	18 (14.2)
	Loss of appetite	16 (12.6)
	Early satiety	11 (8.7)
	Lower limb swelling	10 (7.9)
	Others*	72 (56.7)

*bloating, vomiting, constipation etc

On physical examination, the women were very likely to have a pelvic and abdominal mass in over 70% of the cases and ascites (55% of the cases).

TABLE 5

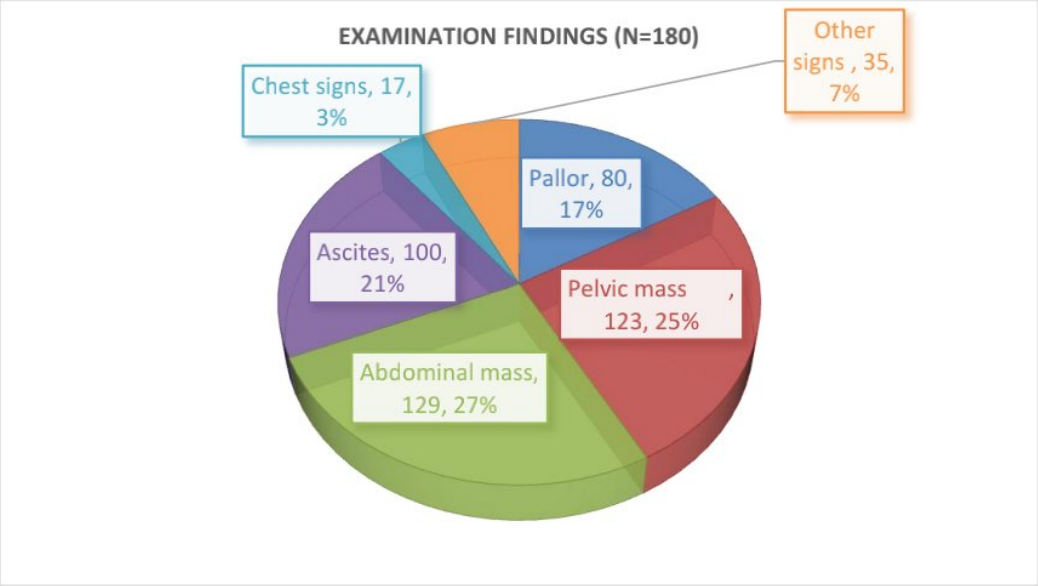


Figure 1 Physical examination

[#] Wasting, dehydration, jaundice etc

USE OF TUMOR MARKERS

The tumor marker CA- 125 was done in 70% of the cases, with less than 20% having had investigations for AFP, CEA and CA 19-9 markers investigated. Only 2 cases had estradiol marker assessed as shown in table 3 below.

Table 6: Laboratory investigations

Characteristic	Value	Freq. (%)
CA125	Yes	132 (73.3)
	No	20 (11.1)
	missing	28 (15.6)
AFP	Yes	18 (10.0)
	No	133 (73.9)

	Missing	29 (16.1)
CEA	Yes	28 (15.6)
	No	123 (68.3)
	Missing	29 (16.1)
Estradiol	Yes	2 (1.1)
	No	147 (81.7)
	Missing	31 (17.2)
CA 19-9	Yes	21 (11.7)
	No	130 (72.2)
	Missing	29 (16.1)
Other lab investigations	Yes[$]	30 (16.7)

[$] Bhcg, ldh, HIV etc, **inhibin**

USE OF IMAGING IN CANCER OVARY

CT scan was the commonest imaging modality done in over 65 % of the cases , AN ABDOMINAL or pelvic ultrasound was done in almost half of the cases .Less than 15% having an MRI scan done as part of the imaging diagnostics as shown in figure 2 below. Interestingly, a chest x-ray was done in only a third of the cases. The others category includes Echo, ECG, Colonoscopy, PET, Endoscopy etc. A PET scan was only done for one of the cases.

TABLE 7

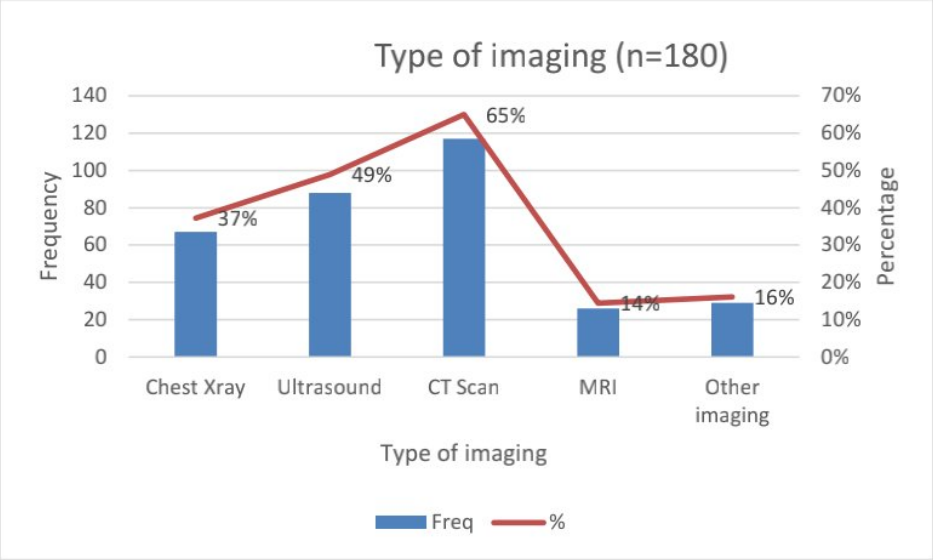


Figure 2 Type of investigation – imaging

SURGICAL STAGING

Data on disease stage was missing in a quarter of the cases. Where staging was done majority of the patients presented in advanced stages 3 and above.

Table 8: SURGICAL STAGE

Surgical Stage	Freq (%)
Missing	42 (23.3)
1A	13 (7.2)
1B	3 (1.7)
1C	9 (5.0)
2B	4 (2.2)
3A	3 (1.7)
3B	15 (8.3)
3C	38 (21.1)
4A	14 (7.8)
4B	39 (21.7)

In 60.5% of the patients had a diagnosis at stage 3 and above. This is an advanced stage disease.

Table 9: Management

Most of the patients had Surgery and chemotherapy in their management in 55% of cases. Chemotherapy alone as the mode of management was provided in over a third of the patients.

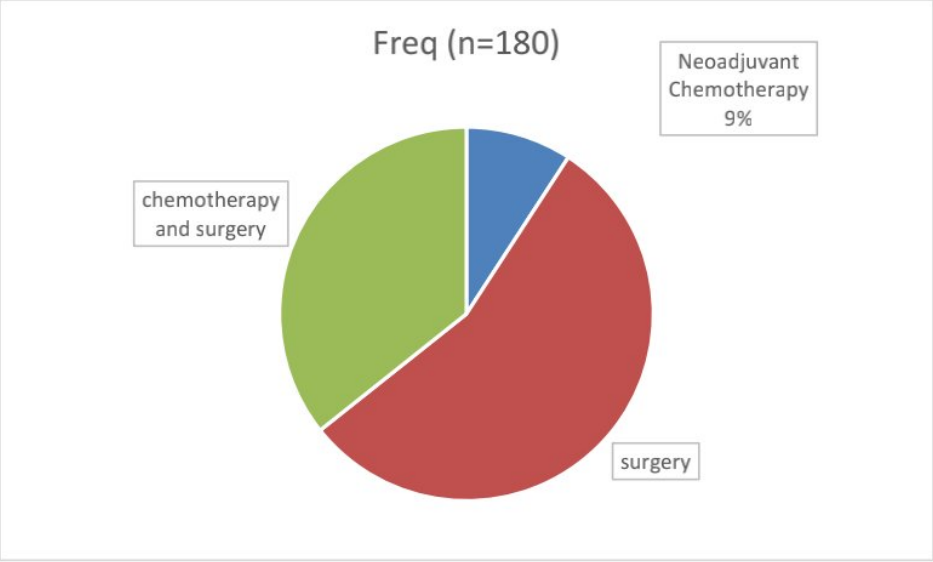


Figure 3 Type of management

PRIMARY CYTOREDUCTIVE SURGERY

27% of the patients who had surgery had total abdominal hysterectomy and salpingoophorectomy, 24% had Total abdominal hysterectomy and omentectomy,16% had oophorectomy alone, whereas 14 % had inoperable disease with laparatomy and biopsy done. Bilateral salpingoophorectomy is considered

suboptimal surgery which is a poor prognostic indicator. It is not indicated in all the files what size of residual tumor was left behind or whether the surgery was optimal or suboptimal. Optimal surgery being when visible tumor left is less than 1 cm.

TABLE 10

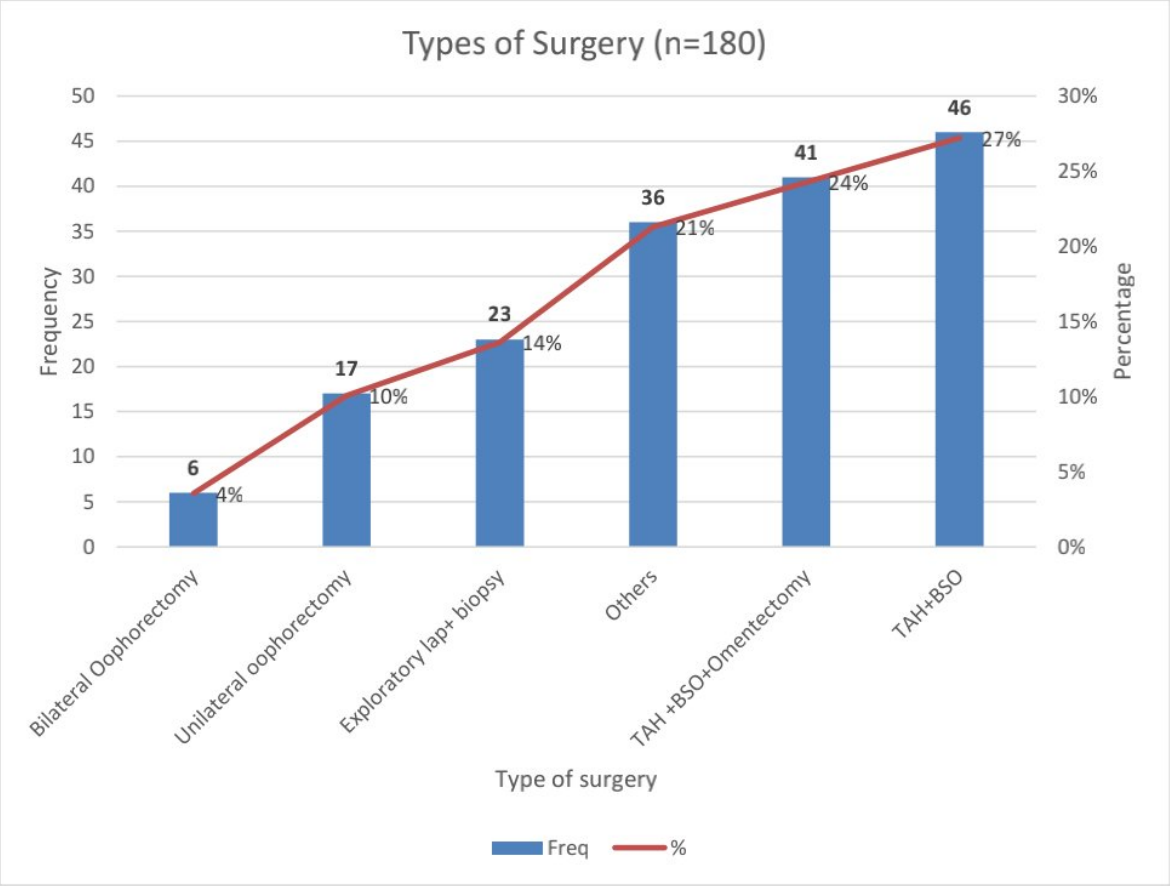


Figure 4 Type of surgery done

14% of patients had inoperable tumors and were only able to have a biopsy done after exploratory laparatomy.

Table 11: Interval between surgery and start of chemotherapy

Interval between surgery and start of chemotherapy	Description	Freq. (%)
	4-6 weeks	18 (10.0)
	6-8 weeks	25 (13.9)
	<4weeks	8 (4.4)
	>8 weeks	26 (15.6)
	Missing	101 (56.1)
Histopathology results	Present	170(94.0)
	Missing values	10 (5.6)
Tumor Grade	Grade 1	7 (3.9)
	Grade 2	21 (11.7)
	Grade 3	30 (16.7)
	Missing	122 (67.8)
First line chemotherapy	Yes	107 (59.4%)
	No	73 (43.4%)
Second line chemotherapy	Yes	13 (7,2)
	No	167 (92.8)
Other chemotherapy	Yes	9 (5.0)

In terms of disease grade 67.8 % of patients had no histological grade indicated in their results. Among those where grading was indicated 16.7% were grade 3, 11.7% grade 2 and grade 1 3.9%.

The interval between surgery to chemotherapy was missing in 56.1%, due largely to missing data or lost old files .15% had an interval of over 8 weeks from surgery to chemotherapy. , 13.9 % between 6-8 weeks.

59.4 of the patients had 1st line chemotherapy (cisplatin and paclitaxel), a large number 43% did not have any chemotherapy and it wasn't indicated form the record whether surgery was deemed optimum or they dropped out of treatment. Only 13% of the patients received second line chemotherapy .

Table 8: Survival rates at 2 and 5 years

	Description	Freq (%)
Two-year survival	Deceased	47 (26.1)
	Recurrence	21 (11.7)
	Resistance	2 (1.1)
	Resolution	20 (11.1)
	Tumor persistence	26 (14.4)
	Missing values	64 (35.6)
Five-year survival	Deceased	19 (45.1)
	Recurrence	2 (4.8)
	Resolution	13 (31.0)
	Tumor persistence	8 (19.1)

Table 9: Survival rate from treatment initiation to recurrence

Time from treatment to recurrence n=16	**Duration in months**	**Freq. (%)**
	0-6	3 (18.8)
	6-12	6 (37.5)
	12-24	4 (25.0)
	>24	3 (18.8)
Time from treatment to death- 2 years n=43	0-6	24 (55.8)
	6-12	13 (30.2)
	12-24	6 (14.0)
Time from treatment to recurrence - 5 years n=1	72	1 (100)
Time from treatment to death- 5 years (n=17)	0-12	3 (17.6)
	12-24	4 (23.5)
	24-36	6 (35.3)
	Over 36	4 (23.5)

Mortality was more likely within the first two months when bilateral oophorectomy alone was done. When more extensive surgery was done the duration of survival was longer.

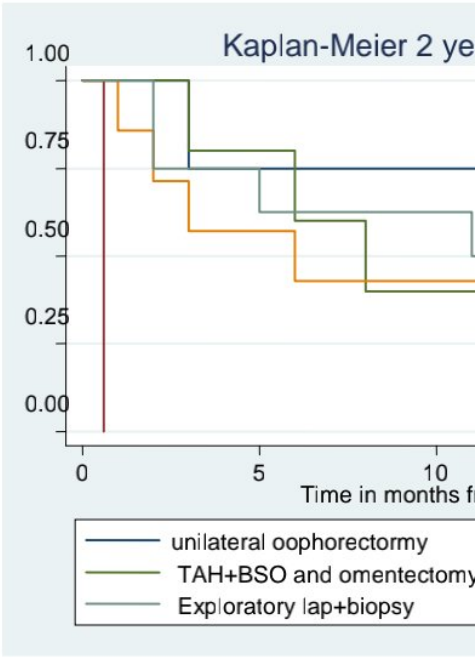


Figure 5 Survival at two-year post surgery

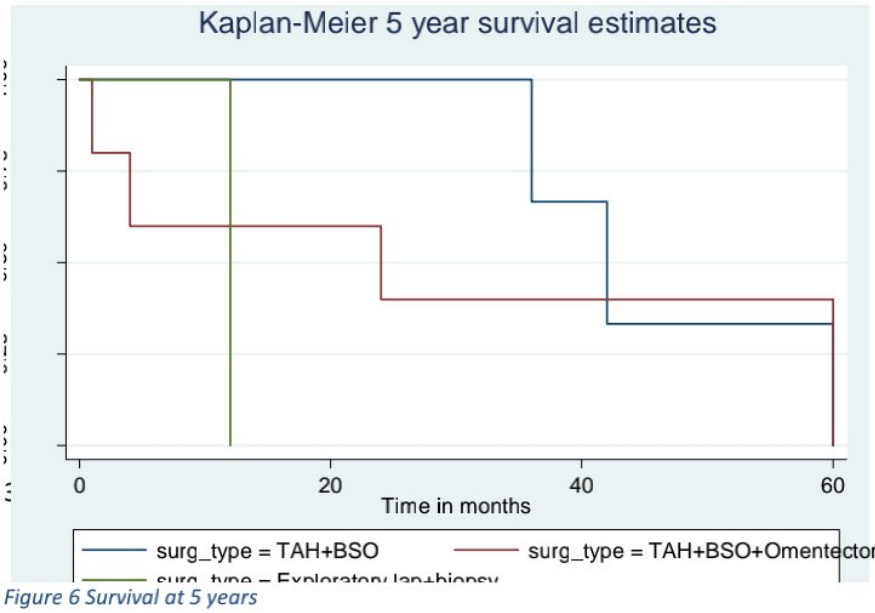
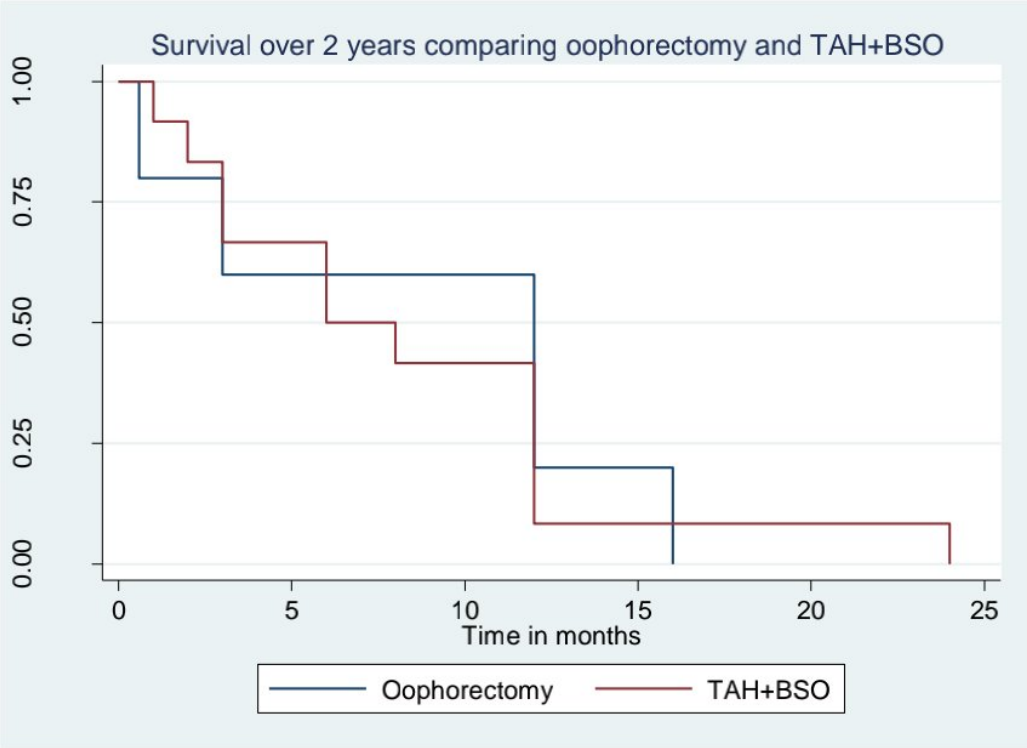


Figure 6 Survival at 5 years

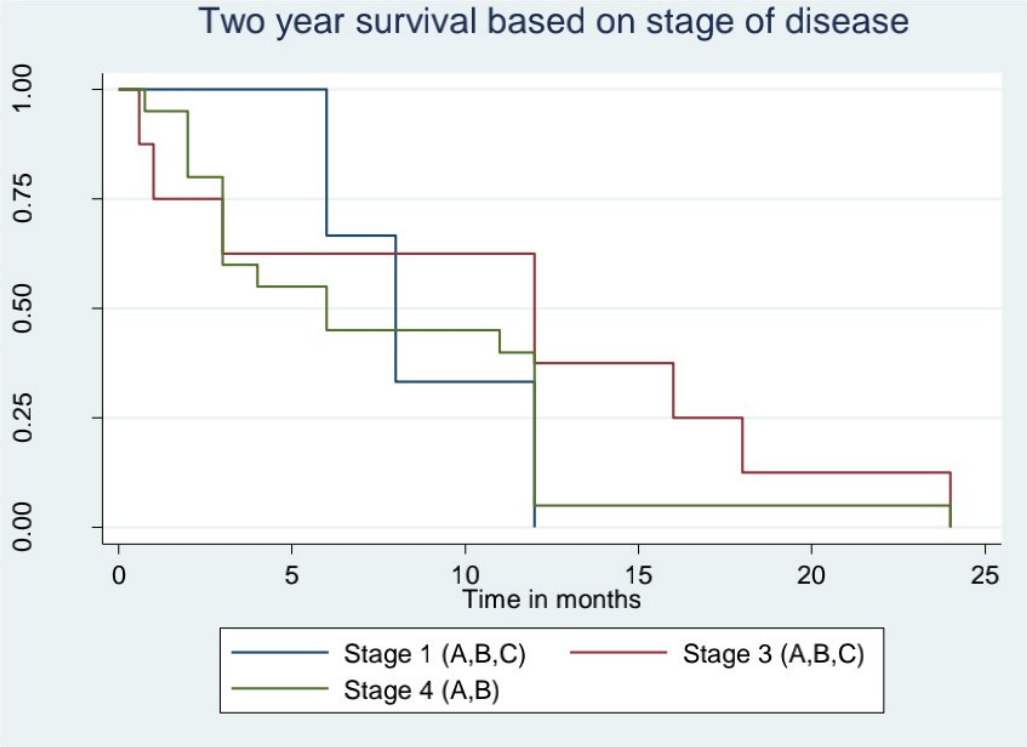
Assessment of the five-year survival shows that when TAH and BSO and

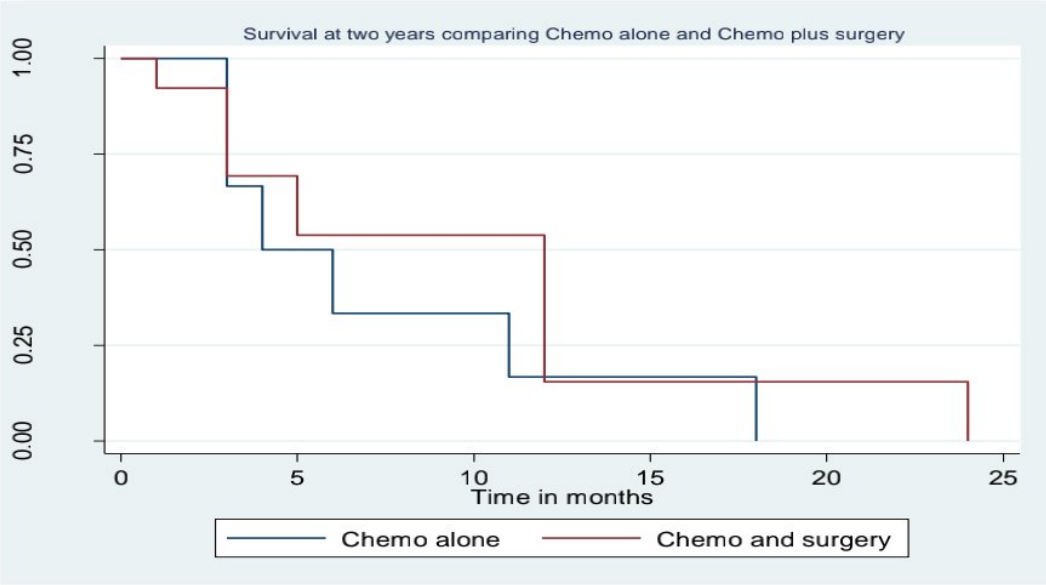
omentectomy was done , the survival is longer when compared to when TAH and bilateral salpingoophorectomy alone was done(could be due to more extensive disease) was conducted as shown in figure 6 below. Patients with more extensive surgery have longer survival

. When Exploratory laparatomy and biopsy was done mortality was delayed as shown in figure 6 below.



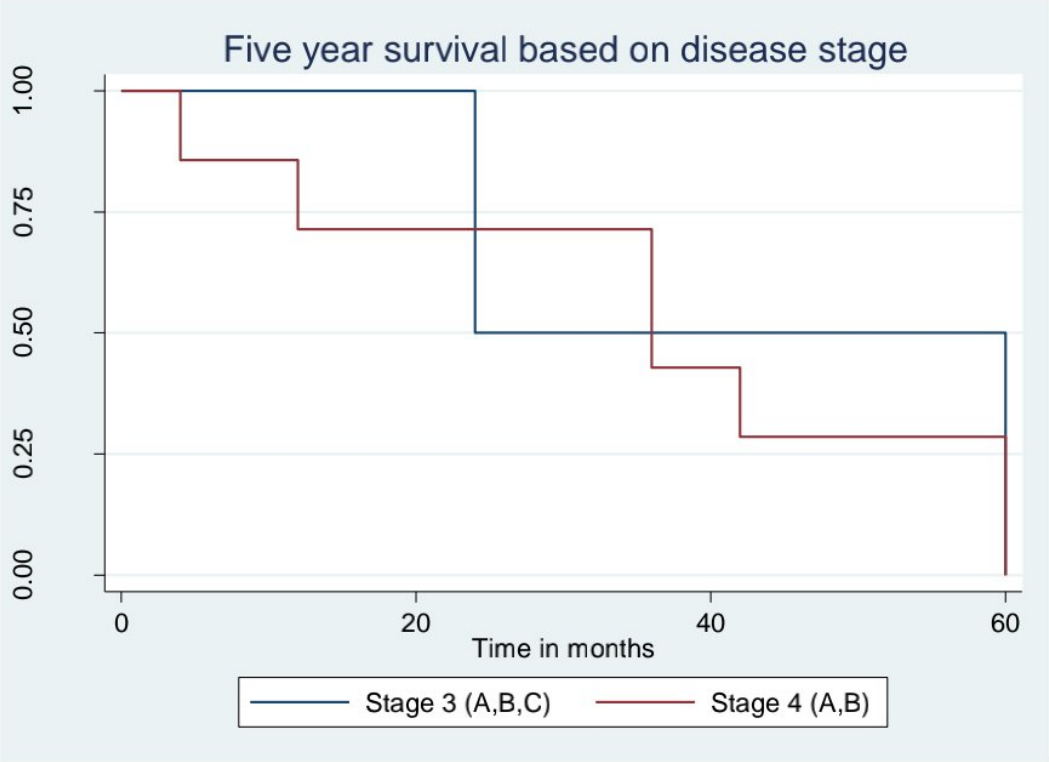
Those who had total abdominal hysterectomy survived longer than those whom had oophorectomy alone. The numbers were too small to make an objective conclusion as to survival between the two groups





Those who had surgery followed by chemotherapy survived longer

X^2 value =1.22; P=0.27 (there is no evidence of a difference in survival for those who were managed with chemotherapy alone compared to those who had surgery plus chemotherapy)



X^2 Value for the log rank test=**0.12 P=0.729** (There is no evidence for a difference in the survival based on the disease stage). 29 patients were censored due to demise or do not qualify for five year assessment

DISCUSSION

The median age for patients with serous carcinoma ovary w as 50 years , with a range from 17 to 98 years., showing a wide distribution in all age groups. This is almost similar to armanda et al in 2013[63] who found a median age of 56.5 years at Anderson cancer centre., Eken et al[66] found age distribution from 19-79 years with a mean of 52 years. Gancroro ep et al[53] found a median age of 58 years with peak incidence in 51-60yrs

CLINICAL PRESENTATION.

The commonest symptoms were abdominal pain, abdominal distension and gastrointestinal symptoms like early satiety, bloating , constipation and vomiting. gancoro ep et al [53]found GIT symptoms in 86.9 % of patients with ca ovary, , Amer Sindian , Basil et al [68] found pain and

abdominal distension to be the commonest symptoms. and 69 % of patients presented in stage III and above in a descriptive study of patie4nts with epithelial ovarian cancer.

On physical examination over 70 % of patients had a pelvic abdominal mass, and ascites. The symptomatology presents in the late stages, only 13% are diagnosed early and over 75% diagnosed late, Michael antony, andy et al( ) intern. molecular sciences journal 2019 feb 2019.

TUMOR MARKERS

The commonest tumor marker done was CA 125 , a glycoprotein, in 70 % of cases

STAGING FOR SEROUS CANCER OF THE OVARY

60.5 % of the patients were diagnosed at advanced stages 3 and 4, this in keeping with what has been found before

cheserem et al 2011[66] found most of the ovarian cancers present in stages 3 and 4, ganchoro ep,[53] Erewel in the African journal of sciences 2006)( )found 73.6 % of the patients presented in late stages 3 and 4., Amanda et al 2013, found 87.3 0f patients presented in stages 3 and above disease. There is no reliable screening tool for cancer of the ovary hence the late stage of presentation, By the time a patient is symptomatic her disease will be found in the later stages in 75-80 % of cases. The symptoms are non specific , hence little likelihood of early diagnosis. Amer sindian et al [67] found 69 % of patients presented in stage 3 and above. sherin in us study had 75% of patients presenting late

SURGERY

55% of the patients had primary cytoreductive surgery. 27% had total abdominal hysterectomy and bilateral salpingoophorectomy (TAH AND BSO), 24 % had additional omentectomy in addition to TAH and BSO.14% had oophorectomy and 14 % had laparatomy and biopsy due to inoperable tumor.

primary cytoreduction to remove all macrospically visible tumor , and optimally to leave a visible tumor not more than 1 cm., to be considered a successful surgery, the level of cytoreduction is the most important prognostic factor (kurmanRJ [24] classification of female ovarian tumors4 th edition WHO 2014), chang sj.44 .Annals of surgical oncology 2012 19’49-impact of complete cytoreduction).grossly visible disease was associated with poor prognosis among 203 patients . I did not find data on volume of residual tumor in our setup recorded in the files.

Due to the advanced stages of disease at presentation at knh and elsewhere only maximum effort surgery can be done,

CHEMOTHERAPY

Only 14.4 % of the patients had neoadjuvant chemotherapy. neoadjuvant chemotherapy has the same outcomes like those who get primary cytoreductive surgery then adjuvant chemotherapy but improves chances of more complete surgery. Studies have shown that use of neoadjuvant chemotherapy has benefits for late stage disease

Lauren p Cobb, Charlotte, [34])gynaecol oncol 2020 sept), Xia Xia[56] , g zhage( ) gynaecol bstet j. 2018, showed similar survival between those who receive neoadjuavnt treatment then interval cytoreduction and those who received primary cytoreduction and adjuvant chemothetherapy.

Almost all patients with serous carcinoma of the ovary require adjuvant chemotherapy the interval between surgery and chemotherapy was not indicated in56% of patients,for the data available the interval was approximately 8 weeks and more.

The recommended interval is 25-30 days in order to prevent tumor regrowth and doubling

ref)59.7% of our patients received first line chemotherapy which is cisplatin and paclitaxel . a small percentage 13% received second line chemotherapy. Cisplatin and paclitaxel; combination improves progress free survival as overall survival than other combinations (107), given as three weekly doses112). the benefits have been shown in studies by McGuire W.P, Hoskins …cylophosphamide and cisplatin compared with cisplatin combined with pacitaxelin stage III and IV ovarian cancer lancet 2002;360-505

survival

Most of the data on patient status at two and five years was not available from the files. Phone call inquiries with oral consent were only successful in a few clients in 30% of clients called.

Where the data was available , the survival for our patients at 2 years was at 73 % with 26 % . At five years the survival was 55% .Tthis is similar to what has been found in other studies byYang feng et al, [60]front med 2014) survival at 3 years was at 67% Sherrit stewart 2017[65], in a study showed survival rates in the US of 39% at five years compared with this study .. the survival for early stage disease in the us study the survival was 86.4%

CONCLUSIONS

The patients presented in mid age at a median of 50 years.

The most common clinical signs and symptoms were abdominal pain , abdominal distension, and GIT symptoms. on physical examination the commonest signs were abdominal mass, distension, pallor and presence of ascites.

Most patients present in advanced disease stage III and IV

The patients had surgery and chemotherapy, with a survival of 74 % at 2 years and 45 5 at 5 years

STUDY STRENGTHS

This study was able to review cases of serous carcinoma of ovary and establish a baseline for further studies into ovarian malignancies.

All cases of serous carcinoma ovary were analysed hence no bias

STUDY WEAKNESS

Since it is a retrospective study there were details that were missing in the patient records that cannot be recovered. There was a significant number of missing files and many files without histological diagnosis. There was a large number of patients lost to follow and could not be reached even on phone calls.

RECOMMENDATIONS

1. Create a template for clerkships and physical examination to capture all information
2. Create a software database for cancer of the ovary for ease of information access
3. There is need for institutional guidelines in management of serous carcinoma and ovarian cancer as a whole

4. Create a follow up structure to minimize loss to follow up and linkages to home base care and palliative care centres

5.Utilize the use of neoadjuvant chemotherapy given its benefits in advanced stage disease before interval cytoreductive surgery.

APPENDICES

APPENDIX1

REFERENCES

1. National Cancer Institute; Surveillance, Epidemiology, and End Results [SEER] Program. SEER stat fact sheets: ovary cancer. http://seer.cancer.gov/statfacts/html/ovary.html.

2. Amos CI, Shaw GL, Tucker MA, et al: Age at onset for familial Epithelial ovarian cancer, JAMA 268:1896, 1992.

3. Gilks CB, Prat J. Ovarian carcinoma pathology and genetics: recent advances. Hum Pathology. 2009; 40:1213-23.

4. . Kurman R.J., Carcangiu M.L., Herrington C.S., Young R.H. WHO Classification of Tumors of Female Reproductive Organs. 4th ed. WHO; Geneva, Switzerland: 2014.

5. Prat J, Ribe A, Gallardo A. Hereditary ovarian cancer. Hum Pathology. 2005;36:861-70.

6. 134. Timmerman D, Bourne TH, Tailor A, et al. A comparison of methods for preoperative discrimination between malignant and benign adnexal masses: The development of a new logistic regression model. Am J Obstetric and Gynecology. 1999;181(1):57–65.

7. Bojesen SE, Pooley KA, Johnatty SE, et al. Multiple independent variants at the TERT locus are associated with telomere length and risks of breast and ovarian cancer. Nat Genet. 2013; 45(4):371–384,

8. Kurman RJ, Shih IM. Molecular pathogenesis and extraovarian origin of epithelial ovarian cancer--shifting the paradigm. Hum Pathology. 2011;42(7):918–931.

9 Song H, Ramus SJ, Tyre J, et al. A genome-wide association
Study identifies a new ovarian cancer susceptibility locus on 9p22.2.
Nat Genet. 2009;41(9):996–1000. .

10. Rubin SC, Benjamin I, Behbakht K, Takahashi H, Morgan MA, LiVolsi VA, et al. Clinical and pathological features of ovarian cancer in women with germ-line mutations of BRCA1. N Engl Journal of Medicine. 1996; 335(19):1413–1416.

11. . Malpica A, Deavers MT, Lu K, et al. Grading ovarian serous carcinoma using a two-tier system. Am Journal of Surg Pathol. 2004; 28:496-504.

12. Malpica A, Deavers MT, Lu K, et al. Grading ovarian serous carcinoma using a two-tier system. Am Journal Surg Pathol. 2004;28:496-504.

13. . O'Neill CJ, McBride HA, Connolly LE, et al. High-grade ovarian serous carcinoma exhibits significantly higher p16 expression than low-grade serous carcinoma and serous borderline tumour. Histopathology. 2007; 50:773-9.

14. . Malpica A, Deavers MT, Lu K, et al. Grading ovarian serous carcinoma using a two-tier system. Am J Surg Pathol. 2004; 28:496-504.

15.. Hirschowitz L, Ganesan R, McCluggage WG. WT1, p53 and hormone receptor expression in uterine serous carcinoma. Histopathology. 2009;55:478-82.

16. Phillips V, Kelly P, McCluggage WG. Increased p16 expression in high-grade serous and undifferentiated carcinoma compared with other morphologic types of ovarian carcinoma. Int J Gynecology PatholOGY. 2009;28:179-86.

17. Vang R, gown AM, Farinola M, et al. P16 expression in primary ovarian mucinous and endometrioid tumors and metastatic adenocarcinomas in the ovary: utility for identification of metastatic HPV-related endocervical adenocarcinomas. Am Journ Surg Pathol. 2007;31:653-63.

18. Jacobs I, Menon U. The sine qua non of discovering novel biomarkers
for early detection of ovarian cancer: Carefully selected preclinical
samples. Cancer Prev Res (Phila). 2011;4(3):299–302.

19. Chiesa-Vottero AG, Malpica A, Deavers MT, et al. Immunohistochemical overexpression of p16 and p53 in uterine serous carcinoma and ovarian high-grade serous carcinoma. Int Journal Gynecol Pathol. 2007;26:328-33.

20.. Yemelyanova A, Ji H, Shih IeM, et al. Utility of p16 expression for distinction of uterine serous carcinomas from endometrial endometrioid and endocervical adenocarcinomas: immunohistochemical analysis of 201 cases. Am J Surg Pathol.

21.Soslow RA. Histologic subtypes of ovarian carcinoma: an overview. Int J Gynecol Pathol. 2008;27:161-74009;33:1504-14.

22.Kato N, Toukairin M, Asanuma I, Motoyama T. Immunocytochemistry for hepatocyte nuclear factor-1beta (HNF-1beta): a marker for ovarian clear cell carcinoma. Diagn Cytopathol. 2007;35:193-7

23. 8. Matulonis U.A., Sood A.K., Fallowfield L., Howitt B.E., Sehouli J., Karlan B.Y. Ovarian cancer. Nat. Rev. Dis. Primers. 2016;2:16061.

24. **.** Kurman RJ, Carcangiu ML, Herrington CS, Young RH, editors. WHO classification of tumours of female reproductive organs. Vol 6, ed 4. Geneva, Switzerland: International Agency for Research on Cancer; 2014. **.**

25. Taylor J, McCluggage WG. Ovarian seromucinous carcinoma: report of a series of a newly categorized and uncommon neoplasm. Am J Surg Pathol. 2015;39:983-92.

26. Ali RH, Seidman JD, Luk M, et al. Transitional cell carcinoma of the ovary is related to high-grade serous carcinoma and is distinct from malignant Brenner tumor. Int J Gynecol Pathol. 2012;31:499-506.

27.**.** Gurzu S, Szentirmay Z, Toth E, et al. Serrated pathway adenocarcinomas: molecular and immunohistochemical insights into their recognition. PLoS One. 2013;8:e57699.

28.Lengyel E. Ovarian cancer development and metastasis. Am. J. Pathol. 2010;177:1053–1064. doi: 10.2353/ajpath.2010.100105.

29. Narod S. Can advanced-stage ovarian cancer be cured? National Review Clinical Oncology. 2016;13:255–261.

30. Vasey PA, Herrstedt J, Jelic S ESMO Guidelines Task Force. esmo Minimum Clinical Recommendations for diagnosis, treatment and follow-up of epithelial ovarian carcinoma. Ann Oncol. 2005;16(suppl 1):i13–15.

31. Salzberg M, Thurlimann B, Bonnefois H, et al. Current concepts of treatment strategies in advanced or recurrent ovarian cancer. Oncology. 2005;68:293–8.

32. Vergote I, Trope CG, Amant F, Kristensen GB, Ehlen T, Johnson N, et al. Neoadjuvant chemotherapy or primary surgery in stage IIIC or IV ovarian cancer. New England Journal of Medicine. 2010;363: 943–953.

33. Kehoe S, Hook J, Nankivell M, Jayson GC, Kitchener H, Lopes T, et al. Primary chemotherapy versus primary surgery for newly diagnosed advanced ovarian cancer (CHORUS): an open-label, randomised, controlled, non-inferiority trial. Lancet. 2015;386: 249–257.

34.Fagotti A, Ferrandina G, Vizzielli G, Fanfani F, Gallotta V, Chiantera V, et al. Phase III

randomised clinical trial comparing primary surgery versus neoadjuvant chemotherapy in advanced epithelial ovarian cancer with high tumour load (SCORPION trial): Final analysis of peri-operative outcome. European Journal of Cancer. 2016;59: 22–33.

- 35 .Wright JD, Herzog TJ, Neugut AI, Burke WM, Lu YS, Lewin SN, et al. Effect of rdical cytoreductive surgery on omission and delay of chemotherapy for advanced-stage ovarian cancer. Obstetricand Gynecol journal. 2012;120(4):871–81.

36. Tewari KS, Java JJ, Eskander RN, Monk BJ, Burger RA. Early initiation of chemotherapy following complete resection of advanced ovarian cancer associated with improved survival: NRG Oncology/Gynecologic Oncology Group study. Ann Oncol. 2016;27(1):114–21. Expub 2015/10/22.

37.. Joseph N, Clark RM, Dizon DS, Lee MS, Goodman A, Boruta D Jr., et al. Delay in chemotherapy administration impacts survival in elderly patients with epithelial ovarian cancer. Gynecologic oncology. 2015;137(3):401–5.

38. Zhou M, Yu P, Qu X, Liu Y, Zhang J (2013) Phase III Trials of Standard Chemotherapy with or without Bevacizumab for Ovarian Cancer: A Meta-Analysis. PLoS ONE 8(12):

39. Pegylated liposomal doxorubicin for relapsed epithelial ovarian cancer
cochrane systematic review - intervention version published: 09 july 2013

40. Nieman K.M., Kenny H.A., Penicka C.V., Ladanyi A., Buell-Gutbrod R., Zillhardt M.R., Romero I.L., Carey M.S., Mills G.B., Hotamisligil G.S., et al. Adipocytes promote ovarian cancer metastasis and provide energy for rapid tumor growth. Nat. Med. 2011;17:1498–1503

41. Markman M. Optimizing primary chemotherapy in ovarian cancer. Hematol. Oncol. Clin. N. Am. 2003; 17:957–968.

42. McGuire W.P., Hoskins W.J., Brady M.F., Kucera P.R., Partridge E.E., Look K.Y., Clarke-Pearson D.L., Davidson M. Cyclophosphamide and cisplatin compared with paclitaxel and cisplatin in patients with stage III and stage IV ovarian cancer. N. Engl. Journ. Med. 1996; 334:1–6.

- 43Scully R.E. Sobin L.H.Serov S.F.Histological Typing of Ovarian Tumours**.**Springer, Berlin,Heidelberg, New York1999

43. Alleti GD, Dowdys et al. quality of improvement oin surgical approach to advanced ovarian cancert , the MAYO experience. American college of surgeon 2009;208, 608-620

44.Chan JK, Tian C, et al. The potential benefits of 6 cycles of chemotherapy in subsets of women with early stage high risk epithelial ovarian cancer an exploratory GOG STUDYgynaecological oncology 2010, 116: 301-306

46. I.Tropé C.G. Amant F.et al. Neoadjuvant chemotherapy or primary surgery in stage IIIC or IV ovarian cancer. N Engl J Med. 2010; 363: 943-953

- *47.* Du Bois A., Reuss A., Pujade-Lauraine E,et al. Role of surgical outcome as prognostic factor in advanced epithelial ovarian cancer: a combined exploratory analysis of 3 prospectively randomized phase 3 multicenter trials: Cance*r.* 2009; 115: 1234-1244

48.Swart A.C.,on behalf of ICON Collaborators . Long-term follow-up of women enrolled in a randomized trial of adjuvant chemotherapy for early stage ovarian cancer (ICON1)**.**J Clin Oncol (Meeting Abstracts). 2007; **25** (Abstr 5509)

49.Chan J.K.,Tian C.,Fleming G.F.et al. The potential benefit of 6 vs. 3 cycles of chemotherapy in subsets of women with early-stage high-risk epithelial ovarian cancer: an exploratory analysis of a Gynecologic Oncology Group study**.** Gynecol Oncology. 2010; **116**: 301-306

50.Lerner J.P. ,Timor-Tritsch I.E. ,Federman A. , Abramovich G. Transvaginal ultrasonographic characterization of ovarian masses with an improved, weighted scoring system.Am Journ. Obstet *Gynecol.* 1994; 170: 81-85

.51. Narod S. Can advanced-stage ovarian cancer be cured? National Review Clinical Oncology. 2016;13:255–261.

52.JAHD Sehemn MD, JAEOH, P, Grawoski MD, , surgery in recurrent ovarian cancer, American cancer journal2019

53.Ganchroro EP, EIREWEL O. Presentation of cancer of ovary, African journal of medical sciences 01 june 2006 35(2) 143-147

54Geishhahm,david M, Sun Charlote .. obstetrics and gynaecology , august 2006, volume 108-issue 2 –page 361-368.

56.Xia xie, gzhage . platinum based neoadjuvant chemotherapy, gynaecol, obstetric journal 2108(2018;83(3) 209-219.

57., Thunia AL RAHAB, Aberto D, Lopes et al, Cochrane database system review 2013 feb28:2013(2),

58.Webb Pm—Epidemiology of epithelial ovarian cancer , best practices, clinical obstetric gynaecol; 2107, 41;3-14.

59. Yuchuno hatamo, kayoko hatamo et al. A comprehensive review of ovarian serous cancer . Advanced anatomical pathology 2019 september 20(5); 329----331

60.Yung Feng F, Xinyu, wang: frontmedical journal 2014(1)91-95

61. Bristow RE, Tomacruz RS, Armstrong DK, Trimble EL, Montz F. Survival effect of maximal cytoreductive surgery for advanced ovarian carcinoma during the platinum era: a meta-analysis. *J Clin Oncol.* 2002;20(5):1248–59

62. Van Altena AM, Karim-Kos HE, de Vries E, Kruitwagen RF, Massuger LF, Kiemeney LA. Trends in therapy and survival of advanced stage epithelial ovarian cancer patients in the Netherlands. *Gynecol Oncol.* 2012;125(3):649–54. doi: 10.1016/j.ygyno.2012.02.033

63.Amer sindiani,basil et al; adescriptive study of clinicopathological and surgical characteristics of patients with primary epithelial ovarian cancer

64.Amanda nickels ,james java; survival in women with serous carcinoma of the ovary, journal of obstetric gynaecol 2020 jan 46(1) ;153-160.

65.Cheserem, Ann Beatrice kihara, Rkosgei—ovarian cancer in knh2011, characteristics and management; Open journal of obstetrics and gynaecology 2013.165—171 february 2013.

66.Eken Okoye, Elizabeth D , clinicopathological characteristics in pateients with serous ovarian cancer, American journal of surgical patholopgy 2016, may,40(5)67-75

67.Lauren p cobs, Charlotte p; interval cytoreductive surgery after neoadjuvant chemotherapy.; gynaecology oncology journal 2020 sept 158(3);63-658

68 Amer SINDIANI, Basil obeidet. a descriptive study of clinicopathological and surgical characteristics of patients with primary epithelial ovarian cancer, a cross sectional study. gynaecol oncology, 2019 sept, 417(4) , 70--83

APPENDIX 2

Table 2

.Staging of ovarian cancer

Stage	Description
Ia	Disease confined to one ovary with no capsular involvement. Peritoneal washings/cytology negative.
Ib	Disease confined to both ovaries with no capsular involvement. Peritoneal washings/cytology negative.
Ic	Disease confined to the ovary/ovaries but ovarian capsulae involved or cyst rupture
IIa	Extension to uterus or fallopian tubes
IIb	Extension to other pelvic tissues
IIc	As for IIa or IIb but one or both ovaries have ruptured capsule or surface tumor; malignant ascites or positive peritoneal washings
IIIa	Histologically confirmed microscopic seeding of abdominal peritoneal surfaces and negative retroperitoneal lymph nodes

IIIb Histologically confirmed implants of abdominal peritoneal surfaces less than 2 cm and negative retroperitoneal lymph nodes

IIIc Histologically confirmed implants of abdominal peritoneal surfaces greater than 2 cm or positive retroperitoneal lymph nodes

IV Distant metastases (including liver parenchyma/positive pleural fluid cytology)

APPENDIX3 TABLES

1 DATA ANALYSIS DUMMY TABLES 4

1.SOCIODEMOGRAPHIC DATA

a)AGE

VARIABLE	n (%),	
A.AGE- i)<20---- ii)20-30 iii)31-40 iv)41-50 v)51-60 vi)>60		

b)MARITAL STATUS

Variable single	%	
married		
Widowed		

c)education

variable nil	%	
primary		
secondary		
tertiary		

d)family history of cancer

variable yes	%	
no		

2.obstetrics and gynaecology

a) parity

Variable	n (%)	
O		
1-2		
3-4		
>5		

c) contraceptive use

Variable	n (%)	
Yes		
No		

3.CLINICAL PRESENTATION

a)

Variable	n (%)	%
i)abdominal pain	yes	no
ii)abdominal distension	yes	no
iii)vaginal bleeding	yes	no
iv) v) others--	yes	no

4.)physical signs(presentation)

variable	N%	N%	
pallor	Yes-	no	
Pelvic mass	yes	no	
Abdominal mass	yes	no	
ascites	yes	no	
Chest signs	yes	no	

5..INVESTIGATIONS

a)TUMOR MARKERS

variable	n (%)	
i)Ca125		
ii)Alpha fetoprotein		
iii)Ca 19-9		
iv) others		

b) imaging done.

variable	n (%)	
i)ultrasound		
ii)CT SCAN		
iii)MRI		
iv) chest xray PET SCAN--		

6NEOADJUVANT CHEMOTHERAPY

VARIABLE	n (%)	
YES		
NO		

7.SURGICAL STAGING

Variable	n (%)	
i)1a		
ii)1b		
iii)1c		
iv)2a		
v)2b		
vi)2c		
vii)3a		
Viii)3b		
ix)3c		
x)4a xi)4b		

8.ASCITIC FLUID CYTOLOGY

VARIABLE	%	%
YES		
NO		

a) HISTOLOGY

VARIABLE	n (%)	
i)serous		
ii)mucinous		
iii)endometrioid		
iv) clear cell		
v)granulosa		
vi) yolk sac		
vii) others(SPECIFY)		

b) Tumor grade

variable	n (%)	
i) well differentiated(grade 1		
ii) moderate differentiation(grade 2)		
iii) poorly differentiated(grade 3)		

TREATMENT MODALITIES

SURGERY		
CHEMOTHERAPY		
RADIOTHERAPY PALLIATIVE CARE		

TYPE OF SURGERY DONE

VARIABLE	N %	N%
Unilateral oophorectomy		
Bilateral oophorectomy		
TAHand BSO		
TAH,BSO, OMENTECTOMY		
Exploratory laparatomy and biopsy others		

7 CHEMOTHERAPY

13.DURATION FROM SURGERY TO CHEMOTHERAPY

DUARTION	%	
<4 weeks		
4-6 weeks		
6-8 weeks Over 8 weeks		

14

Chemo therapy regimens	n (%)	
i) cisplatin/carboplatin		
ii)paclitaxel		
iii)cyclosphamide		
Iv)second line		

Number of cycles a)4 b)6 c)9		

9..STATUS AFTER CHEMOTHERAPY(treatment)

Tumor markers monitoring

CA125		
Ca19-9		
afp		
cea		
others		

16.. 2 YEAR SURVIVAL

Variable	n (%)	Time from diagnosis
a)resolution		
b) persistence		
c)resistance d)recurrence deceased		

17. .5 YEAR SURVIVAL

Variable	n (%)	Time from diagnosis
a)resolution		
b)persistence		
c)resistance		
d) recurrence e)deceased		

APPENDIX5. **CANCER OF THE OVARY / SEROUS CARCINOMA DATA ABSTRACTION FORM**

Study No:_____

1. SOCIAL DEMOGRAPHIC DATA

Patient Age at diagnosis in

Years_____

Marital status: a) Single [ ] b) Married [ ] c) Seperated [ ] d) Widowed[ ]

Education : a) Nil [ ] b) Primary [ ] c) Secondary [ ] d) Tertiary[ ]

Employment status: a) Not employed [ ] b) Self Employed [ ] c) Formal Employed [ ]

2. OBSTETRICS AND GYNAECOLOGY HISTORY

(i)Parity : a) 0 [ ] b) 1- 2 [ ] c) 3 - 4 [ ] d) >4 [ ]

(II)Contraceptive use

Yes [ ] No [ ] If yes specify:_____

(iii)Age at Menarche:_____ Age at Menopause:_____

3. CLINICAL PRESENTATION

a) Abdominal pain Yes [ ] No [ ]

b) Abdominal distension Yes [ ] No [ ]

c) Vaginal bleeding Yes [ ] No [ ]

d) Estrogenic features Yes [ ] No [ ] If Yes Specify_____

e) Androgenic features Yes [ ] No [ ] If Yes Specify_____f) Others: [ ]

Specify_____

4. PHYSICAL EXAMINATION

Pallor Yes [ ] No [ ]

Pelvic mass Yes [ ] No [ ]

Abdominal mass Yes [ ] No [ ]

Ascites Yes [ ] No [ ]

Chest signs Yes [ ] No [ ] Specify_____

Others: [ ]

Specify_____ **5.**

INVESTIGATION

5Laboratory

a) CA125 Yes [ ] No [ ] Lab value_____

d) Inhibin Yes [ ] No [ ] Lab value_____
c) AFP Yes [ ] No [ ] Lab value_____
d) CEA Yes [ ] No [ ] Lab value_____
e) Estradiol Yes [ ] No [ ] Lab value_____
b) CA19-9 Yes [ ] No [ ] Lab value_____
f) Others: [ ] Specify_____

Imaging
a) Chest X-ray Yes [ ] No [ ]Specify abnormality_____
b) Ultrasound Yes [ ] No [ ]Specify abnormality_____
b) CT scan Yes [ ] No [ ]Specify abnormality_____ c) MRI Yes [ ] No [ ]Specify abnormality_____
d) PET Yes [ ] No [ ]Specify abnormality_____
e) Others: [ ] Specify_____

6. NEOADJUVANT CHEMOTHERAPY
Yes [ ] No [ ] If Yes indication_____

7. SURGICAL STAGE

1A [ ] 1B [ ] 1C [ ]
2A [ ] 2B [ ] 2C [ ]
3A [ ] 3B [ ] 3C [ ]
4A [ ] 4B [ ]

8. ASCITIC FLUID FOR CYTOLOGY
Taken [ ] Not taken [ ] If taken Positive [ ] Negative [ ] Not stated [ ]

9. TREATMENT GIVEN
Surgery [ ] Chemotherapy [ ] Chemoradiation [ ]Radiation [ ] Palliative Care [ ]

10. TYPE OF SURGERY PERFORMED

a) Unilateral Oophorectomy [ ]

b)Bilateral Oophorectomy [ ]

c)TAH + BSO [ ]

d)TAH + BSO + Omentectomy [ ]

e) Exploratory lap + biopsy [ ]

11. HISTOPATHOLOGY RESULTS

Present [ ] Not Present[ ] Histological diagnosis_____

12. TUMOR GRADE

a) Grade 1[ ] b) Grade 2[ ] c) Grade 3[ ]

13. CHEMOTHERAPY REGIMES

b) First line chemotherapy [ ]

Specify_____

c) Second line chemotherapy [ ]Specify_____

d) Others [ ]Specify_____

e) Number of cycles_____

14. STATUS AFTER TREATMENT

YEAR SURVIVAL

a) Resolution[ ] b) Persistence [ ]

c) Recurrence [ ] if recurrent time from treatment to recurrence _____

d) Deceased [ ] if diseased time from treatment to death _____

FIVE YEAR SURVIVAL

a) Resolution[ ] b) Persistence [ ]

c) Recurrence [ ] if recurrent time from treatment to recurrence _____

d) Deceased [ ] if diseased time from treatment to death _____ –
Others, Specify _____

CONSENT FOR PHONE CALLS FOR FINDING THE SURVIVAL STATUS OF PATIENTS LOST TO FOLLOW UP

I Dr. Alfred mokomba , Am conducting a study on serous carcinoma of the ovary on patients managed at Kenyatta national hospital ,2012—2017. This involves finding the patient status at 2 and 5 years. I am calling to find out the status of patient----------progress since the last clinic visit.

Answering the questions is voluntary and you may decline if you don't find it comfortable. Your answers will not affect your follow up management in any way and where necessary we will continue with full care whenever you come to the hospital.

Your participation will help us to improve on care for [patients with a similar condition. You may call this number for any clarification on any issues that may not be clear about our questions, 0733946609.

Thank you for your participation through a phone call.

University of Nairobi
A world-class university committed to scholarly excellence

H117/27759/2019 ALFRED MOGAKA DR MOKOMBA (Regular/Integrated)

Your SIM card is ready for collection at **TELKOM KENYA(NAIROBI - T-MALL)** .
Kindly arrange to collect it at your convenient time.

ID/PP No.	Type : New (First Time)	Make Request				
Previous Requests						
	Request Date	**Status**	**Receipt No.**	**Validity**	**Remarks**	
1.	13-NOV-2021	PENDING			ID Card Available for Printing.	1.

Procedure for getting the new generation Student ID Card

1. Ensure that your fees (including that of Student ID) is paid and receipted before making the ID card request.
2. Fees for Re-Issue of lost ID card must be paid and receipted separately.
3. Place your request for the Student ID through the Student Portal.
4. Request for renewal of expired ID card should be made **NOT MORE THAN ONE MONTH BEFORE EXPIRY OF THE CURRENT ONE** .
5. Ensure that your photo has been taken and uploaded into the System.The University Photographer is located at JKML Library.
6. Allow at least two working days for the processing of your ID card.
7. Keep checking the status of your ID request through the Student Portal.
8. Collect your printed Student ID from your Faculty / School / Institute Office once the STATUS of your request is reflected as PRINTED.

Note:

1. Validity for Re-Issued ID Card will be the same as that of previously Issued (Lost) ID.
2. Validity for Replacement / ID Re-New will start after expiry of current Issued ID.

GOVERNMENT-SPONSORED (MODULE I) STUDENTS PAYMENT INSTRUCTIONS

1. Bank Account
=> Cash Deposits,EFT or RTGS transfer to UON MODULE I Collection Account No. 2032770838 at ABSA Bank, Plaza Branch
2. M-Pesa Pay Bill
=> The Business Number is 503003
=> The Account Number is your "Student Registration Number"

SELF-SPONSORED PROGRAMMES (MODULE II) PAYMENT INSTRUCTIONS / OPTIONS

1. Bank Account
=> Cash Deposits, EFT or RTGS transfer to UON MODULE II Collection Account No. **2032771362** at ABSA Bank, Plaza Branch
=> Cash Deposits, EFT or RTGS transfer to UON US$ Dollar Account No. **2032770625** at ABSA Bank, Plaza Branch
2. M-Pesa Pay Bill
=> The Business Number is **300059**
=> The Account Number is your **"Student Registration Number"** (or **"Admission Ref Number"** for new student)
NOTE: CASH, AGENCY BANKING AND ATM DEPOSITS ARE NOT ALLOWED