The pattern and management of ovarian cancer at Muhimbili National Hospital, Dar Es Salaam, Tanzania

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THE PATTERN AND MANAGEMENT OF OVARIAN CANCERS AT MUHIMBILI NATIONAL HOSPITAL, DAR ES SALAAM, TANZANIA

By

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Dissertation Submitted in (Partial) Fulfilment of the Requirement for Degree of Master of Medicine (Obstetrics and Gyneacology) of

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CERTIFICATION

The undersigned certifies that he has read and hear by recommends for acceptance by the Muhimbili University of Health and Allied Sciences, a dissertation entitled: “The Pattern and Management of ovarian cancer at the Muhimbili National hospital, Dar Es Salaam, Tanzania” in partial fulfillment of the requirements for the degree of Master of Medicine (Obstetrics and Gynecology) of the Muhimbili University of Health and Allied Sciences.

Professor SirielMassawe

Date

DECLARATION AND COPYRIGHT

I, **Wilmot L. Smith,** declare that this dissertation is my own original work and that it has not been presented and will not be presented to any other University for a similar or any other degree award.

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DEDICATION

I dedicate this work to my family and parents for all of their tireless support during my period of study.

ABSTRACT

Ovarian cancer is one of the most common gynecological malignancies of the female reproductive tract and has a very poor prognosis. Globally the five year survival is only 15 to 20 percent in patient with clinically advanced disease. The sign and symptoms are often vague, and as such many patients present with the disease when they are already in late stages. When diagnosed early, survival is far better. The treatment is optimal debugging which is followed by chemotherapy depending on the extent of spread of the cancer. At Muhimbili National Hospital, majority of ovarian cancer patients are presenting with advanced stage disease and many of the women delay to commence chemotherapy after surgery.

Objective: the aim of this study was to determine the pattern of ovarian cancer patients admitted at MNH and their management.

Methodology: This was a retrospective descriptive study of ovarian cancer cases over a five years period (2012-2016) admitted and treated at Muhimbili National Hospital, the largest tertiary referral hospital in Dar es Salaam. The source of data was patients' files, medical records retrieved from the Central Pathology Laboratory, admission books, operating theatres, and the gynecology ward round book.

Data was collected using a standardized checklist for all cases with confirmed histology and information was obtained from the case file which included socio-demographic profile, parity, histological type of cancer, clinical presentation, treatment options and outcome. Thereafter, the case records were followed up at the Ocean Road Cancer Institute, where these patients are referred for chemotherapy after cytoreduction at Muhimbili National Hospital. Other patient information such as the onset and type of chemotherapy that was given and the outcome were obtained at the Ocean Road Cancer Institute. The data was entered into Statistical Package for Social Sciences SPSS ver. 23, and presented by frequency tables, proportions and absolute counts.

Results:

Of the total number of 3,401 gynecological cancers admission, ovarian cancers constituted 8.03% of all gynecological cancers admitted and treated at the MNH. Epithelial ovarian cancer constituted 83.1%, while germ cell and sex cord stromal accounted for 4.7% and 3.5%

respectively. Serous epithelial cancers accounted for 43.6%, while mucinous epithelium cancer accounted for 21.5%. About Eighty-five percent of patient presented with advanced stages of the disease, with median age of 50 years. Nulliparous women accounted for 22.1% of the cases. The number of women receiving chemotherapy after cytoreduction was 40.9%, and the average number of days from cytoreduction to chemotherapy was 45.1 days (SD 24.8). About Seventeen percent of women were discharged stable after treatment and 33.6% of patients were counsel for palliative care while 18.1% of the women succumb during treatment at both MNH and ORCI.

Conclusion

Majority of women presented to hospital with advanced stage epithelial ovarian cancer. The main stay of treatment was surgery and chemotherapy, and majority of women delayed in starting chemotherapy after surgery.

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LIST OF ABREVIATIONS

ACS	American Cancer Society
BOC	Breast, ovarian and colorectal cancer
BOTs	Borderline Ovarian Tumors
BRCA	Breast Cancer
CA125	Cancer Antigen 125
CPL	Central Pathology Laboratory
EOC	Epithelial Ovarian Cancer
FIGO	International Federation of Gynecology and Obstetrics
KNH	Kenyatta National Hospital
MNH	Muhimbili National Hospital
NCCS	National Cancer Control Strategy of Tanzania
ORCI	Ocean Road Cancer Institute
TAH &BSO	Total abdominal hysterectomy and bilateral salpingo-oophorectomy
TVS	Transvaginal ultrasound

OPERATIONAL DEFINITIONS

Complete file is a case file with note regarding treatment modality and outcome.

Early stage ovarian canceris stage 1 and stage 2.

Five year survival rateis the percentage of people with a given cancer who are alive 5 years or longer after diagnosis.

Incomplete file is a case file without note regarding treatment modality and outcome.

Late stage of ovarian cancer is stage 3 and stage 4.

Modality of treatment is the method of treatment of ovarian cancer; that is, surgical only, surgical followed by chemotherapy, chemotherapy only, or palliative.

Optimal debulking is surgical removal of tumor with remnant less than 2cm.

Pattern of ovarian cancer is defined as the histological subtype, proportion, stage, demographic profile and treatment modality of ovarian cancer.

1.0INTRODUCTION

1.1 Background

Ovarian cancer is the second most common gynecological malignancy and the most common cause of death from gynecological malignancy in the United States.Though it is less common, ovarian cancer causes more deaths than any other cancer of the female reproductive system(1). A total of 224,747 new cases of ovarian cancer were reported in 2008 throughout the world, with 99,521 cases being diagnosed in more developed regions, and 125,226 being diagnosed in less developed regions. This cancer was the seventh most common cancer diagnosed among women in the world overall, and fifth most common cancer diagnosed among women in more developed regions(2). The cancer tends to be more common in elderly women as compare to younger women. In less developed countries, ovarian cancer rates are relatively lower, and this may be due in part to the lack of quality data from these countries(3). It is the third commonest cause of cancer death from gynecologic tumors at the Kenyatta National Hospital (KNH)(4), while in a teaching hospital in Nigeria, it is the second common gynecological malignancy and a major cause of death from female gynecological cancers(5).

Ovarian carcinogenesis is not well understood and there are several postulated mechanisms as regards to its pathogenesis. One of these is the "incessant ovulation theory" whereby repeated damage and trauma to the ovarian epithelium is postulated during each ovulatory cycle. As a result, there is an increased potential for genetic mutation and ovarian neoplasm during the process of repair. There is a 6% increase in risk of the cancer with each full ovulation year(6)**.** Factors linked to an increase in ovarian cancer risk include: increasing age, obesity after menopause, family history of ovarian cancer, family history of breast or colorectal cancer, genetic mutations, BRCA1 and BRCA2, and breast cancer(7,8). Whereas, factors linked to lowering the risk include: pregnancy, breastfeeding, birth control pills, salpingo-oophorectomy andhysterectomy(7,9–13)Even though symptoms are vague, the most common ones are abdominal distension or bloating, pelvic or abdominal pain, early satiety, urinary frequency, tiredness, upset stomach, back pain, dyspareunia, constipation, and menstrual changes(14,15).

About 95% of the cancer is derived from epithelial cell tumor and the rest aregerm cell tumors and sex cord stromal tumor.They are classified into three main histologic groups: epithelial tumors, sex cord-stromal tumors, and germ cell tumors(3). Epithelial ovarian cancers appeared

in the following serotype: serous, mucinous, endometrioid, and clear cell adenocarcinomas. Otherless common subtypes are transitional, squamous, mixed, and undifferentiated subtypes(16,17). The cancer is also classified by histo-pathological grades(one to three)(15). Germ cell tumors include teratoma, dysgerminoma, yolksac tumor, embryonal carcinoma, polyembryoma, nongestationalchoriocarcinoma and mixed germ tumor. Sex cords stromal tumors include thegranulosa-stromal cell tumors, sertoli-stromal cell tumors, sertoli-leydig tumor, thecoma and fibroma(18).Ovarian cancers share many similarities to the rare malignancies,primary peritoneal cancer (PPC) and primary fallopian tube cancer (PFTC). These three cancers are clinically managed in a similar manner(19).

Borderline ovarian cancers are associated with a better prognosis and constitute approximately 20% of all epithelial neoplasms.More than 96% of borderline ovarian tumors (BOTs) are serous or mucinous with other rare type being endometrioid, clear cell, or Brenner (transitional tumor)(20).

In Tanzania, the government is implementing the National Cancer Control Strategy (2013-2022), whose aim and goals areto strengthen and accelerate the translation of cancer control knowledge into Public health action. At Muhimbili National Hospital (MNH)many of these patientswith ovarian cancer are presenting with late stages of the disease.Cytoreduction and histological confirmation are done at the MNH, thereafter the patients are transferredtoOcean Road Cancer Institute (ORCI) for chemotherapy depending on the extend of spread of the disease.

The available modalities of screening include transvaginal ultrasound (TVS), CA125 levels, chest X-ray, abdominal and pelvic ultrasound.Other tests include, biopsy (confirmatory), computer tomographic scan (CT Scan), magnetic resonance imaging (MRI), positron emission topographic (PET), colonoscopy and laparoscopy(14). CA125 is elevated in almost all patients with late stage epithelial ovarian cancer although it is nonspecific(6). The cancer is difficult to diagnose in the early stages, however, patients with a strong family history of breast, ovarian or colon cancer required special attention including a much higher index of suspicion. Further investigation including risk evaluation and sometimes genetic testing need to be considered to identify high risk women. If screening is done for women who are particularly at high risk, the yield and cost-effectiveness will be much more(6).

The disease is usually treated by surgery followed by timely chemotherapy except in stage 1a which is usually treated by surgery only. When diagnosed early, the survival is far better than at advanced stages of the disease at which point the 5-year survival is about 30% and there is an increased tendency for the development of chemoresistant after surgery(9)(21).Over 70% of the patients with advanced stage epithelial ovarian cancer experience recurrence within 2 years after initial treatment (22).

Studying the incidence and patternsof the disease by region can assist with assessment of environmental or cultural factors that may increase risk(23).Theaccurate assessment of the cancer burden is important as incidence data are used togenerate hypotheses regarding the etiology, resource allocation and funding toward new treatment discovery(3). This may alsodetermine which populations of women may benefit from more education or greater surveillance for the disease. Targeted prevention can be done in these population to interrupt early carcinogenesis in these women(3)(10)**.**

1.2Literature Review

Despite advances in research, diagnosis and treatment, ovariancancer remains the deadliest cancer of the female reproductive tract(24). According to the American Cancer Society, approximately 21,000 women are diagnosed with ovarian cancer in the United States and 14,000womenwill succumb to this disease annually(24). The signs and symptoms are often vague that the cancer is most often diagnosed in the late stages.The difficulty in diagnosing the disease is usually worsened by a low index of suspicion.(6)

Prevalence of ovarian cancer

Ovarian cancer is the second leading cause of cancer admission in the USA(1). In the teaching hospital in Nigeria and Ghana, it is the second leading cause of gynecological cancer admissions next to cervical cancer accounting for 19.2% and 25.3% respectfully(25,26)**.** The rate of the cancer is estimated to be 6.3 per 100,000 worldwide with the rate in developed countries and regions being 9.3 as compared to others.Rates range from 11.8 in Northern Europe to 8.7 in North America, 5.1 in Asia, and 4, in East Africa(2,3).

Globally, ovarian cancer incidence rates increase with advancing age and range from 0.2 among those aged 0-14 to 29.2 among those aged above 75 years(2). In the United States, ovarian cancer incidence rates range from 0.3 in those aged 5-9 years to 44.2 in women aged above 85 **years**(19). The peak ovarian cancer incidence rate of 50.6 is found among women aged 80-84 in the United States(19). Ovarian germ cell tumors are found in the highest rates among those aged 15-19 (3). In Ghana, the mean age of ovarian cancer cases seen in a teaching hospital was 46.4(SD15.0) years (26). At the KNH, the mean age of the patient diagnosed with ovarian cancer was 49.8 (SD15.7) years while at a tertiary medical center in Enugu, Nigeria, the mean and median age of ovarian cancer was 45.4(SD17.1) and 48 years respectively.Again, in South Eastern Nigeria, parous women constituted 72.1% of all ovarian cancer caseswhilein Kenya, 65% of the women had more than one child.(4,25)

Histological Subtypes of ovarian cancer

About 91.9% of ovarian tumors were reported to be epithelial with serous adenocarcinoma accounting for 37.7%(23)**.**Sex cord stromal were found equally in all ages while germ cell tumors occurred predominantly in young women(23). At KNH, epithelial tumors accounted for 86.2% of all ovarian cancer with 45.7% of them being the serous type (4). Epithelial ovarian cancer constituted 68% of cases of ovarian cancers while germ cell and sex cord stromal constituted 16% each in a teaching hospital in Nigeria(25).BOTs accounts for approximately 15% to 20% of all epithelial ovarian cancer, and more than 96% of these BOTs areserous or mucinous(20)..

Epithelial ovarian cancer still has a poor prognosis despite aggressive surgery and chemotherapy. Women with germ cell tumor, stromal cell tumor, borderline tumor and stage Ia epithelial ovarian cancer can be managed by preserving their fertility potential without compromising curability(6).

Symptoms for ovarian cancer can be vague and gastrointestinal in nature. Because of this, many ovarian tumors are diagnosed at advanced stages(3)**.** Many Patients may report abdominal fullness, dyspepsia, early satiety, or bloating and findings on physical examination may include ascites, pleural effusions, and an umbilical mass(27).In the United States, about 20% of all ovarian cancer cases are localized at diagnosis, about 13% at regional stage, and the majority is distant stage (58%). Sex cord-stromal and germ cell tumors are more often diagnosed at localized stages (>50%) compared to epithelial tumors (19%)(3,28). About seventy-five percent of patients with epithelial ovarian cancer present with advanced disease(5,15). In a teaching hospital in Nigeria over 84% of patients presented in stages 3 and 4 of the disease(25).

Most patients with BOTs generally present with stage I disease which has a good prognosis(6). The 5-year survival rate for stage I BOTs is approximately 95% to 97%, and stage II to III BOTs have 5-year survival rates of 65% to 87%(20). For epithelium ovarian cancer, the 5 year survival rate for early stage cancer is about 90%, whereas the 5 year survival rate in advanced disease is 10% - 30%(29). The two year survival rate of ovarian cancer after diagnosis was 50% in a hospital in Kenya while in a centerin Nigeria the one year case-specific mortality rate was at least 70%(4,25).

Even though epithelium ovarian cancer patients are often diagnosed in the late stages, the key to identifying symptoms pointing to the cancer appears to occur frequently. The ‘Symptom

Index' is considered positive if a woman is currently experiencing any one or more of six specific symptoms that are present for less than one year and occur more than 12 times a month.(30). The symptoms include bloating, increased abdominal size, pelvic or abdominal pain, difficulty eating, and early satiety. Follow-up should be encouraged in women reporting symptoms, as prompt assessment for ovarian cancer in these women using currently available tests (CA-125 and TVS) could result in earlier diagnosis of the cancer at which time the prognosis may be better(30). There are no documented effective screening methods for ovarian cancer that reduce the mortality of the cancer(3).

Demographic profile

Age, parity and strong family history are important risk factors for the cancer(7,31,32). Epithelium ovarian cancer rate increases with advancing age which is often diagnosed in the late stages. However, most patients with borderline ovarian tumors are 10 to 15 years younger than patient with invasive ovarian cancer. Young women with borderline or early stage disease who desire to have a family may have fertility sparing surgery thus influencing the management of the disease(6). Approximately 10% of epithelial ovarian cancers are thought to be related to a germ line genetic mutation. Breast Cancer 1 (BRCA1) and Breast Cancer 2 (BRCA2) are the most commonly affected genes,accounting for approximately 90% of the mutations in hereditary ovarian cancer(15).These genes are responsible for majority of familial ovarian cancers(31,32).A woman with a strong family history may have total abdominal hysterectomy with bilateral salpingo-oophorectomy which may be protective against the cancer(6,9,13).

Management

Investigations for ovarian cancer includetransvaginal ultrasound (TVS), CA125 levels, chest X-ray, abdominal and pelvic ultrasound, full blood count, urea, electrolytes, and liver function tests(6)**.** Other tests include, biopsy (confirmatory), CT Scan, MRI, PET, colonoscopy and laparoscopy(14). Tumor markers for germ cell and sex cord include β-hCG, Alpha fetoprotein and Lactate dehydrogenase(18).

Treatment depends on the stage of the cancer. The standard surgical staging approach consists of surgery which usually involved a total abdominal hysterectomy and Bilateralsalpingo-oophorectomy(BSO). This is done along with examination of all peritoneal surfaces, an infracolic,omentectomy, biopsies of pelvic and para-aortic lymph nodes and clinically

uninvolved areas, and peritoneal washings(15).For early stage 1a cancer, surgery is done only. Beyond this stage, surgery followed by chemotherapy is usually offered to the patient. Fertility sparing surgery that allows optimal removal of ovarian tumour and adequate staging but at the same time preserving reproductive potential may be performed in a young womanwith borderline ovarian tumour, germ cell tumour, stromal cell tumour and stage Ia epithelial ovarian cancer(6).Patients presenting with early (stages I or II) disease are divided into two categories relevant to a role for adjuvant chemotherapy. For those patients with well differentiated (grade 1) stage IA or B disease, adjuvant chemotherapy is not recommended since more than 90% of them will have long-term (>10 year) disease-free survival without further treatment.Those Patients that are presenting with stage IA or B (high grade), stage IC, and stage II ovarian cancers will have improved survival if given adjuvant chemotherapy after surgical staging(15).

Maximal cytoreductive surgery is one of the most powerful determinants of survival in patients with stage III and IV ovarian cancer(33). A significant survival benefit has been found in patients with maximum cytoreduction or whom had ≤ 2 cm residual disease(6,15). During cytoreduction, tissues are taken for biopsy to confirm the cancer. All of the obvious sites of the tumor must be removed as much as possible in addition to total abdominal hysterectomy and bilateral salpingo-oophorectomy. However, achieving 'optimal debulking' is associated with a complicationrisk of 8% to63% and a mortality rate of 1% to 6%, and as such neoadjuvant chemotherapy has been proposed as an alternative option. Following neoadjuvant chemotherapy, there has been a significant decrease in CA-125 levels(29)**.**Standard first line adjuvant chemotherapy is six cycles of paclitaxel and cis- or carboplatinum(15)**.** The response rate to platinum based chemotherapeutic treatment is around 80% initially(34). In advanced disease, the majority of patients (60–70%) will experience a recurrence and ultimately succumb to their disease.Survival with primary chemotherapy is non-inferior to primary surgery with stage III or IV ovarian cancer. Giving primary chemotherapy before surgery is an acceptable standard of care for women with advanced ovarian cancer (35).Intraperitoneal administration of cisplatin can be given as primary chemotherapy after cytoreduction of epithelial ovarian cancer as it has resulted into 20 to 30 % improvement in the progression freeand overall survival times as compared to intravenous delivery. However, this has not been universally accepted because of its toxic effects and

complications which include intraperitoneal adhesions and infections(15,36,37). The time from primary cytoreduction to surgery has been shown to be between 25 to 35 days for better survivor(38,39).

1.3Problem Statement

Majority of ovarian cancer patients are admitted in hospitals with the advanced stage of the disease(15,29).Globally, the five-year survival is only 15–20% for patients with clinically advanced ovarian cancer despite aggressive surgery and platinum based chemotherapy (6).

In recent years, there have been gradual increases in the number of cases of ovarian casesin less developed countries. The lack of a quality data of ovarian cancer patients from most of these countries undermines efforts to describe the incidence pattern that can assist with assessment of environmental or cultural factorsthat may increase the risk of the disease(3). The number of advanced stages ovarian cancer cases admitted at MNH has increased couple with the delay to commence chemotherapy, despite the fact that the Government is implementing the National Cancer Control Strategy (NCCS). Precise data describing the disease pattern and treatment modalities at MNH is not available. This in turn had limited the health authorities to adequately access those factors that may increase the risk for the disease and its progression, thus undermining efforts that could lead to early detection and prevention of the disease progression.

1.4Rationale

The incidence of cancer is increasing throughout the world. Ovarian cancer is the most lethal gynecological malignancy. With late patient presentation and poor prognosis, it distresses not only the family members but also burden thehealth system of most developingcountries in term of patient care, treatment and psychological disturbances associated with cancers as a whole.Efforts aim at early detection of the cancer at stage I and 2 is being sought worldwide since at this time the five -year survival rate is about 90%(15).

In addition to providing the cancer prevalence, demographic, and clinical pattern of the diseaseand emphasizing the need for timelytreatment at the national hospital, findings from this study could be used to guide policy efforts in ovarian cancertreatment and palliation, which is in line with the Tanzania government National cancer control strategy (NCCS).

1.5Research Question

What is the pattern of ovarian cancer at MNH from 2012 to 2016?

1.6Objectives

1.6.1 Broad Objective

To describe the patternof ovarian cancer patients admitted at MNH (2012 to 2016).

1.6.2Specific Objectives

i. To determine the proportionand socio-demographic profile of ovarian cancerdiagnosed at MNH.
ii. To describe the histological types and subtypes of ovarian cancer at MNH.
iii. To determine the proportion of patients admitted at an early and late stage of the disease.
iv. To determine the stages of the disease and treatment modalities provided to patient admitted at MNH.

2.0METHODOLOGY

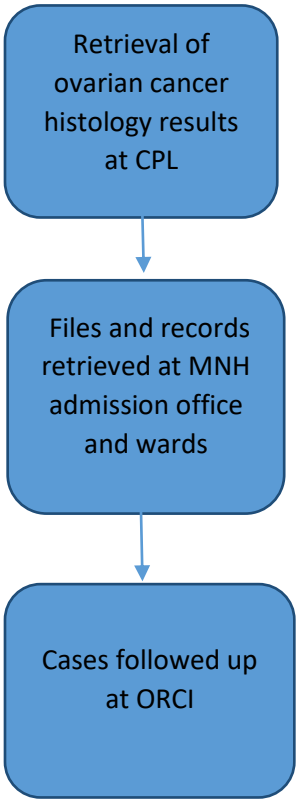


Figure 1: study flow diagram

All ovarian tumors histological diagnosis at the CPL was retrieved and the confirmed malignant neoplasms and BOTs were separated from the benign and unconfirmed neoplasms. The case notes and files of the confirmed cases were traced and also retrieved from the records and admission office, the respective wards and the operating theatre at MNH. The patients' records were then followed and traced at the ORCI where theywere transferredfor chemotherapy.

2.1 Study design

The study was a retrospective descriptive study, which thoroughlyreviewed files and relevant medical records of patients admitted and treated for ovarian cancer.

2.2Study Duration

The study covered a fiveyearperiod, from 2012 to 2016. This period was chosen to enable the principal investigator retrieved as many ovarian cancer cases as possible since the cancer is not so commonly reported, while at the same time minimizing the possible lost cases since this period is not in the distant passed.

2.3Study setting

This study was conducted at Muhimbili National Hospital in the Department of Obstetrics and Gynecology and the ORCI. MNH is the largest consultant and a teaching hospital in Tanzania for the Muhimbili University of Health and Allied Sciences (MUHAS). The hospital is located in the city of Dares Salaam which has a total population of about 4.5 million with annual growth rate of 5.6%(40). It receives referred patientsfrom hospitals within Dar es Salaam and across the country. The Department of Obstetrics and Gynecology has the obstetrics and gynecologic blocks, and the latter block has two large wards where the gynecologicalpatients are admitted. The hospital also has a main operating theatre with several operating rooms, and aCentral Pathology Laboratory where histological sample are analyzed. Patients files and medical records are kept in Admission and Records section. The ORCI, also situated in Dar es Salaam, is one of the oldest health institutions in Tanzania, and it is the National cancer referral hospital that treats all cancer patientsfrom across the country. All ovarian cancer patients admitted at MNHare surgically managed except those who are too ill and cannot withstand the stress of surgery. The surgeries are mainlyperformed by specialists and consultant gynecologists. During cytoreductive surgery, tissues samples are taken for histology including lymph node biopsy depending on the experience of the surgeon. There is a lack of practice to do peritoneal washing during debulking surgery and often these ovarian cancer patients are not stage. The biopsy results usually take up to three weeks after which time confirmed patients are transferred to ORCI for chemotherapy. For those patients who are too sick to undergo surgery the decision to continue palliative care or to start neoadjuvant chemotherapyis made through the tumor board. The tumor board is a multidisciplinary team composed of consultants, specialist doctors and clinicians caring for these patients. The board usually include gynecologists, oncologists, pathologists, surgeons, nurses and others health care workers.

2.4 Study Population

All patients withdiagnosis of ovarian tumors at MNHover the last five years.

2.5 Sample Size

All eligiblehistological confirmed cases of ovarian cancers were retrieved for the study.

2.6Training of Research Assistants

A onedaytraining of four research assistants was conductedat MNH. Two of the assistants were trained on how to collect relevant histopathological informationfrom the CPL and the other two were trained on the types of file to retrieve from the admission offices both at MNH and ORCI. This training was conducted by the principle investigator.

2.7Data collection

The pathology laboratory was the initial entry point for data collection. After getting the histology results, a list of all ovarian cancer diagnosis was made, and case file and other medical record were traced from the records office, the respective wards and operating rooms' analysis book and important information were recorded. Additional listing ofall ovarian diagnosis not seen from the CPL was made from the wards, the record officeand the hospital information system and the files were retrieved. All clinically diagnosed ovarian cancer cases whose histology results could not be found were noted as suspected cases, and were not included in the study. The cases were also followed and retrieved at the ORCI from the admission office, the ward admission book and the hospital's electronic data system. Information such as date of admission, type and onset of chemotherapy, treatment duration and outcome were recorded.Two assistants retrieved the histology results from the CPL while the other two retrieved file from the records offices of both MNH and ORCI. The principle investigators traced, recorded and verified all available relevant information regarding the study from the wards' admission and discharged books, operating room analysis book, and the hospitals' electronic information system. A structured checklist wasused to collect the relevant information from the patient file and records which included: socio-demographic profile, clinical presentation, laboratory results, imaging findings, therapeutic options, and duration of hospital stay and outcome of patient. For the purposed of this study, all the women were staged into having early and advanced stage disease. This was achieved by thoroughly assessing all of the clinical notes, investigation results, intraoperative, post-operating surgical findings such as spread of the tumor, malignant confirmation of ascitic fluidand lymph nodes

biopsy. All of these were usedin consistent with FIGO staging to stage a patient ashaving early or advanced disease. All other investigations and imaging results such as abdominal pelvic ultrasound, CT/MRI, chest X-ray, were used to complement the staging process. All patients with FIGO stage 1 and 2 disease, were considered as having early stage disease while those with stage 3 and 4 were taken as having advanced stage disease(4,15,26).Levels of CA125, AFP, and β-hcgwere also used to support the diagnosis.

2.8Data Management

The data was coded with a unique identification number, cleaned and matched appropriately with records from ORCI. Corrections of data and missing information weredone from alternative source of patient records including the Hospital's Information System, admission, discharge, round and treatment books, surgical procedure books, laboratory and nursing reports. From the several sources of data collection for a case, a single harmonized form was completed for each patient that was used for data entry.

2.9Data Analysis and Results

The cases that met the inclusion criteria wereentered into Statistical Package for Social Sciences (SPSS) version 23. The data was presented appropriately using frequency table, mean, medium, absolute count and proportion.

2.10Inclusion Criteria

All ovariancancer and borderline tumors diagnosed at MNH.

2.11Exclusion Criteria

Allhistological unconfirmed ovarian cancer and krukenburg's tumorsat MNH.

2.12Ethical Consideration

The study was conducted in accordance with existing ethical guidelines. Scientific and ethical approval of the study was obtained from the Senate Research & publication Committee of MUHAS. Permission to conduct the study was also obtained from the Executive Director of MNHand the Executive Director of the ORCI. Although the case from which data was obtained had name, the data collected used unique identification study code to ensure confidentiality.

3.0 RESULTS

3.1 Preamble

A total of 3,401 admissions of gynecologic cancers, ovarian malignancy accounted for 273 (8.03%)`admissions while cervical cancer and endometrium cancer accounted for 2,641 and 393 admissions respectively. The others included vulva cancers 62,choriocarcinoma 26 and vaginal cancers 6. One hundred and seventy-two ovarian cancer cases by confirmed histology were traced, out of which149 completedcase files wereretrieved.Only 6.5% of the files were staged post-operatively by the surgeons.Completed files were those that had notes regarding treatment modalities and outcome whereas the incomplete files did not have data regarding treatment modalities and outcome.

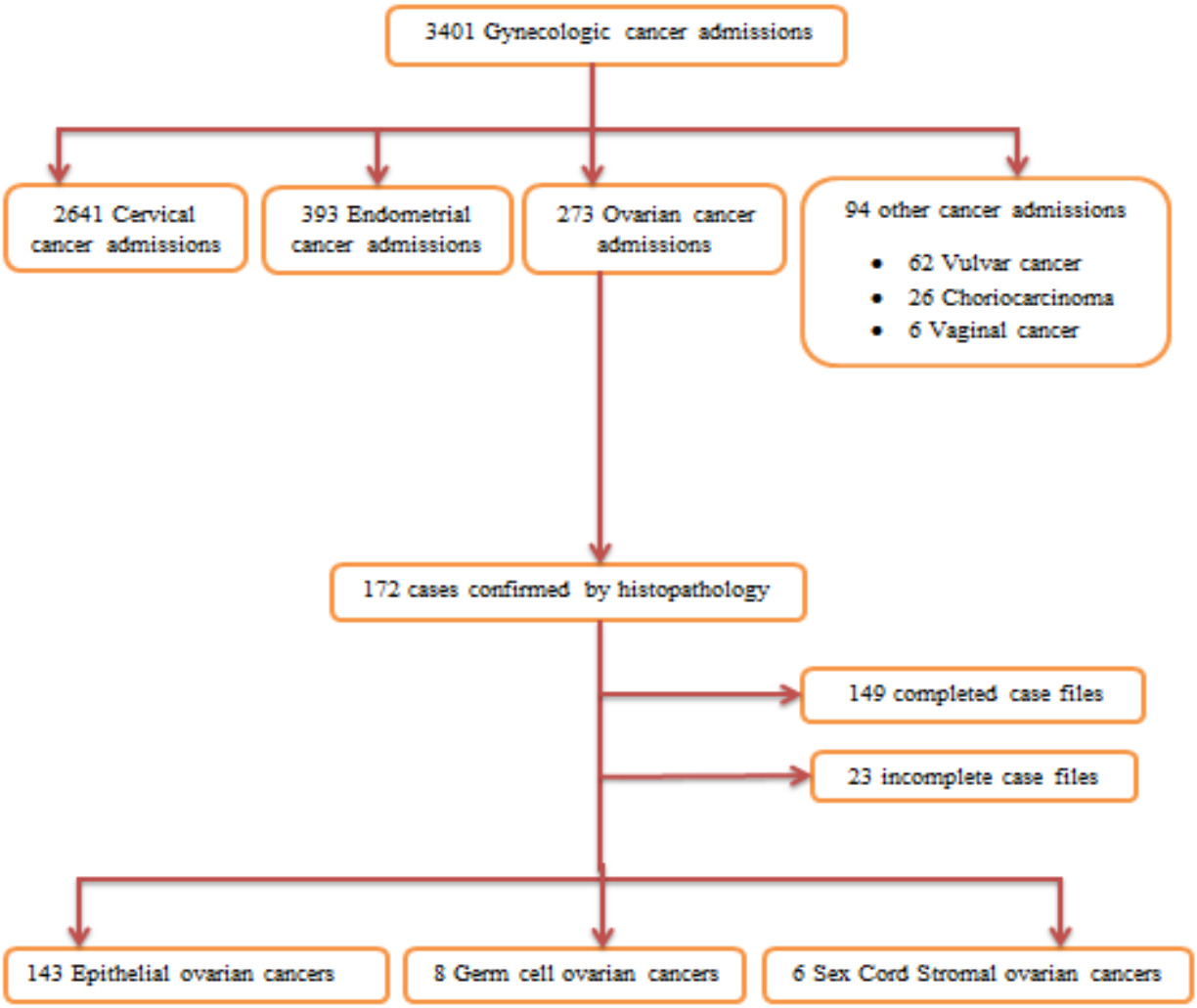


Figure 2: Flow chart of case recruitment and follow up

Table 1: Demographic characteristics and clinical manifestations of study participants (n=172*)

Variable	n (%)
Age	
< 30	32 (18.6)
30-39	17 (9.9)
40-49	36 (20.9)
50-59	35(20.3)
60-69	34 (19.8)
>=70	18(10.5)
Mean age	48.4 (S.D 16.5)
Median age	50
Parity	
0	38 (22.1**)**
1-4	80 (46.5)
>=5	30 (17.4)
Not stated	24 (14.0)
Educational level	
None	22 (12.8)
Primary	38 (22.1)
Secondary	11 (6.40)
Post-Secondary	5 (2.90)
Not indicated	96 (55.8)
Occupation	
Housewife	27(15.7)
Farmer	19(11.0)
Self employed	18 (10.5)
Employed	7 (4.10)
Unemployed	5 (2.90)
Student	7 (4.10)
Not indicated	89(51.7)
Marital Status	
Single	17 (9.90)
Married	81(47.1)
Divorced/separated	6 (3.50)
Widow	13 (7.50)
Not indicated	55 (32.0)
Symptoms**	
Abdominal pain	149 (86.6)
Abdominal distension	130 (75.6)
Respiratory distress	96 (55.8)
Family history of cancer	4 (2.3)

*All available records retrieved from completed and incomplete case files were analyzed.Nulliparous women accounted for 22.1% of cases.**There were multiple responses in this category.

Table 2: Distribution of cases admitted by regions (n=172)

Regions	n (%)
Dar es Salaam	69 (40.1)
Kilimanjaro	16 (9.3)
Tanga	14 (8.1)
Morogorro	11 (6.4)
Singida	10 (5.8)
Zanzibar	8 (4.7)
Pwani	7 (4.1)
Dodoma	5 (2.9)
Arusha	4 (2.3)
Mwanza	4 (2.3)
Iringa	4 (2.3)
Lindi	4 (2.3)
Mbeya	3 (1.7)
Shinyanga	3 (1.7)
Kigoma	3 (1.7)
Mara	2 (1.2)
Tabora	2 (1.2)
Kagera	1 (0.6)
Ruvuma	1 (0.6)
Mtwara	1 (0.6)

Sixy-nine (40.1%) women came from Dar es Salaam followed by Kilimanjaro, 16 (9.3%) and Tanga 14 (8.1%).

Table 3: Distribution of the histological types of ovarian cancer (n=172)

Variable	n(%)
Types	
Epithelial	143(83.1)
Germ cell	8(4.7)
Sex cord stromal	6(3.5)
Borderline epithelial tumor	6(3.5)
Squamous cell carcinoma of ovary	4(2.3)
Sarcoma	3(1.8)
Malignant lymphoma	2(1.1)
Epithelial Subtypes	
Serous	75(43.6)
Mucinous	37(21.5)
Endometroid	10(5.8)
Clear cell	4(2.3)
Not stated	26(15.1)
Germ cell subtypes	
Dysgeminoma	3(1.7)
York Sac tumor	4(2.3)
Embryonic cell carcinoma	1(0.6)
Sex cord subtype	
Granulosa cell tumor	5(2.9)
Sertoli- Leydig cell	1(0.6)
Borderline tumor	
Serous	4(2.3)
Mucinous	2(1.2)

The most common histological type of ovarian cancers found among the women were epithelial type, 143 (83.1%), while serous epithelial was the most common subtypes, 75 (43.3) %. Squamous cell carcinoma of the ovary, a rare type of ovarian cancer, constituted 2.3% of the ovarian cancers.

Table 4: Distribution of histology by age group of study participants (n=172)

Variable	Less than 50 years	50 and more years	Total
Epithelial	65 (45.5%)	78 (54.5%)	143 (100%)
Germ cell	6 (75%0)	2 (25%)	8 (100%)
Sex cord stromal	3 (50%)	3 (50%)	6 (100%)
Borderline Epithelial tumor	5 (83.3%)	1(16.7%)	6(100%)
Other rare tumors	6 (66.7%)	3 (33.3%)	9 (100%)
Total	85 (49.4%)	87 (50.6%)	172 (100%)

Germ cell and borderline tumor occurred more in the women less than 50 years.

Table 5: Distribution of treatment modalities of study participants (n=149*)

Variable	n (%)
Treatment option	
Surgery only	82(55.0)
Surgery followed by chemotherapy	61(40.9)
Neoadjunvant Chemotherapy followed by surgery	3(2.01)
Neoadjuvant chemotherapy only	1(0.7)
Conservative management	2(1.34)
Surgical procedure**	
Inoperable at surgery	13 (8.84)
Total abdominal hysterectomy and Bilateral salpingo-oophorectomy	66(44.9)
Sub-total abdominal hysterectomy and bilateral salpingo-oophorectomy	6 (4.08)
Unilateral salpingo-oophorectomy	16 (10.9)
Cystectomy	2 (1.36)
Other debulking procedures	41 (27.9)
TAH & BSO with Colostomy	3 (2.04)
Number of days from surgery to chemotherapy***	
>30days	38(62.3)
30 days or less	19 (31.14)
Not indicated	4 (6.56)
Average number of days from surgery to chemotherapy	45.12(SD 24.8)

Colostomies were done on three women with advanced disease that underwent total abdominal hystecyrectomy and bilateralsalpingo-oophorectomy with bowel involvement while two patients with ovarian cyst underwent cystectomy. Other debulking procedures included those procedures not started in the case notes. ** Total number of surgical procedures were 147 as two patients did not undergo surgery but were confirmed by cytology and biopsy from metastatic nodules. *** Total number of participants that started chemotherapy after surgery was 61. * Total cases analyzed in this category were 149.

Table 6: Ovarian cancer stage and treatment options of study participants (n=149)

Stage	Surgery only	Surgery followed by chemotherapy	Neoadjuvant Followed by surgery	Neoadjuvant chemotherapy only	Palliative management	Total
Early	16(69.6%)	7(30.4%)	0(0.0%)	0(0.0%)	0(0.0%)	23(100%)
Advanced	66(56.8%)	54(42.9%)	3(2.4%)	1(0.8%)	2 (1.6%)	126(100%)

Sixteen patients with early stage diseasedid not received chemotherapy after surgery. Two patients who were diagnosed by cytology and biopsy from metastatic umbilical nodule received palliative treatment without surgery or chemotherapy.

Table 7: Distribution of treatment outcome according to cancer stage of study participants (n=149)

Outcome	**Early stage**	**Advanced stage**	**Total**
Stable and discharge	14(60.9%)	12(9.5%)	26(17.4%)
Counsel and discharge for palliative care	0(0%)	50(39.7%)	50(33.6%)
Loss to follow up	9(39.1%)	33(26.1%)	42(28.2%)
Relative requested discharge	0 (0%)	1(0.8%)	1(0.7%)
Died in hospital	0 (0.0%)	27 (21.4%)	27(18.1%)
Not stated	0 (0%)	3 (2.4%)	3(2.0%)
Total	23 (100%)	126(100%)	149(100%)

Fourteenwomen with early stage disease were discharged stable.Forty-two women (28%) who underwent surgery and referred for chemotherapy were lost to follow up treatment at the cancer institute.Twenty-seven (21.4%) womendied while receiving treatment.

4.0 DISCUSSION

The study found that ovarian cancer patients presented withadvanced stage disease with the main clinical manifestation of abdominal pain, abdominal distension, and respiratory distress.This is supported by other studies in the regions which revealed that many patients with ovarian cancer may delay to seek appropriate treatment due to the nonspecific early symptoms and signs of the disease and its low index of suspicion(6,29).More than three quarters of the cases in this study were of epithelial type and the cancer was almost equally distributed among the age groups with the mean age being 48.4 (SD16.5) years. This shows an increasing incidence of epithelium ovarian cancer in reproductive age women in this region and this is supported by other studies in the developing countries, but contrary to other literatures in the developed world where the cancer incidence is more common in advanced age(3,25,26). The study also found that ovarian cancer was the third most common gynecological cancer admission at the Muhimbili National Hospital, after cervical and endometrial cancers. This finding differ slightly from other studies in the developing regions where it was found to be second to cervical cancer(25,26). It is postulated that environmental or cultural factors may affect the incident pattern of the disease(23), and this could perhaps explain the differences.

The main stay of treatment in this study were surgery followed by chemotherapy which is consistent with other studies(4,15). The management of these women were multidisciplinary involving gynecologists, pathologists, general surgeons (in some advanced cases), and oncologists. About a tenth of the patient were inoperable at the time of presentation and less than half of these women underwent total abdominal hysterectomy and bilateral salpingo-oophorectomy (TAH & BSO) which indicated the advanced nature of the disease during admission. Other surgical procedures included subtotalabdominal hysterectomy, unilateral salpingo-oophorectomy and cystectomy.The reasons for these procedureswere not clearly stated but two women thought to have had benign ovarian disease (ovarian cyst) underwent cystectomy.

The main chemotherapeutic options given to these women were platinum based chemotherapy of paclitaxel and cis or carbo-platin which is the standard first line chemotherapy for treating ovarian cancer.Nearly two-third of the women started chemotherapy after 30days, and this was

considered a delay in this study.This delay was noted mainly between the times of referral after surgery to the start of chemotherapy. Chemotherapy is normally started afterconfirmation of the cancer and when the patient becomes stable after surgery. At MNH, histological confirmation of ovarian cancer usually takesabout 21 days. This may have also contributed to the delay, as some of the women who are discharged after surgery may even delay further in coming back for the histology result because of the three-week interval which may be apparently long. Delay in the initiation of surgery has been noted to cause the remnants of the tumor cell to start proliferating (38,39).

Even though socio-demographic information was poorly documentedas evidenced from the number of missing data, the study shows high incidence of ovarian cancer among parouswomen. This is supported by other studies in the developing countries(25,26).However, this may be quite different in the developed world(15). Environmental, hereditary, social and cultural factors need to be studied to explain other factors that may be involved in the incident of the cancer in this region. Few of the cases recorded a positive family history of cancer which points to the hereditary nature of the disease. Many of these women had no or only primary level education and were mostly housewives and farmers. Their low socioeconomic status may have contributed to their delay in starting timely treatment. Fourof the women could not start chemotherapy on time due to financial constraints and were among those who delayed to start treatment even though they presentedon time to the cancer institute.

About half of these women came from Dar es Salaam. This may not be a true reflection as many of these women may have come from other regions but may have indicated their relative place in Dar es Salaam where they resideto seek treatment as their place of residence. The others regions included Kilimanjaro in the Northern zone,Tanga, Morogorro and Pwani in the Eastern zone, Singada and Dodoma in theCentral zone and Zanzibar. The increase in number of these women seeking care at MNH from these regions may be because of theaccessibility and closed proximity to Dar es Salaamfrom these regions.

About two-third of the women with early stage disease were discharged stable after treatment while many of the women with advanced stage disease were counseled for palliative care.Almost one-fifth of the womenwith advanced stage disease died in the hospital while undergoing treatment andmore than half of these women died prior to starting chemotherapy.

This shows how ill these patients were upon admission at the hospital. This is consistent with many studies that advanced stage ovarian cancer has a poor prognosis.(25)(29)

Loss in the continuum of care was observed in more than one-fourth of the women that underwent cytoreduction at MNH and was transferred to ORCI. There were no records of these women at the cancer institute and hence they did not receive chemotherapy. Some of these patients were potentially curable patients with early stage disease and this was a missed opportunity to have received chemotherapy.

5.0STUDY LIMITATIONS AND STRENGTHS

Only the information written in the patient's file and available records was studied. Missing patient's files and other medical records which were unable to be retrieved were not studied. Some of the wards' admission and discharge books could not be located, and some files and histological results could not be traced. The wards lack adequate storage facility for storing the many ledgers over the years,therefore, tracing data have been difficult and thus increasing the number of missing data. The movement of patientsfiles from MNH to ORCI after they have been transferred may have also caused some of the files to have been lost. There waspoor documentation of some important information in the patient's files which also increase the number of missing data.

Staging a patient as having early stage disease from intra-operative findings without results from peritoneal washing and lymph node biopsy were a limitation in this study as some of these patients could have had positive peritoneal washing and lymph node biopsy indicating spread outside the pelvic and thus changing the stage to advanced stage.

The strength of the study was that missing information from the patient's file was collected from alternative sources including the Hospital's electronic information system, admission, discharge, round and treatment books on the gynecologic wards, operating theatre gynecology ledgers and the general surgery operation ledgers. Also at the ORCI, alternative sources such as the ward admission and discharge books and the hospital information system was used to retrieve missing information for the patients.Another major strength of the study is that it gives an overall picture of the current state of ovarian cancer pattern and management at MNH.

6.0 CONCLUSION AND RECOMMENDATIONS

6.1 Conclusion

From this study, the most common type of ovarian cancer was epithelial with the serous subtype being the most common. Majority of the women presented to the hospital with advanced stage disease. The main stay of treatment was surgery and chemotherapy, and majority of women delayed in starting chemotherapy after surgery.

6.2 Recommendations

1. There should be a specially designed clinical note sheet for history taking and examination of all cancer patients in the hospitals for recording of appropriate cancer information including capturing the stage of the disease post operatively.
2. Strengthen the linkage and coordination between MNH and ORCI regarding patient transfer to avoid unnecessary delay in continuing care.

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APPENDICES

Appendix I: FIGO staging of ovarian cancer

FIGO STAGES	DEFINITION
I	Tumor confined to ovaries or fallopian tubes
IA	Tumor limited to one ovary (capsule intact) or fallopian tube surface; no tumor on ovarian or fallopian tube surface, no malignant cells in ascites or peritoneal washings
IB	Tumor limited to both ovaries (capsule intact) or fallopian tubes; no tumor on ovarian or fallopian tube surface, no malignant cells in ascites or peritoneal washings
IC	Tumor limited to one or both ovaries or fallopian tubes with any of the following:
1C1	Surgical spill
1C2	Capsule ruptured before surgery or tumor on ovarian or fallopian tube surface
1C3	Malignant cells in ascites or peritoneal washings
II	Tumor involves one or both ovaries or fallopian tubes with pelvic extension (below pelvic brim) or peritoneal cancer
IIA	Extension and or implants on uterus and/or tube(s) and/or ovaries
IIB	Extension to other pelvic intraperitoneal tissues
III	Tumor involves one or both ovaries or fallopian tubes, or peritoneal cancer, with cytological or histologically confirmed spread to the peritoneal outside the pelvic and/or metastasis to the retroperitoneal lymph nodes
IIIA	Positive retroperitoneal lymph nodes and/or microscopic metastasis beyond the pelvis
IIIA1	Positive retroperitoneal lymph nodes only(cytological or histologically proven)
IIIA1(i)	Metastasis up to 10mm in greatest dimension
IIIA1(ii)	Metastasis more than 10mm in greatest dimension
IIIA2	Microscopic extrapelvic (above the pelvic brim) peritoneal involvement, with or without positive retroperitoneal lymph nodes

IIIB	Macroscopic peritoneal metastasis beyond the pelvic up to 2 cm in greatest dimension, with or without positive retroperitoneal lymph nodes
IIIC	Macroscopic peritoneal metastasis beyond the pelvic up to 2 cm in greatest dimension (include extension to the liver and spleen without parenchymal involvement of either organ), with or without positive retroperitoneal lymph nodes
IV	Distant metastasis (excludes peritoneal metastasis)
IVA	Pleural effusion with positive cytology
IVB	Parenchymal metastasis and metastases to extra-abdominal organs (including inguinal lymph nodes and lymph nodes outside the abdominal cavity)

FIGO 2016

Appendix II: Checklist and questionnaire

Please answer Y(Yes) or N(No) and give values or short answers in the blank space provided where necessary**.**

Registration number-----

Form number-----

Date of admission-----

Descriptive demographic statistics

Age

Education

Primary -----

Secondary ----

Tertiary -----

Others ----------

Not indicated -----

Marital status

Single ----

Married ----

Divorced/Separated-----

Not indicated----

Occupation----

Not indicated----

Parity-

Not indicated ----

Family planning

Yes ----

Oral----

Injectable ----

Others ----

Name of FP (if indicated)-----

No----

Not indicated----

Age of Menarche (if indicated)----

Age of Menopause(if indicated)----

Family history of cancer------

Histological result----

Diagnosis----

Histological type

Epithelial tumor----

Serous--

Mucinous--

Endometrioid—

Clear cell adenocarcinoma—

Other---

Germ cell tumor---

Teratomas—

Dysgeminomas—

York sac tumor—

Mixed germ cell tumor—

Ovarian germ cell tumor—

Other----

Sex cord stromal tumor---

Fibromas—

Granulosa cell tumor—

Sertoli-Leydig tumors—

Steroid cell tumor---

Gynandublastoma---

Others----------

Borderline tumor

Serous—

Mucinous—

Endometroid—

Clear cell tumor—

Other----------

Clinical manifestation

Bloating -----

Pelvic or abdominal pain----

Early satiety----

Urinary frequency ----

Respiratory Distress----

Constipation---

Vaginal bleeding---

Other Symptoms(Specify)---

Abdominal distension----

Ascites----

Plural Effusion---

Pallor---

Mild---

Moderate--

Severe---

Blood transfusion---

Before surgery---

During surgery---

After surgery---

Number of unit received---

Investigations

Result

Blood serum----

Tumor markers----

CA125---

CEA-----

AFP---

LDH--

Others--

Full Blood Picture (FBP)

WBC---

HB-

Platelet (count)-

Others-

Imaging

Chest X-ray---

Ultrasound---

CT Scan----

MRI----

Others--------

Treatment modality

Surgery--

Maximal cytoreduction--

Not indicated-

Date of Surgery-----

Conservative management---

Others----

Surgical Findings

Capsule intact--

Capsule ruptured----

Before surgery---

During surgery---

Color Ascites fluid---

Omentum cake---

Tumor involved both ovaries---

Tumor involved only Pelvic structures---

Tumor involved distant abdominal structures ----

Frozen abdomen ----

Types of surgery-----

Oophorectomy ----

Salpingoophorectomy---

Total Abdominal Hysterectomy plus BSO

Total Abdominal Hysterectomy plus USO

Others---

Stage at diagnosis

Stage I ---

Stage II---

Stage III---

Stage IV---

Not indicated--

Or

Early stage--

Advanced stage---

Not indicated—

Outcome at MNH

Discharged---

Referred for chemotherapy---

Died---

Others---

Date of arrival at ORCI----

Chemotherapy

Neoadjuvant chemotherapy only---

Neoadjuvant chemotherapy followed by surgery-----

Surgery followed by chemotherapy---

Not indicated---

Date of start of chemotherapy----

Name of chemotherapy----

Number of cycle of chemotherapy------

Date of completion of chemotherapy----

Conservative management---

Others -------

Outcomes

Referred---

Discharged--

Died---

Others--

Loss to follow-----

Duration of hospital stay ---

Follow up visits----

Number of Follow up visits

Recurrence---

Others----------

Appendix III: Ethical Clearance

MUHIMBILI UNIVERSITY OF HEALTH AND ALLIED SCIENCES
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Ref. No. MU/ PGS/SAEC/Vol. IX/

29th June, 2017

Dr. Wilmot Lorenzo Smith
MMed. Obstetrics and Gynaecology
MUHAS.

RE: APPROVAL OF ETHICAL CLEARANCE FOR A STUDY TITLED: "THE MANAGEMENT OF OVARIAN CANCERS AT MUHIMBILI NATIONAL HOSPITAL"

Reference is made to the above heading.

I am pleased to inform you that, the Chairman has, on behalf of the Senate, approved ethical clearance for the above-mentioned study. Hence you may proceed with the planned study.

The ethical clearance is valid for one year only, from 29th June, 2017 to 28th June, 2018. In case you do not complete data analysis and dissertation report writing by 28th June May 2018, you will have to apply for renewal of ethical clearance prior to the expiry date.

Prof. Andrea B. Pembe
DIRECTOR OF POSTGRADUATE STUDIES

cc: Director of Research and Publications
cc: Dean, School of Medicine

Appendix IV: Introduction letter to Muhimbili National Hospital

MUHIMBILI UNIVERSITY OF HEALTH AND ALLIED SCIENCES
OFFICE OF THE DIRECTOR OF POSTGRADUATE STUDIES

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Ref. No. HD/MUH/L.121/2015

3rd July, 2017

Executive Director
Muhimbili National Hospital
P.O. Box 65000
DAR ES SALAAM.

Re: INTRODUCTION LETTER

The bearer of this letter Dr. Wilmot L. Smith is a student at Muhimbili University of Health and Allied Sciences (MUHAS) pursuing MMed.Obstetrics and Gynaecology.

As part of his studies he intends to do a study titled:"***The Management of ovarian cancers at Muhimbili National Hospital".***

The research has been approved by the Chairman of University Senate.

Kindly provide him the necessary assistance to facilitate the conduct of his research.

We thank you for your cooperation.

Ms. A. Ndyeikiza
For: DIRECTOR, POSTGRADUATE STUDIES

cc: Dean, School of Medicine
cc: Dr. Wilmot L. Smith

Appendix V: Introduction letterto Ocean Road Cancer Institute

MUHIMBILI UNIVERSITY OF HEALTH AND ALLIED SCIENCES
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Ref. No. HD/MUH/L.121/2015

5th July, 2017

Executive Director
Ocean Road Cancer Institute
DAR ES SALAAM.

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cc: Dean, School of Medicine
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