TREATMENT OUTCOME AND ASSOCIATED FACTORS FOR OVARIAN CANCER PATIENTS ATTENDED AT OCEAN ROAD CANCER INSTITUTE DAR ES SALAAM, TANZANIA

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By

Nuru Festo Mlagalila

A Dissertation Submitted in (Partial) Fulfilment of the Requirements for the Degree of Master of Medicine (Clinical Oncology) of

Muhimbili University of Health and Allied Sciences
October, 2017

CERTIFICATION

The undersigned certifies that he has read and hereby recommends for acceptance by Muhimbili University of Health and Allied Sciences a dissertation entitled: ***"Treatment outcome and associated factors for ovarian cancer patients attended at Ocean Road Cancer Institute, Dar Es Salaam, Tanzania"*** in (partial) fulfilment of the requirements for the degree of Master of Medicine (Clinical Oncology) of Muhimbili University of Health and Allied Sciences.

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Dr. Nazima J. Dharsee

(Supervisor)

_____

Date

DECLARATION AND COPYRIGHT

I, **Dr. Nuru Mlagalila**, 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.

Signature: …… **Date**:……

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DEDICATION

This work is dedicated to my lovely family.

ABSTRACT

Ovarian cancer is a common malignancy among women in Tanzania and worldwide. It is associated with high morbidity and mortality especially in developing countries. Surgery and chemotherapy plays major role in the management of ovarian cancer. Response to treatment is influenced by several clinical factors like disease stage, initial tumor burden, histology, performance status of the patient, modality of treatment and age of the patient.

Objective: To explore the social demographic characteristics, histological presentation, treatment modalities and treatment outcome of the patients with ovarian cancer who had attended at Ocean Road Cancer Institute, Tanzania from 2012 to 2016.

Patients and methods: This is a retrospective cross sectional study designed to determine one year overall survival among ovarian cancer patients, and factors related to it. Data were obtained from patients medical files and filled into data collection form. Data was collected from patients who were diagnosed from January 2012 to January 2016. This study was done at Ocean Road Cancer Institute, Dar Es Salaam.

A total of 96 patients with ovarian carcinoma with all stages and histological confirmation, were followed up one year post treatment. Patients were treated either with surgery alone, or surgery then chemotherapy or neoadjuvant chemotherapy followed by surgery then adjuvant chemotherapy, and lastly those who received chemotherapy alone.

Evaluation and analysis**:** Patients were evaluated one year post treatment. Survival was evaluated using Kaplan Meir method. Social demographic and Clinical factors were analyzed using frequency and percentage as well as mean and standard deviation. Survival curves were estimated by the Kaplan-Meier method. To identify factors predictive of survival outcome the variables were analyzed by univariate analysis by using log-rank test and multivariate analysis by using Cox Regression model. All drop outs were considered as censored. An association was regarded as statistical significance if the p-value < 0.05.

Results

A total of 96 patients were included in the analysis among them 22 were in curative intent group (treated according to NCCN protocol and ORCI protocol for ovarian cancer) and 74 were in palliative intent group(all patients who were under treated). Mean age 51.4 years with the range of 19 years up to 97 years, standard deviation of 17.3. Most patients had epithelial cell tumor about 85.4%. In most patients, 55.2%, surgery was done first followed by chemotherapy while 27.1% had surgery alone and about 12.5%, received chemotherapy alone and only 5.2 % received neoadjuvant chemotherapy followed by surgery and then finished up with adjuvant chemotherapy. Most patients received taxanes and platinum based chemotherapy (60.3%), followed by BEP (Bleomycin, Etoposide and Cisplatin) 6.3% patients and other chemotherapy regimen 6.3%. Among patients who received chemotherapy only 27% received more than 6 cycles.

Overall survival and associated factors

After one year, among 22 patients who were in curative intent group, only 4 had passed away while in palliative group we had 74 patients and 40 patients had passed away after one year post treatment. Patients who have received curative treatment had more survival 82% as compared to the patients who had received palliative treatment 40% (P value 0.003). In both curative intent and palliative intent group, patients who received chemotherapy less than 35 days from time they had surgery had better survival compared to patients who received chemotherapy more than 35 days from surgery with p value 0.02 and 0.001 respectively.

In curative intent group, OS was favoured more in age below 51 years (p value 0.001). Patients with no residual disease, early stage and less than ECOG 2, had better OS, though the association was not statistically significant. Also OS had no association with histological type of tumor, number of chemotherapy cycles or type of chemotherapy in curative intent group.

In palliative intent group, patients who came earlier to ORCI for adjuvant treatment(within 30 days of surgery) had better survival when compared to patients who came late and the association was statistically significant (p=0.001). Furthermore, in this group patients who had ECOG status less than 2 and FIGO stage three had better survival with p value 0.04 and

p=0.04 respectively. There was no association between OS and histology type (p=0.907), number of cycles (p=0.667) nor treatment modality in palliative intent group (p=0.135).

Conclusion:

The study has shown that patients in curative intent group had greater survival than in palliative intent group and in both groups, delay in starting chemotherapy more than 35 days after surgery is associated with poor overall survival. In curative intent group, younger age was associated with good Overall survival while in palliative intent group poor ECOG status was associated with poor overall survival.

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ABBREVIATIONS

AIDS	Acquired Immunodeficiency Syndrome
CA 125	Cancer Antigen 125
CI	Confidence Interval
CXR	Chest X-ray
EOC	Epithelial Ovarian Cancer
ERT	Estrogen Replacement Therapy
HIV	Human Immunodefficiency Virus
HRT	Hormonal replacement therapy
MUHAS	Muhimbili University of Health and Allied Sciences
NCI	National Cancer Institute
OC	Oral contraceptives
OR	Odds Ratio
ORCI	Ocean Road Cancer Institute
USPTF	United States Prevention services Task Force
USS	Ultrasonography Scan

DEFINITIONS OF KEY TERMS

Ovarian Cancer: Is abnormal growth of ovarian cells commonly epithelia cells

Treatment Outcome: This is overall survival following treatment.

Clinical Features: Conditions associated with course of certain disease

Histology: The study of structures seen under microscopy (microscopic anatomy)

Curative intent: Refers to health care practices that treat patients with the **intent** of curing them, not just reducing their pain or stress.

CHAPTER ONE

1.0 INRODUCTION

1.1 Background

Ovarian cancer is one of the frequent causes of cancer death from gynaecologic tumors in the United States(1). Cancer of the ovary is the sixth most frequent cancer in women worldwide and accounts for less than 5% of all cancers in women. In the United States, the incidence of ovarian cancer is 12.1 per 100,000 women per year, based on 2008-2012 cases. The incidence of ovarian cancer has been slowly decreasing since the mid-1980s; it decreased by 0.9% per year from 2007 to 2011.(2) . In Tanzania annual mortality rate (per 100,000) is 0.4. At ORCI 2014 the total number of patients attended were 49 patients.

The higher the number of ovulatory cycles, the greater is the risk of the disease. Therefore factors associated with suppression of ovulation such as pregnancy and oral contraceptive usually have a protective effect.

Late menopause, use of replacement therapy and family history of breast cancer increase risk of ovarian cancer while contraceptive use has a protective effect (3) also BMI can increase the risk of ovarian cancer.(4) There is an increase risk of having nonmucinous histological type with increase in number of lifetime ovulatory cycles but all histological types has been decreased with use of contraceptives. (5).Increase number of children and older age at menarche decrease risk of ovarian cancer(6). Women using estrogen replacement therapy show an increase incidence of endometrial cancer (7) but the use of combination oral contraceptives(OC) formulations with high-progestin potency has been associated with reduction in ovarian cancer risk than the ones with low-progestin potency.(8)

Epithelial ovarian cancer can occur in girls as young as 15 years, but the mean age at diagnosis is 63 years, and most cases are diagnosed in women 55-64 years of age. In the United States, the estimated lifetime risk is 1.3%.

Clinical Manifestation

Early ovarian cancer causes minimal, nonspecific, or no symptoms.

Symptoms independently associated with the presence of ovarian cancer include pelvic and abdominal pain, increased abdominal size and bloating, and difficulty eating or feeling full. Symptoms associated with later-stage disease include gastrointestinal symptoms such as nausea and vomiting, constipation, and diarrhoea. Physical findings are uncommon in patients with early disease. Patients with more advanced disease may present with ovarian or pelvic mass, ascites, pleural effusion, or abdominal mass or bowel obstruction.

Diagnosis

The presence of advanced ovarian cancer is often suspected on clinical grounds, but it can be confirmed only pathologically by removal of the ovaries or, when the disease is advanced, by sampling tissue or ascitic fluid.

Imaging procedures like abdominal pelvic Utrasound, CT Scan and MRI can be used for staging

The US Preventive Services Task Force (USPSTF) recommends against screening (with serum CA125 level or transvaginal ultrasonography) for ovarian cancer in the general population.

NCCN PROTOCOL, 2016

This is NCCN protocol 2016 which gives us guideline on treatment of epithelial ovarian cancer.

Stage	Grade	Adjuvant treatment
Stage 1a or 1b	Grade 1	Observe
	Grade 2	Observe or IV taxane/carboplatin for 3-6cycles
	Grade 3	IV taxanes/carboplatin for 3-6 cycles
Stage 1c	Grade 1,2,or 3	IV taxane/carboplatin for 3-6 cycles
Stage II Stage III Stage IV		Intraperitoneal chemotherapy for <1cm optimal debulked stage III patients OR IV taxane/carboplatin for a total of 6-8 cycles Completion surgery as indicated by tumor response and potential respectability in some selected patients

Malignant germ cell tumors

BEP (Bleomycin 30 units per week ,etoposide 100mg per m2 daily for day 1-5, cisplatin 20 mg/m2 daily for day 1-5). Repeat cycle every after 21 days.

For selected patient with stage IB-III resected dysgerminoma for whom minimizing toxicity etoposide/ carboplatin can be used (Carboplatin 400mg/m2 on day 1 plus etoposide 120mg/m2 on day 1,2 and 3 every 4 weeks for 3 cycles).

Malignant sex cord stromal tumors

BEP (Bleomycin, etoposide and cisplatin).

Follow Up

Elevations in CA125 and radiological findings may precede symptoms of recurrence by several months. While detection of recurrences by physical exam alone is unusual, a thorough exam in conjunction with reported symptoms and elevated CA125 is sufficient to detect 80-90% of recurrences. A spiral CT scan may be used to confirm recurrence in the setting of asymptomatic CA125 elevation and a PET/CT can yield additional insight if the CT is inconclusive. Initiating chemotherapy prior to the development of symptoms, even in the setting of elevated CA125, does not impact overall survival. More information about tumor biology and ways to predict which patients will benefit from available treatment options is required. Consequently, the approach to post-treatment surveillance should be individualized taking into account the clinical benefit of the second-line therapy, versus the costs and morbidity of the surveillance method.(1)

Most of ovarian cancer patients who attend at ORCI are from other hospitals where surgery in most cases is already done. At ORCI basic investigations are usually done for example abdominal pelvic Utrasound and chest X-ray to assess if there is liver and lung metastasis. Renal function test and full blood count to assess if the patient is eligible for chemotherapy.
Most patients receive Taxane and platinum based chemotherapy. Then the patients are being followed up every three month post treatment.

1.2 Literature Review

Risk Factors

Decrease socioeconomic status is associated with increase risk for ovarian cancer.(9) Histologically, mucinous or clear-cell histology is associated with a worse PFS (progression free survival) and OS compared with serous carcinoma, also patients with poor performance status(PS) and patients with microscopic residual disease have an increased risk of recurrence and death.(10). Carriers of a breast ovarian cancer susceptibility gene have an increase chance of having breast or ovarian cancer mostly at the age of 59 years.(11)

Treatment modalities and treatment outcome

A study by Piccart et al showed that, paclitaxel and carboplatin are recommended as a new standard regimen for treatment of patients with advanced ovarian cancer(12)**.** Cisplatin is being used as second line therapy, as it has showed to be effective in increasing overall median survival.(13). ECOG status is the major determinant of prognosis as it has shown in study by Onetto N et al (14)there is better response to treatment with better ECOG status. Use of 3 cycles compared to 6 cycles of Carboplatin and Paclitaxel, 6 cycles do not significantly alter the recurrence rate in high risk early stage EOC but are associated with more toxicity (15) while an ICON 1(International Collaborative Ovarian Neoplasm study) study by Mannel et al showed that patients with early stage ovarian cancer can receive 3 cycles then (16)observe rather than maintenance paclitaxel weekly for 24 weeks (17)

A study by ICON collaborators showed that platinum-based adjuvant chemotherapy improves survival and delays recurrence in patients with early stage ovarian cancer (18)**.** Topotecan and Paclitaxel has been used as a second line treatment for ovarian cancer but a multicenter study by Wim B et al, showed that there is no difference in median survival in patients treated with topotecan compared with paclitaxel (19), also Cisplatin/Paclitaxel or carboplatin /paclitaxel regimen has been used as first line treatment for ovarian cancer but the study done by Bois A et al showed there were no difference in progression-free or overall survival in patients received either of the regimen (20). There is advantage of using bevacizumab in patients with

advanced epithelial ovarian cancer after first line treatment as it prolongs the median progression-free survival by about 4 months as reported by Fleming GF et al .(21)

An increased initial disease burden remained a significant prognostic indicator despite type of surgery done. In study by Horowitz NS et al showed that increase disease Burden is associated with shorter progression free survival and overall survival as compared with those with moderate or low disease burden respectively (22)but patients with gross residual disease who receive Intraperitoneal therapy have enhanced survival which is best improved with increasing number of Intraperitoneal cycles.(23). Patients with optimal surgical debulking and better performance status have more survival as compared to those with suboptimal debulking, in patients with Stage IV epithelial ovarian cancer. This also has been seen in patients with unresectable liver metastasis, where by optimal debulking of extrahepatic disease is associated with a significant survival advantage. (24) (25)

Use of panipazonib has been in high use in developed countries, but study by Kim J et al, showed maintenance pazopanib only prolong progression-free survival with no difference in Overall survival (26) also use of Bevacizumab cause improvement in gastrointestinal symptoms during chemotherapy for platinum-resistant ovarian cancer. (27) Study by Bristow et al showed that, maximal cytoreduction is a powerful determinant of survival among patients with stage III or IV ovarian carcinoma. (28)

The study done by Kuhn W et al showed that higher tumor resection rates are associated with longer median survival. (29) Moreover, study by Hegazy et al, showed that primary chemotherapy followed by interval debulking surgery in a select group of patients permits a less aggressive surgery to be performed(30).

A study done by Morrison et al showed that, there is no difference between patients who had neoadjuvant chemotherapy versus surgery as initial treatment for ovarian cancer. Another study by Morice P et al showed that, the only prognostic factor for patients with advanced stage borderline tumour is the type of peritoneal implant. (31)

Time interval between surgery and chemotherapy

Study by Seagle BC et al, showed that survival benefit may be obtained by starting chemotherapy between 21 and 35 days from primary debulking surgery. (32) and this was supported by study done by Tewari KS et al, which showed that survival for women with advanced ovarian cancer may be inversely affected when initiation of chemotherapy occurs more than 25 days following surgery. (33).

A study done by Concin et al showed that delayed initiation of chemotherapy might compromise overall survival especially when the tumor was suboptimally debulked(34). However, study by Mahnar et al showed no difference in survival with time interval between surgery and chemotherapy.(35). A study done by Wright DJ showed that, extended cytoreductive surgery and perioperative complications significantly delay initiation of chemotherapy (36)

A study done by Gadducci et al showed that, the interval from surgery to the start of taxane plus platinum-based chemotherapy seems to have neither a predictive value for response to treatment nor a prognostic relevance for survival of advanced ovarian cancer patients(37)

Use of single agent carboplatin in treatment of advanced ovarian cancer

The ICON 3 study, by Petty RD et al showed that single-agent carboplatin or cisplatin are as effective as a paclitaxel/carboplatin combination in survival terms when used as first line therapy in advanced ovarian cancer (38) and an ICON 3 study by David Michelin et al, showed that there is an impact of single agent carboplatin on progression-free survival. (39)

1.3 Problem Statement

Ovarian cancer is among common causes of gynaecological malignancy death in Tanzania and other Sub-Saharan countries.

In Tanzania there was no study that has been done to assess survival in patients who have been treated for ovarian cancer at ORCI. Therefore we had no current data on survival of ovarian cancer patients treated at this centre.

Most of our patients come from upcountry and usually they come late for chemotherapy after surgery and this might affect the overall survival. However, we did not know if the time from surgery to arrival at ORCI and time from surgery to starting chemotherapy affected overall survival and the magnitude of that effect.

Patients with ovarian cancer usually present with late stages but optimal cytoreductive surgery with chemotherapy can ensure long term survival. Therefore this study will be able to provide necessary information on overall survival and predictors of overall survival in patients with ovarian cancer.

1.4 Study Rationale

The study will help to evaluate treatment modalities for ovarian cancer and their response in terms of survival. Therefore the results of this study will contribute in making sound and evidence based clinical decisions locally and hence improving patients care.

This study will also assess the association between chemotherapy delay with and overall survival .This information will be used in addressing the referral system to reduce the delays and ultimately improve the standard of care for ovarian cancer patients.

Finally,the study findings will open the room for more research on new management options for ovarian cancer in pace with the developed world.

1.5 Research Question

1. What are the socio-demographic characteristics of patients with ovarian cancer patients treated at ORCI?
2. What are the histological presentation of ovarian cancer patients attending at ORCI?
3. What are the treatment modalities offered to ovarian cancer patients attending at ORCI?
4. What is the impact of time delay to start adjuvant chemotherapy on overall survival?
5. What is the one year overall survival for ovarian cancer patients who have been treated at ORCI?

Null hypothesis

There is no difference in overall survival of patients with ovarian cancer with regard to social demographic factors, histological presentation and treatment modality.

Alternative hypothesis

There is a difference in overall survival of patients with ovarian cancer with regard to social demographic factors, histological presentation and treatment modality.

1.6 Objectives

1.6.1 Broad Objective

To explore the social demographic characteristics, histological presentation, treatment modalities and one year overall survival of the patients with ovarian cancer who had attended at Ocean Road Cancer Institute, Tanzania from January 2012 to January 2016.

1.6.2 Specific Objectives

1. To describe the socio-demographic characteristics of patients with ovarian Cancer who presented at ORCI from 2012 to 2016.
2. To determine the histological presentation of ovarian cancer patients attending at Ocean Road Cancer Institute, Tanzania from 2012 to 2016.
3. To describe the treatment modalities of ovarian cancer patients attending at Ocean Road Institute, Tanzania from 2012 to 2016.
4. To determine time from diagnosis to arrival at ORCI and time from surgery to chemotherapy for patients treated from 2012 to 2016 and correlate with one year OS.
5. To determine the one year overall survival of ovarian cancer patient treated at Ocean Road Cancer Institute, Tanzania from 2012 to 2016.

CHAPTER TWO

2.0 METHODOLOGY

2.1 Study design

The study is a retrospective cross sectional study of ovarian cancer patients treated from 2012 to 2016.

2.2 Study setting

The study was conducted at Ocean Road Cancer Institute in Dar es Salaam, Tanzania. Ocean road cancer institute offers inpatient and outpatient services like diagnostic imaging, laboratory services, radiotherapy, chemotherapy, palliative care services, screening for breast and cervical cancer, HIV/AIDS care and trainings for undergraduates and postgraduates.

TREATMENT PROTOCOL AT ORCI

Below is the summary of the ORCI treatment protocol for ovarian cancer.

PRE-OPERATIVE

CA 125 –is used as a tumor marker for follow-up in epithelial tumors while in non epithelial ovarian cancer, the tumor markers includes Alpha feto-protein, B-HCG, CEA, Ca 19-9. The primary management of ovarian cancer is surgery to optimally debulk the tumor.

ADJUVANT THERAPY

For stage I: Adjuvant Chemotherapy is not given only for Stage 1a, for stage 1b and for stage 1c is optional from 3 to 6 cycles.

Choice of regimen:

Carboplatin 400mg/m2 + paclitaxel 135mg/m2. This is preferred to Cisplatin 75mg/m2 + Taxol due to long term nephrotoxicity for cisplatin.

For stage II-IV, should receive 6-8 cycles of paclitaxel and carboplatin for epithelial tumors and for non epithelial tumors receive bleomycin, Etoposide and Platinum based chemotherapy.

RECURRENT OVARIAN CANCER

The choice of a second-line regimen depends on the disease-free interval.

1. For patients with platinum-sensitive disease - 12 months remission – retreat with platinum.

2. Failure within 6 months is regarded as progressive disease on treatment. Several agents have been shown to have activity in refractory ovarian cancer and should be considered like Cyclophosphamide, 5 FU and leucovorin and Etoposide.

3. Between 6 and 12 months - Patients may respond to platinum based chemotherapy.

IRRESECTABLE OVARIAN CARCINOMA

1. Debulking surgery is undertaken if the patient is fit enough.
2. An alternative approach is to give three cycles of chemotherapy, then, if the CA 125 drops by two standard deviations, then proceed to debulking surgery.

2.3 Study participants

Target population: All patients with diagnosis of ovarian cancer in Tanzania.

Accessible population: All patients referred to ORCI for treatment with diagnosis of ovarian cancer.

Study population: All patients with ovarian cancer who fulfil the eligibility criteria.

2.4 Eligibility criteria

2.4.1 Inclusion criteria

All patients, 18 years and above, referred to ORCI with histological diagnosis of ovarian cancer from 2012 to 2016, and whose baseline characteristics were determined before beginning of the therapy and had at least 3 follow-up visit for 12 month from finishing treatment.

Curative intent group: All patients who received curative treatment as in NCCN protocol

This included patients who had cytoreductive surgery and had received curative dose and adequate number of chemotherapy cycles as per NCCN guidelines i.e for stage 1B can either receive 3-6 cycles or observe, and 6 cycles for other stages of adjuvant chemotherapy which include platinum and taxanes for epithelial tumors and Bleomycin, Etoposide and Platinum compounds for germ cell tumors and sex cord tumors. Then the curative group was divided between patients with no residual disease after surgery and those with residual disease.

Palliative intent group: Includes all patients who were undertreated due to multiple factors like very advance stage.

2.4.2 Exclusion criteria

Patients who had previous chemotherapy or radiotherapy due to same or different malignancy, or who had incomplete medical records especially surgical notes.

End points

Overall survival was calculated from end of treatment to death or loss of follow up where by loss of follow up was defined as failure to attend 2 or more follow up clinics.

Death was confirmed through medical records by checking death certificate or contacting next of kin.

Alive was defined as patient being alive at last follow up clinic scheduled or alive after confirming with next of kin.

2.5 Sampling procedure

Eligible patients who attended ORCI between 2012 and 2016 with a diagnosis of ovary cancer were identified from the central hospital register. Hospital case notes were retrieved for each patient. Details about patient demographics, diagnosis, disease severity and laterality, time from surgery to ORCI and time from surgery to starting chemotherapy, treatment modality and outcome, was recorded. Stage was obtained post surgical and CXR and abdominal pelvic USS was used to assess lung and liver metastasis respectively.

2.6 Data collection

Research assistants under the supervision of the principal investigator used data extraction forms to retrieve data from patients records stored in manual files and or files on computer. The data extraction forms captured demographic characteristics, severity of disease, treatment modalities and primary end point and other variables of interest. During this time in case of missed two or more clinics we contacted next of kin, if the patient is dead then we had to know exactly date of death and if failed to do so we consider as loss of follow up.

2.7 Data Management and Statistical Analysis

Data Management

The data extraction forms were carefully reviewed for completeness and consistency. In case of missing or inconsistent data we checked the patient periodical records or medical registers while ensuring most confidentiality of patient records and identity.

2.8 Study variables

Independent variables

- Demographic characteristics (age, education, occupation)
- FIGO Stage of the disease
- Histological type of the disease
- ECOG performance status

- Type of treatment received
- Chemotherapy type received
- Number of chemotherapy cycles received
- Time from diagnosis to presentation at ORCI.
- Time from surgery to start chemotherapy
- Treatment intention

Dependent variables

One year overall survival

2.9 Study Area

This study was conducted at Ocean Road Cancer Institute. It is located along Indian Ocean in Dar-Es Salaam, Tanzania.

The facility is one of the oldest health centre in Tanzania established in 1895 by German Colonial Government. It offers clinical services and training programs for undergraduates and postgraduate students as well as other health care workers.

The hospital has service for inpatient and outpatient cares both public and insurance companies like National Health Insurance and Tanesco.

2.10 Data Collection

In this study, data was collected after ethical clearance was granted by Institutional Review Board of MUHAS and accepted by the ORCI administration. The research assistants collected sociodemographic information that comprised of age, residence, level of education and occupation, as well as ECOG performance status of the patients, time from surgery to starting chemotherapy and time from diagnosis to ORCI. A pilot study was done to evaluate the user friendliness of the designated form. A total of ninety six cases of ovarian cancer were identified and found eligible for inclusion in the study from 2012-2016.

2.11 Data Management

The data extraction form was carefully reviewed for completeness and consistency. Data was recorded in a secured computer where access is restricted to ensure maximum confidentiality.

2.12 Quality control

The data obtained was coded, edited and cleaned before any statistical analysis was carried out on the data. Additional internal documentations such as variable and value labels was added and any necessary additional variables was created through algebraic or logical expressions. Data capture sheet was pre-tested to improve consistency. Data was double checked entered to control for errors.

2.13 Data Analysis

Data entry and data analysis was done using the SPSS version 21 for windows. Social demographic and Clinical factors was analyzed by using frequency and percentage as well as mean and standard deviation. Survival curves were estimated by the Kaplan-Meier method. To identify factors predictive of survival outcome the variables were analysed by univariate analysis by using log-rank test. Factors which were found significant on univariate analysis were assessed using multivariate analysis by using Cox Regression model. All drop outs were considered as censored. An association was regarded as statistical significance if the p-value < 0.05.

2.14 Ethical Clearance

Before doing this study, the study protocol was submitted to MUHAS High Degree Research and Publications Committee for ethical clearance. The permission to do the study at ORCI was given from the Institutional Review Board ORCI. To ensure confidentiality patients names were not included in the data collecting form. The files were immediately returned to medical records department soon after data extraction.

In case of missing information, telephone was used to contact next of a kin to volunteer to give patients information. If the information given by the volunteering next of a kin was death then exact date of death was sought and recorded.

CHAPTER THREE

3.0 RESULTS

This paragraph presents the analysis of the data and findings as far as the treatment outcome of ovarian cancer patients. Broadly it analyses and discusses issues related to clinical and histology presentation of ovarian cancer patients, treatment modalities of ovarian cancer patients and the treatments outcomes of ovarian cancer patients presented at ocean road cancer institute from 2012 to 2016. It also analyses the socio-demographic characteristics of the patients under study; specifically among other issues the study has identified and discussed the variables related to age, level of education and occupation.

A total of 126 patients with ovarian cancer, were treated at ORCI from January 2012 to January 2016. Among them only 96 met the eligibility criteria. About 30 patients were not able to be included in the study due to number of reasons. Among them 22 were having incomplete medical records especially surgical notes on admission with no telephone number and 8 had previous exposed to chemotherapy and radiation.

Table 1: Demonstrating distribution of social-demographic characteristics of study participants (n=96)

Variable		Frequency	Percent
Age	<51 years	49	51
	>51 years	47	49
Education level	None	30	31.2
	Primary education	47	48.9
	Secondary education	8	8.3
	Post secondary	11	11.5
Occupation	Peasant	11	11.5
	Housewife	21	21.5
	Student	7	7.3
	Civil servant	9	9.4
	Self employed	25	26.0
	Unknown	23	24.0
Residential area	Northern zone	23	24.0
	Coastal zone	41	42.7
	Lake zone	4	4.2
	Central zone	14	14.6
	South zone	5	5.2
	Zanzibar	9	9.4

According to table 4, majority of the study participants were less than 51 years old (51%). The mean and median age at diagnosis were 51.4 and 53 years respectively. Most of the study participants had primary school education (48%) and majority were self employed (26%). Almost half of the study participants (42.7%) were coming from coastal zone.

Table 2: Distribution of clinical characteristics of study participants(n=96)

Variable		**Frequency**	**Percent%**
ECOG	<2	8	8.3
	>2	88	91.7
Disease stage	One	1	1.0
	Two	3	3.1
	Three	7	7.3
	Four	85	88.5
Histology type	Epithelia tumors	82	85.4
	Non epithelial tumors(germ cell and stromal cell tumors)	14	14.2

According to table 5 most of the patients were stage IV (88.5%). The largest number of patients (91.7%) had ECOG status greater than 2. Most of the patients had epithelial tumors (85.4%).

Table 3: Distribution of treatment modalities of study participants (n=96)

Variable		Frequency	Percentage%
Treatment intention	Curative	22	22.9
	Palliative	74	77.1
Surgery result	No residual disease	4	4.2
	Residual disease	92	95.8
Treatment modality	Surgery alone	26	27.1
	Surgery followed by chemotherapy	53	55.2
	Neoadjuvant chemotherapy then surgery then adjuvant chemotherapy	5	5.2
	Only chemotherapy	12	12.5
Surgery	TAH &BSO	82	85.4
	Unilateral salpingoophorectomy	3	3.1
	inoperable	11	11.5
Chemotherapy type	Taxanes and platinum based	58	60.3
	BEP	6	6.3
	Others	6	6.3
	missing	26	27.1
No of chemotherapy cycles	<6 cycles	44	45.8
	>6cycles	26	27.1
Time from diagnosis to attending at ORCI	<30days	32	33.3
	>30 days	64	66.7
Time from surgery to chemotherapy	<35 days	21	21.9
	>35days	49	51

According to table above, most of the study participants (77%) were treated with palliative intention with only 22.9% receiving curative intent treatment. Most of the patients had residual disease after surgery. The commonest initial treatment modality was surgery followed by chemotherapy (52.3%) and the commonest type of surgery was TAH and BSO (85.4%).

The commonest adjuvant protocol was taxanes and platinum based (60.3%) and majority of patients had less than 6 cycles (46.9%). Most of the study participants had a delay of more than 35 days (51%) before starting chemotherapy.

TREATMENT RESULT

Among 96 patients, 45.8% of the participants were dead while 54.2% were alive after 1 year post treatment. 22.9% the study participants were in the curative intent group while in palliative intent group had 77.1% of the participants. Among them 18 participants (81.8%) were alive at the end of one year in curative group and 34 participants (45.9%) were alive in palliative intent group.

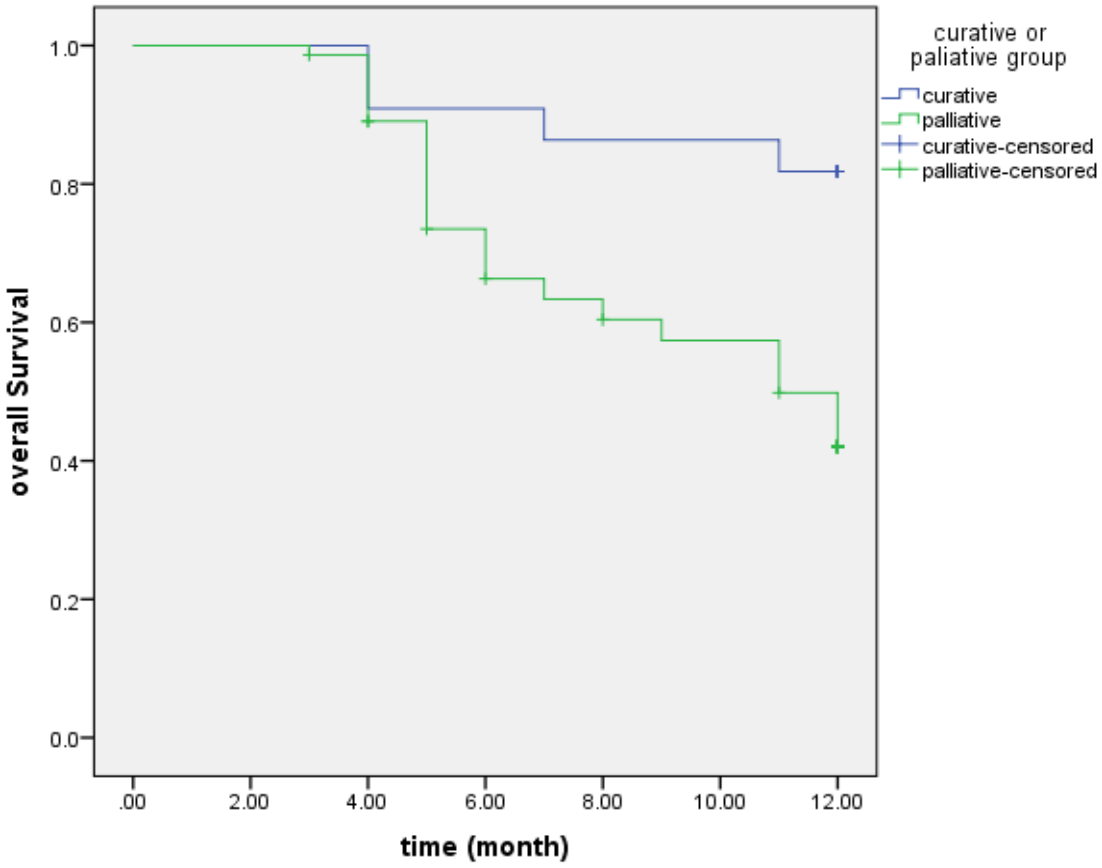


Figure 1: Overall survival rate between curative intent group and palliative intent group

The figure above shows that patients who were treated with curative treatment had a higher 1 year overall survival 82% than those who received palliative treatment 46% (P=0.003)

UNIVARIATE ANALYSIS CURATIVE AND ASSOCIATION FACTORS

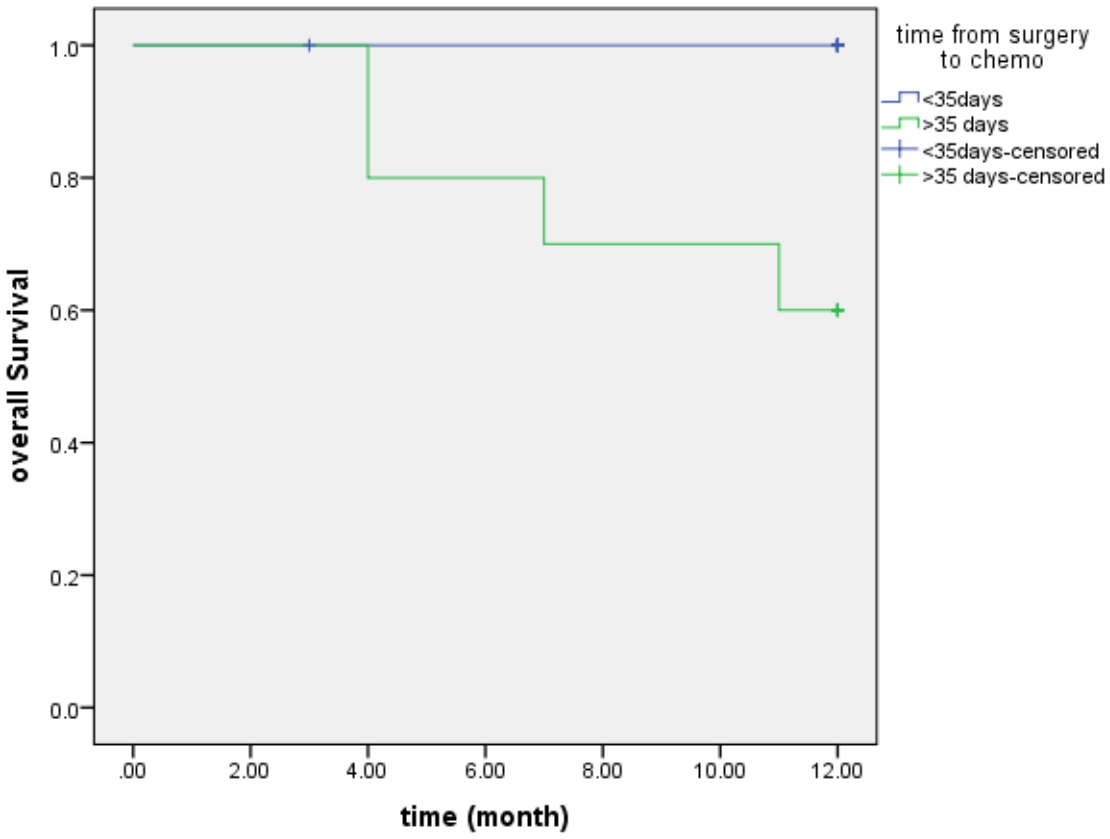


Figure 2: Association of OS and time from surgery to start chemotherapy in curative intent group.

In figure above the patients who received chemotherapy less than 35 days from time they had surgery had greater survival compared to patients who received chemotherapy more than 35 days from surgery in curative intent group and was statistically significant (p=0.02)

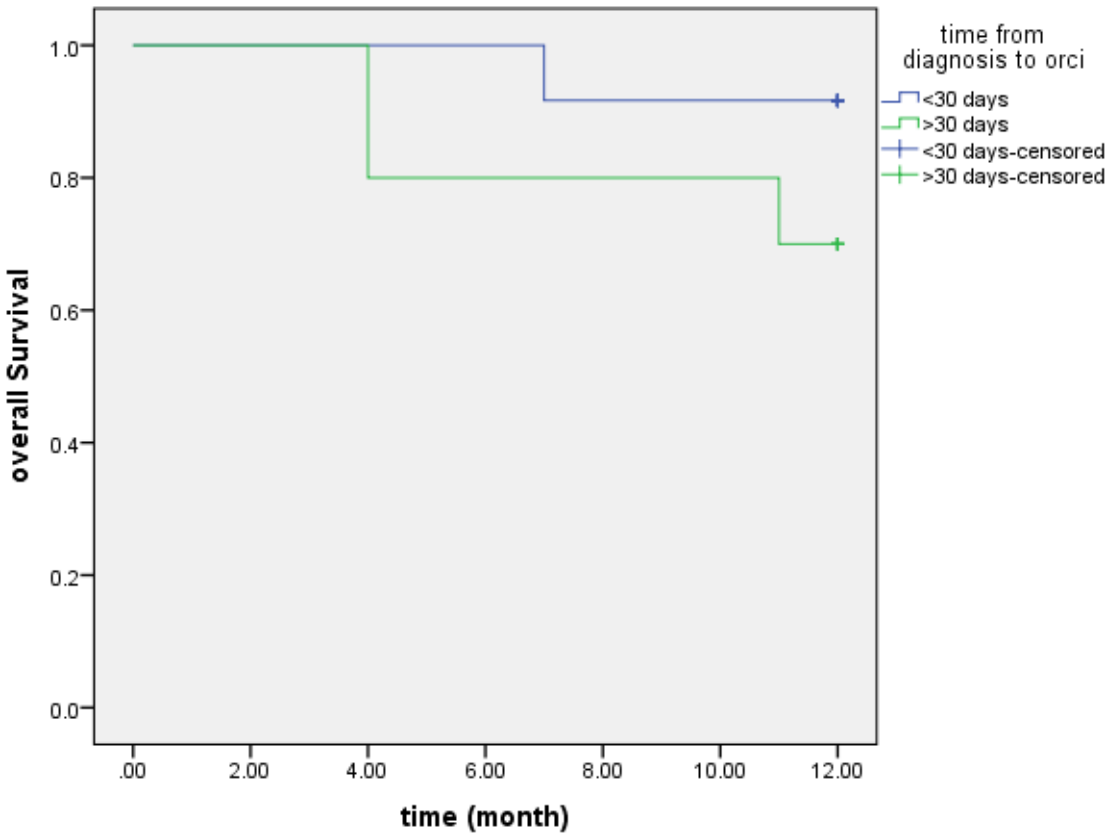


Figure 3: Association between OS and time from diagnosis to ORCI in curative intent group.

Patients who came early less than 30 days had better survival as compared to patients who were late though it wasn't statistical significant in curative intent group (P =.194).

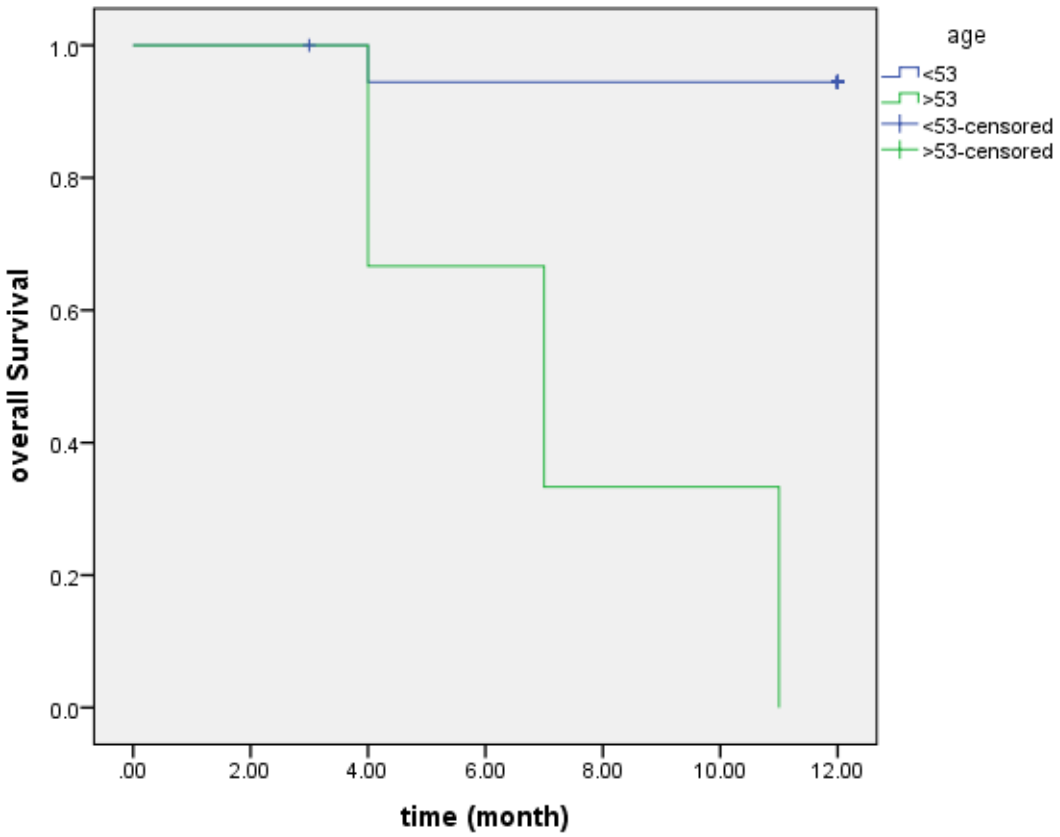


Figure 4: 5The association between OS and age in curative intent group.

Patients who had age below 53 years had more OS as compared to patients with more than 53 years and the association was statistically significant with (p=0.001)

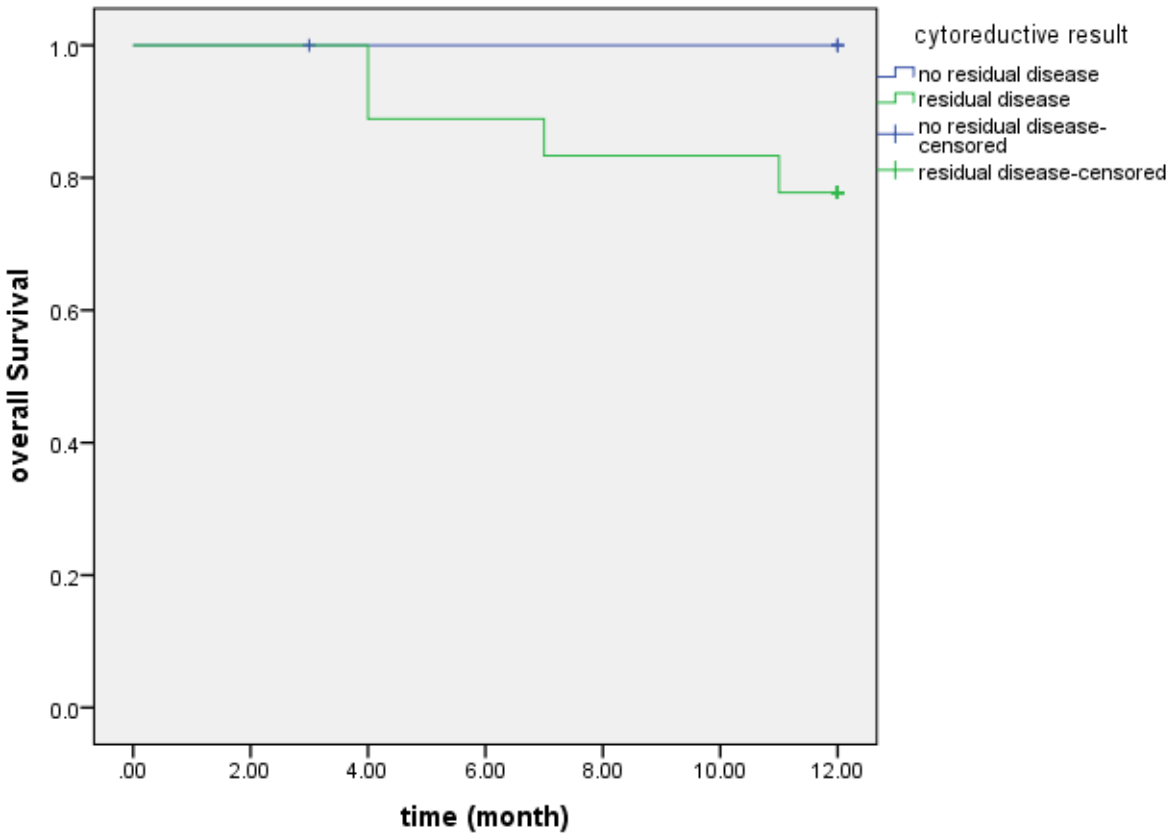


Figure 5: The association between OS and surgery outcome in curative intent group.

Patients with no residual disease stage which include stage 1 and 2 has more survival than patients who had residual disease but the association was not statistical significant.

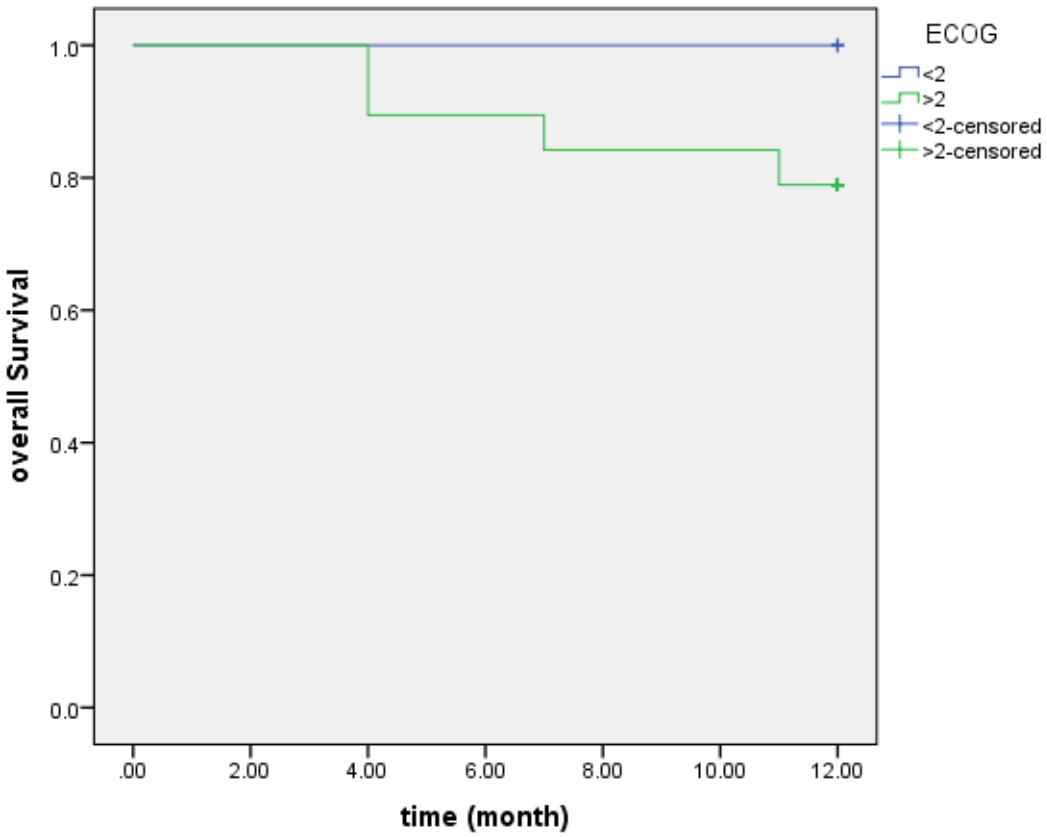


Figure 6: Association of OS with ECOG in curative intent group.

There was no statistical association between ECOG and OS although patients who had ECOG status of less than 2 had more OS as compared to patients with higher ECOG status.

OS had no association with histological type of tumor, disease stage, number of cycle nor type of chemotherapy in curative intent group. There was one patient who had stage 1 and received less than 6 cycles of chemotherapy, hence by NCCN protocol and ORCI protocol, for stage Ib disease, you can either observe or give 3-6 cycles of hence was grouped in curative intent. The rest had six or more cycles.

Table 4: Summary of univariate and multivariate analysis in curative intent group (n=22)

Variable		N	1year Os(%)	Univariate Analysis	Multivariate Analysis
Age	<51 years	19	94.7	0.001	0.04
	>51 years	3	0.0		
Surgery result	No residual disease	4	100	0.32	-
	Residual disease	18	77.8		
Stage	I	1	100		
	II	3	100	-	-
	III	5	100		
	IV	14	69.2		
ECOG	<2	3	100	0.404	-
	>2	19	78.9		
Histology	Epithelia tumors	18	83.3		-
	Non epithelial tumors (Germ cell tumors Sex cord tumors)	4	75	0.772	
Surgery	TAH &BSO	20	80	0.508	-
	Unilateral oophorectomy	2	100		
Time from diagnosis to ORCI	<30 days	12	91.7	0.194	-
	>30 days	10	70		
Time from surgery to chemo	<35 days	12	100	0.02	0.03
	>35 days	10	60		

UNIVARIATE ASSOCIATION OF OS IN PALLIATIVE INTENT GROUP WITH VARIABLES

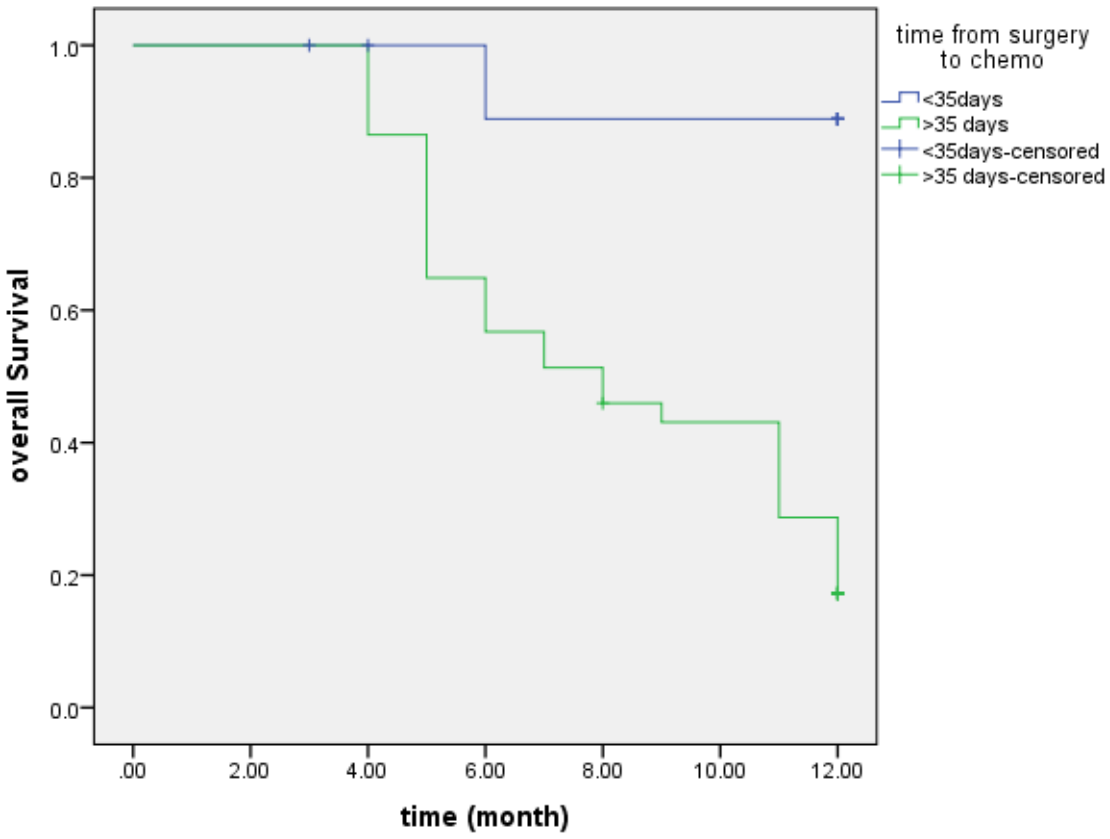


Figure 7: the association between OS and time from surgery to chemotherapy in palliative intent group.

Patients who received chemotherapy less than 35 days from the time they had surgery had better one year survival compared to patients who received chemotherapy in more than 35 days and the association was statistically significant(p=0.001)

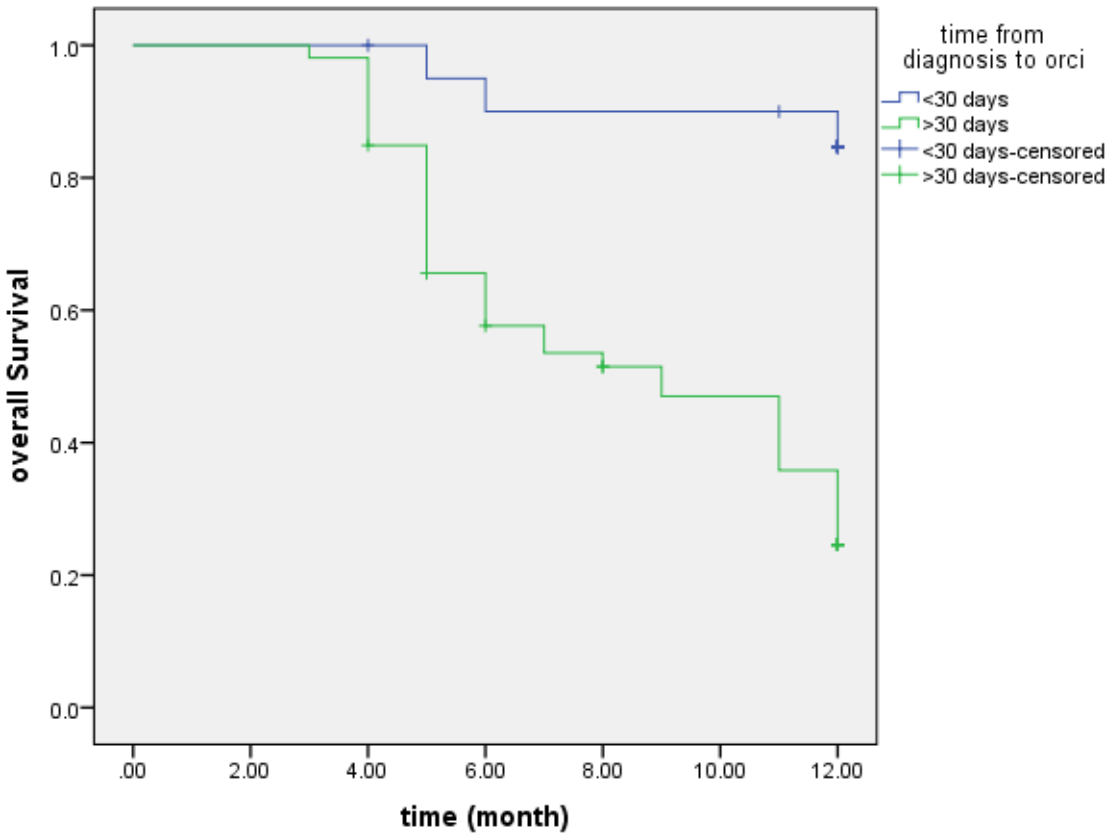


Figure 8: Association between OS and time from diagnosis to ORCI in palliative intent group

Patients who came earlier to ORCI for more treatment had better survival when compared to patients who came late and the association was statistically significant (p=0.001).

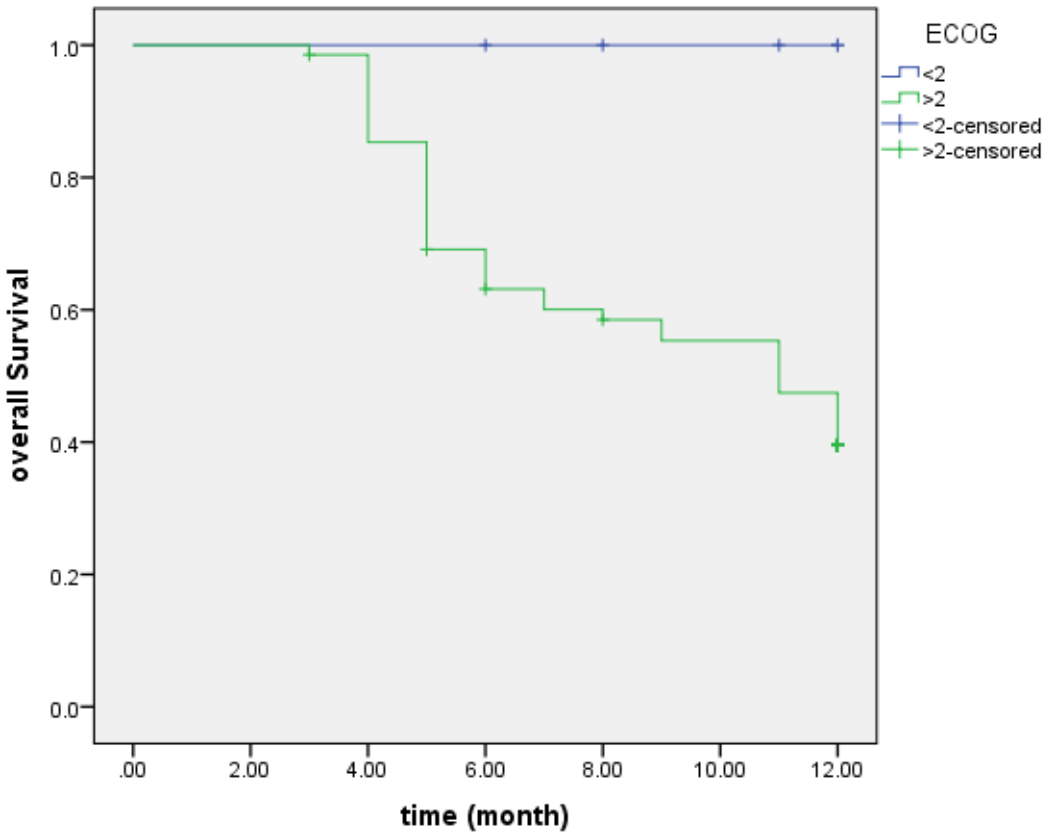


Figure 9: Association between ECOG and OS in palliative intent group

Patients who have ECO status less than 2 has more survival than patients with ECOG status greater than 2 and was statistically significant with p value 0.04

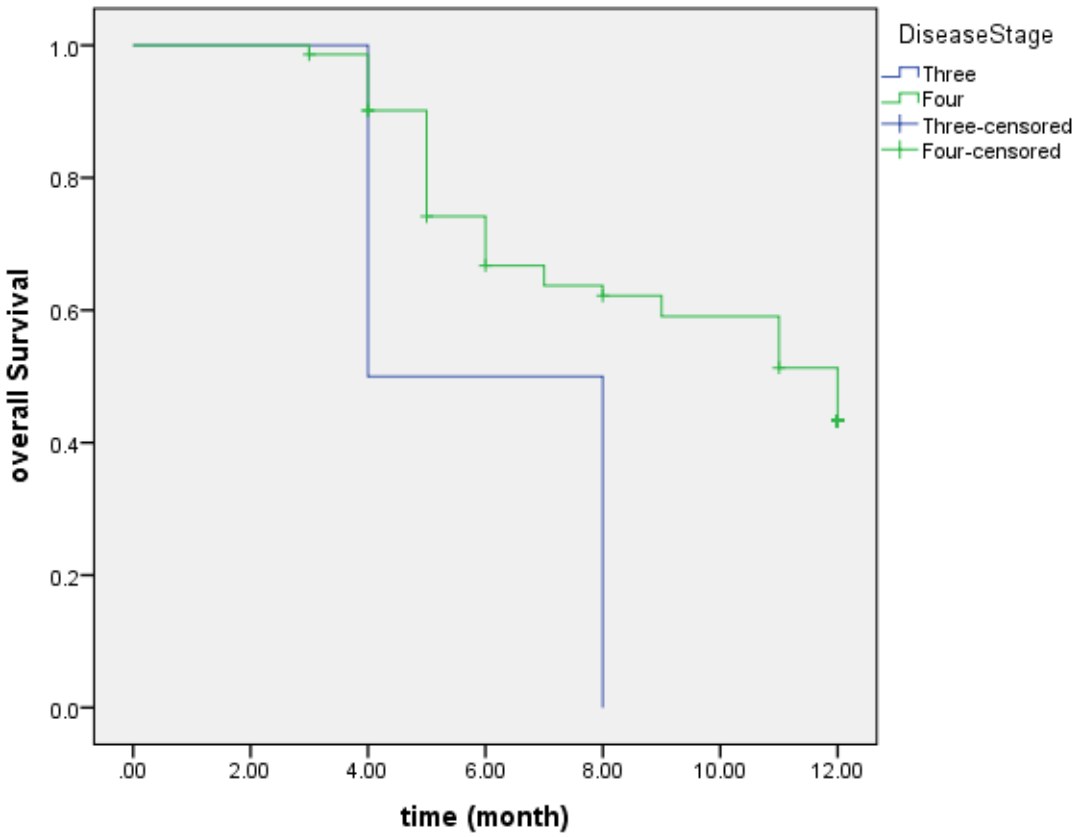


Figure 10: Association between OS and disease stage in palliative intent group

In palliative group patients who had FIGO stage three had better survival as compared to FIGO stage four and the association was statistically significant (p=0.04).

There was no association between OS and histology type (p=0.907), number of cycles (p=0.667) nor treatment modality in palliative intent group (p=0.135). All patients in palliative intent has residual disease after primary surgery.

Table 5: Univariate and multivariate analysis in palliative intent group (N =74)

Variable		N	1YEAR OS %	UNIVARIATE ANALYSIS	MULTIVARIATE ANALYSIS
Age	<51	30	40	0.72	-
	>51	44	50		
Stage	III	2	0	0.047	-
	IV	72	47.9		
ECOG	<2	5	100	0.04	-
	>2	69	42		
Histology	Epithelia tumors	64	45.3	0.90	-
	Non epithelial tumors	10	50		
Treatment modality	Surgery alone	26	64.5	0.135	-
	Surgery then chemotherapty	31	32.3		
	Neoadjuvant surgery then adjuvant chemo	5	40		
	Chemotherapy alone	12	41.7		
Time from diagnosis to orci	<30 days	20	90	0.001	-
	>30 days	54	29.6		
Time from surgery to chemotherapy	<35 days	12	91.7	0.001	0.008
	>35 days	36	16.7		
Number of cycles					
	<6 cycles	44	34.1	0.66	-
	>6 cycles	5	60		

CHAPTER FOUR

4.0 DISCUSSION

Ovarian cancer has high rate of morbidity and mortality due to its late presentation, where combination of surgery and chemotherapy remain the standard treatment as shown by Marc Buyse et al(40) . In this study, all participants were females who were followed for one year from finishing treatment.

Most of the patients in this study were in the middle ages and elders (80.2%), as study done by mondal et al(41). There are still several factors that hinder diagnosing ovarian cancer in its early stages; it could probably be due lack of awareness, lower level of education and poor socioeconomic status. Very late presentation has been observed in this study, where by more than 94.8% were diagnosed with FIGO stage III and IV. About 80.1% of the study participants had no formal education or had appeared in the primary level education and this might have contributed to poor early seeking of treatment due to lack of knowledge. This is in line with study (9) by Albert et al which showed higher level of education were inversely associated with ovarian cancer risk while increase income have non significant association with lower risks.

Most of the patients in this study who come from coastal zone and most of them are found in Dar es salam and this could be misleading due to improper registration, because most patients don't document where they come from instead they mention the relatives place in Dar es Salaam.

The histological pattern in this study seemed to be the same as in study done by Nassar et al(42), Mondal et al (41) and Yasmin et al (43). where Epithelia tumors is leading as compared to other studies . The histology had no significant statistical difference in treatment response. Also most patients received taxanes and platinum based chemotherapy and this is in hand with study done by Bois et al (20) and Bookman et al(44) which support the use of either taxane with carboplatin or with cisplatin, since there was no difference in efficacy of treatment

outcome when either of them is used. And in these studies taxanes can be used in both early and advanced stage diseases and is superior to other regimen.

One year survival was greater in curative 82% group as compared to palliative group 46% with p value 0.003. Study by Forman D et al (45) shows that one year overall survival for patients with ovarian cancer is 70.4%.This seem to be higher compared to overall survival in this study which was found to be 54.2%.This observed difference might be due to a fact that a higher proportion of participants in this study were in the palliative treatment intent group.

The interval between surgery and chemotherapy should be short because increase in time between surgery and chemotherapy may allow some micrometastases to proliferate and hence affect survival. For patients in curative intent group the chances of death were highly associated with increased time from surgery to chemotherapy and likewise in palliative group. Initiation of chemotherapy after 35 days was considered as a delay in this study and is supported by a study done by Seagle et al (32). This period allows the patients enough time for recovery from surgery especially for those who had extensive cytoreductive procedures and also allows some referral processes to be made and hence be able to undergo chemotherapy. There were some patients who came a bit early to ORCI but due to financial constraints, they could not pay for chemotherapy drugs hence the delay in starting chemotherapy. The patients who had chemotherapy less than 35 days in both curative intent group and in palliative intent group had better survival compared to those who came late p value= 0.04 and p=0.001 respectively.

The impact of time from surgery to chemotherapy has been investigated before in patients with solid tumors ,some of these studies include study by Seagle BC et al that showed that survival is greater when starting chemotherapy between 21 and 35 days from primary debulking surgery (32) while study by Tewari KS et al showed that survival improves significantly when chemotherapy is initiated <25 days following surgery. (33)

Maximum cytoreduction is usually associated with better survival as supported by Bristow et al (28) and Kuhn W et al (29), although this mainly depends on amount of initial tumor burden, where by Horowitz NS et al, showed that increase disease Burden is associated with shorter progression free survival and overall survival as compared with patients who will have moderate or low disease burden respectively (22). This was also shown in this study which revealed that, patients with complete cytoreductive surgery had better one year survival as compared to patients who had residual disease in curative intent group although that was not statistically significant. This could be due to small number of participants in curative intent group (only 4) who had no residual disease and the rest had residual disease.

Early stages are usually associated with better survival as compared to patients with late stage, and this appears to be the same in this study. This findings is comparable with study done by Nassar et al and Crack et al (42)(46), which showed advanced stage was significantly associated with poor disease free survival and overall survival.

Most patients received less than 6 cycles of chemotherapy and this might be due to high cost of taxane drugs. Study done by Petty RD et al, proved that single-agent carboplatin or cisplatin are as effective as a paclitaxel/carboplatin combination in survival terms when used as first line therapy in advanced ovarian cancer, hence should be encouraged. (38).

Patients with good ECOG performance status had shown to have better survival in many literature. The study done by Maxwell et al (10) has shown poor performance status is associated with poor prognosis in patients with ovarian cancer. This is in hand with this study, where good ECOG status in palliative intent group was statistically significant associated with increase overall survival.

Lower age has been associated with good OS as it has been shown in study done by Maxwell et al (10) and nassar et al (42), where increase age was associated with poor treatment outcome. This also has been seen in my study, where by in curative group, patients with less than 51 years are associated with good OS as compared to patients with much higher age and it was statistically significant.

CHAPTER FIVE

5.0 CONCLUSION AND RECOMMENDATIONS

5.1 Conclusion

The study has shown that patients who were treated with curative intent had greater one year survival than in palliative intent group and in both groups, delay in starting chemotherapy more than 35 days after surgery is associated with poor overall survival. In curative intent group, younger age was associated with good Overall survival while in palliative intent group poor ECOG status was associated with poor overall survival.

5.2 Recommendations

1. Any suspicious ovarian mass during abdominal pelvic imaging should be properly investigated so as to capture the disease in early stage
2. Proper education to the Patients receiving chemotherapy on important of finishing whole number of cycles as planned.
3. The Government should ensure the chemotherapy drugs are available at cancer centers.
4. Surgeons should encourage patients to come early for adjuvant chemotherapy.
5. A large prospective study needed and this will help to improve standard of care to our patient
6. To encourage colleagues to use single agent carboplatin in treating advanced stage ovarian cancer, since it has almost the same outcome in overall survival and progressin free survival and it is less expensive.

5.3 Study Strengths

Most of the patients whose records were not obtained in the files were contacted through their mobile phones.

5.4 Study Limitations

Incomplete information in some files.

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APPENDICES

Appendix I: FIGO Staging ovarian cancer

Stage I

The tumor (cancer) is only in the ovaries. Cancer may be found in one or both ovaries. But, it has not spread to any other organs or tissues in the body.

Stage IA

– Cancer is only in one ovary and the tumor is contained inside the ovary. The outer sac (capsule) of the ovary is intact. There is no cancer on the outside surface of the ovary. No cancer cells are found in ascites or washings.

Stage IB

– Cancer is in both ovaries. The capsules are intact and there is no cancer on the outside surface of the ovaries. No cancer cells are found in ascites or washings.

Stage IC

– Cancer is in one or both ovaries. And, one or more of the following has happened:

Stage IC1

– The capsule of the ovary broke open (ruptured) during surgery. This is called surgical spill.

Stage IC2

– The capsule ruptured before surgery, or cancer is on the outer surface of the ovary.

Stage IC3

– Cancer cells are found in ascites or washings.

Stage II

Cancer is in one or both ovaries and it has spread to other organs or tissues within the pelvis. Cancer has not spread outside the pelvis or to any lymph nodes.

Stage IIA

– Cancer has grown into and/or spread implants on the uterus, fallopian tubes, or both.

Stage IIB

– Cancer has grown into and/or spread implants on other organs or tissues in the pelvis. This may include the bladder, sigmoid colon, rectum, or the peritoneum within the pelvis. The peritoneum is the tissue that lines the inside of the abdomen and pelvis and covers most organs in this space.

Stage III

-Cancer in is one or both ovaries. It has spread outside the pelvis to tissues in the belly (abdomen). And, one or both of the following has happened:

1) Cancer has spread to the tissue lining the inside of the abdomen (peritoneum); or 2) cancer may have spread to lymph nodes in the back part of the abdomen behind the peritoneum.

Stage IIIA1

– Cancer has spread outside the pelvis, but only to lymph nodes in the back part of the abdomen—called retroperitoneal lymph nodes.

Stage IIIA1 (i)

– Cancer in the lymph nodes is 10 mm (millimeters) or smaller.

Stage IIIA1 (ii) – Cancer in the lymph nodes is larger than 10 mm.

Stage IIIA2– Cancer has spread to the tissue lining the abdomen, but it is so small it can only be seen with a microscope. Cancer may have also spread to lymph nodes in the back of the abdomen.

Stage IIIB

– Cancer has spread to the tissue lining the abdomen and it can be seen without a microscope. The areas of cancer spread are 2 cm (centimeters) or smaller. Cancer may have also spread to lymph nodes in the back of the abdomen.

Stage IIIC

– Cancer has spread to the tissue lining the abdomen and it can be seen without a microscope. The areas of cancer spread are larger than 2 cm. Cancer may have spread to lymph nodes in the back of the abdomen. It may have also spread to the outer surface of the liver or spleen.

Stage IV

Cancer has spread to distant sites in the body beyond the pelvis and abdomen. Cancer may have spread to distant organs such as the lungs, brain, or skin. It may have spread to the inside of the liver or spleen. Cancer may have also spread to lymph nodes outside the abdomen—called distant lymph nodes.

Stage IVA

– Cancer cells are found in the fluid around the lungs called pleural effusion. But, cancer has not spread anywhere else outside the abdomen.

Stage IVB

– Cancer has spread to the inside of the liver or spleen, to distant lymph nodes, or to other organs outside the abdomen.

Appendix II: Data Extraction Form

1. Patients initials ……..
2. Registration No……
3. Form No……
4. Residential area.....
5. Age (years)…..
6. Highest formal education achieved.

    a. none
    b. primary school
    c. secondary school
    d. post-secondary

7. Occupation: (a) Peasant (b) Housewife (c) Student
   (d) Civil servant (e) Self-employed (f) Unknown

8. Diagnostic investigation done before treatment
    a. Laparotomy and Biopsy
    b. Imaging

9. Findings of diagnostic investigation done in question 8
   .....

10. Investigation done and the result

Investigation done	Yes or No	Result
Abdominal USS		
CXR		

11. Disease stage:
    a. One
    b. Two
    c. Three
    d. Four
    e. Missing

12. ECOG: a) 0 b) 1 c) 2 d) 3 e) 4 f) 5 g) Missing

13. Tumour size (volume):.....

14. Histology type .....

15. Treatment Modalities:
    a. Surgery alone
    b. Surgery followed by chemotherapy
    c. Neoadjuvant chemotherapy, Surgery ,adjuvant chemptherapy
    d. Only chemotherapy .

16. Chemotherapy
    a. Regimen.....
    b. Number of cycles prescribed.....
    c. Number of cycles received.....

17. Time from diagnosis to ORCI
    a.less than 30 days
    b.more than 30 days

18. Time from surgery to chemotherapy
    a..less than 35 days
    b. more than 35 days

19. Surgery outcome

a. Residual tumor less than 1cm
b. Residual tumor greater than 1cm
c. No residual tumor

20.treatment intent

a.curative intent

b. palliative intent

21.Post-treatment outcome after 1 year post treatment

i. Dead
ii. Alive
iii. Loss to follow up

Appendix III: Introduction Letter

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

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Ref. No. HD/MUH/T.201/2014

14th July, 2017

Executive Director
Ocean Road Cancer Institute
P.O. Box 3592
DAR ES SALAAM.

Re: INTRODUCTION LETTER

The bearer of this letter Dr. Nuru F. Mlagalila is a student at Muhimbili University of Health and Allied Sciences (MUHAS) pursuing MMed. Clinical Oncology.

As part of his studies he intends to do a study titled:"***Treatment outcome of ovarian cancer patients attended at Ocean Road Cancer Institute from 2012 to 2016 ".***

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

Kindly provide her the necessary assistance to facilitate the conduct of her research.

We thank you for your cooperation.

Ms. A. Ndyeikiza
For: DIRECTOR, POSTGRADUATE STUDIES

cc: Dean, School of Medicine
cc: Dr. Nuru Mlagalila

Appendix IV: Ethical clearance Letter

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

13th July, 2017

Dr. Nuru F. Mlagalila
MMed. Clinical Oncology
MUHAS.

RE: APPROVAL OF ETHICAL CLEARANCE FOR A STUDY TITLED: "TREATMENT OUTCOME OF OVARIAN CANCER PATIENTS ATTENDED AT OCEAN ROAD CANCER INSTITUTE FROM 2012 TO 2016"

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 12th July, 2017 to 11th July, 2018. In case you do not complete data analysis and dissertation report writing by 11th July, 2018, you will have to apply for renewal of ethical clearance prior to the expiry date.

Dr. E. Balandya
DEPUTY DIRECTOR OF POSTGRADUATE STUDIES

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