CLINICO-PATHOLOGICAL CHARACTERISTICS, TREATMENT MODALITY AND SURVIVAL OF PATIENTS WITH LUNG CANCER AT OCEAN ROAD CANCER INSTITUTE, TANZANIA.

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DEPARTMENT OF CLINICAL ONCOLOGY

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By

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A Dissertation Submitted in (Partial) Fulfillment of the Requirements for the Degree of Master of Medicine (Clinical oncology) of the

Muhimbili University of Health and Allied Sciences.

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CERTIFICATION.

The undersigned certify that they have read and hereby recommend for acceptance by the Muhimbili University of Health and Allied sciences this research project: **Clinico-Pathological Characteristics, Treatment Modalities and Survival of Patients with Lung Cancer Treated at Ocean Road Cancer Institute. Tanzania** in partial fulfillment of the requirements for the degree of Master of Medicine in Clinical Oncology of the Muhimbili University of Health and Allied sciences.

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DECLARATION AND COPYRIGHT

I, Dr Fred Nyanga'u Ogora Omari, 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.

To my lovely wife, Abigail: you supported this life-changing pursuit by unconditionally allowing me to leave you with our little angels ELIZ and LUCRATIA at that age when they needed their dad most, thank GOD am coming back home.

To my lovely daughters, ELIZ and LUCRATIA; It's been long enough, I'm coming back home.

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To mum: It's your prayers that keep me going.

To my sister, Grace for your continued encouragement and prayers.

To my brothers, Patrick and George you played with my little angels when I was away.

ABSTRACT.

Background: Lung cancer is the most common cancer worldwide, accounting for 13% of all incident cancers and it is more common in males than females. Lung cancer is the leading cause of cancer deaths worldwide with rate of 18.4% of total deaths**.** High incidences of lung cancer are reported in developed countries than developing countries. The risk factors associated with lung cancer include smoking tobacco -most common, occupational exposure, environmental dust, Gender, Age, and Genetics. Lung cancer is classified into two main categories; Small cell lung cancer (SCLC) 10-15% or non- small cell lung cancer (NSCLC) 80-85%.There is a scarcity of data on the burden of lung cancer in East Africa due to misdiagnosis. Most patients who present with cough, chest pain are more often diagnosed with pulmonary tuberculosis and pneumonia. In view of this, lung cancer data is limited.

The objective of the study was to determine the clinico- pathological characteristics, treatment modalities and survival rate of patients with lung cancer treated at ORCI from January 2014 to December2018.

Methodology: Retrospective analytical study was used in which data was extracted from medical charts of patients treated at ORCI between January 2014 and December 2018.Exracted information included social demographics, risk factors, clinical presentation, pathological features, treatment modalities and survival. The analysis was done using SPSS IBM version 23. Frequency and percentage were used to summarize categorical variables and means and standard deviation were used to summarize continuous variable. T-test was used to compare means and chi square test/fisher's exact test was used to compare proportions. Survival curves were drawn using Kaplan Meier and log-rank test was used to test the difference in survival times. Cox regression was used in multivariate analysis to assess for possible confounders. $p<0.05$ was **considered** statistically significant.

Results.

The study recruited 79 patients. The mean age of the study population was **56.85 years**. Male to female ratio was **1.4:1**. **36.7%** of patients were peasant farmers.**41.8**% of the patients were smokers while **46.8%** were non- smokers. Family history of lung cancer was present in only **17.7%.** The most common symptoms were cough (84.8%) and chest pain (73.4%) while the least common symptom was chest tightness (16.5%). 39.2% of the patients were

misdiagnosed with pulmonary tuberculosis. More than two third of patients had ECOG less than 2. 92.4% of patients had NSCLC while SCLC accounted for 7.6%. About two thirds of the patients had stage 4 disease and the commonest site of metastasis was contralateral lung with pleural effusion (**35.6%).** Surgery (lobectomy) was done in only **5.4%.** All most all patients **(96.2%)** received chemotherapy. About one third of the total patients received radiotherapy. Out of all patients who received radiotherapy only 9 **(33.3%)** of 27 were treated with curative intent. Only 8.9% of patients received targeted therapy and all were NSCLC. The agents used were Bevacizumab, Erlotinib, and Dabrafenib. The two year overall survival was about **37%**. The mean overall survival rate was **10.14 months** and the median overall survival was **8 months**. Surgery, radiotherapy use, Chemotherapy use and ECOG status of less than 2 were positive predictors of survival while weight loss, hemoptysis, metastasis to bone and ECOG status more than 2 were negative predictors of survival.

Conclusion

Patients treated at Ocean Road Cancer Institute had characteristics and survival rates that are similar to data from international literature. A high proportion of patients were diagnosed at advanced stages and the outcomes remained poor because many of them were not able to complete treatment prescribed.

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ABBREVIATIONS.

AJCC	American Joint Committee on Cancer.
ALK	Anaplastic lymphoma kinase.
B- RAF	v-raf murine sarcoma viral oncogene homolog B1.
CT	Computed tomography.
ECOG	Eastern Cooperation Oncology Group.
EGFR	Epidermal growth factor receptor.
ESMO	European Society of Medical Oncology.
GLOBOCAN	Global Cancer Incidence, Mortality and Prevalence.
HER- 2	human epidermal growth factor receptor **2.**
KPS	Karnofsky performance status.
KRAS	Kirsten rat sarcoma viral oncogene homolog
MNH	Muhimbili National Hospital.
MUHAS	Muhimbili University of Health and Allied Sciences.
NCCN	National Comprehensive Cancer Network.
NSCLC	Non -small cell lung cancer.
ORCI	Ocean Road Cancer Institute.
OS	Overall survival.
PFS	Progression-free survival.
PIK3CA	Phosphatidylinositol 3-kinase catalytic alpha polypeptide
SCLC	Small cell lung cancer.
SEER	Surveillance, Epidemiology and End Results.

DEFINITION OF TERMS.

Adjuvant chemotherapy - Chemotherapy given after surgery.

Clinical characteristics - will includes, patient biodata, risk factors of lung cancer, symptoms and signs at presentation to hospital.

Pathological features – Includes abnormalities demonstrated on the cells by viewing of the slides (histological types and grade) and those gross abnormalities on tissues or organs detected by use of different imaging modalities.

Overall Survival - Interval between diagnosis and death from any cause.

Patient performance status - is a score that estimates the patient's ability to perform certain activities of daily living like getting dressed, eating, and bathing without the help of others. It uses two different scales: ECOG (Eastern Cooperative Oncology Group) scale which has scale ranges from 0 to 4, with 0 being fully functional and asymptomatic, and 4 being bedridden and Karnofsky scale with scale ranges from 10 (moribund-state of dying) to 100 (no limitations).

CHAPTER ONE

INTRODUCTION

1.1 Background Information.

Lung cancer is the most common cancer worldwide, accounting for 11.4% of all incident cancers and a leading cause of cancer deaths at 18.0%. (1).The incidences are higher in United States and European countries while low in African, Central and South America and Asia countries. Many reports have shown that the highest incident rates are in Northern America 35.8% and Northern Europe 33.7%, a relatively high rate in Eastern Asia 19.2% and the lowest rates in middle Africa 3.4% and Western Africa 2.8% (1).

Many studies have shown that exposure to Tobacco, environmental dust, occupational agents like asbestos, mines increases the risk of lung cancer. Most African countries where Tanzania is one of them, are developing at a very high rate, therefore a lot of carcinogens are emitted to the environment from the industries this may lead to increased incidences of lung cancer (2).

Non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC) are the two main types of lung cancer. NSCLC accounts for 80-85 % of all lung cancer and has three major subtypes namely, Adenocarcinoma, Squamous cell carcinoma and large cell carcinoma. SCLC accounts for about 10 – 15 % of all lung cancers, most patients are diagnosed at advanced stage because it's more aggressive than NSCLC (3).

In most of African countries patients with lung cancer are usually diagnosed in advanced stage, partially due to late presentation or limited diagnostic equipment and expertise. Treatment modalities depend on patient performance status, stage and cell type at the time of diagnosis. Each country has its own customized treatment protocols. The main treatment modalities include; surgery, radiotherapy, chemotherapy and targeted therapy.

Study done in Taiwan reported that 5-year survival rate of lung cancer patients in 2010 was 17.34% (12.60% in male, 25.40% in female) (4). In most Africa countries the actual survival rates are not known.

1.2 Literature Review.

1.2.1 Incidence of Lung cancer.

According to Globocan 2020, it was estimated that there would to be 2.2 million new cases of lung cancer. Men forming the majority 1.6 million while women having 400,000 cases. Globally in male, lung cancer is the second most common cancer diagnosed after prostate cancer. In females lung cancer comes second after breast cancer (1).

Globocan 2020, reported that in US Lung cancer accounted for (9.5%) 116 335 of all new cancer cases in males while (10.6%) 111 540 of all new cases in female (1). As reported by Globocan 2020, many studies have shown a decrease in incidence of lung cancer in males while there is an increase in female incidences (1).

According to Lung cancer Europe (LUCE) report 2018, there was total of 312,000 new lung cancer cases, male accounting around 213,663 (68%) and female 98,982 (32%) women (5). Like in US the incidence rates of lung cancer in women are lower, but are on the rise in many countries (6).

It has been reported by many studies that the incidences of lung cancer in Africa is low due to poor health seeking behavior, poor diagnostic techniques and poor cancer registry data. The incidence of lung cancer in South Africa is 5.8 per 100,000 (7).

Globocan estimates that the incidence rates of lung cancer in East Africa is 3.8 % for males and 2.2% for females (1).

The data from the ORCI Cancer registry from the year 2013 to 2019 showed that on average there were 18 new cases each year. .

1.2.2 Prevalence of lung cancer.

Globally the prevalence of lung cancer is higher in developed countries as compared to developing countries. The 5 year prevalence of lung cancer in the Northern Africa is 9.93 per 100,000 while in eastern Africa is 1.96 per 100,000 (1).

A study done in Kenya Nairobi, which analyzed cancer registry of different African countries and reported the following results on lung cancer prevalence; Kenya 5.4 per 100,000 male and 3.2 per 100,000 female, Uganda 5.2 per 100,000 male and 5.1 per 100,000 female, Malawi 1.2 per 100,000 male and 0.2 female (8).

Globocan 2020 also reported that Lung cancer in Uganda was ranked number 12 out of all cancer sites with a 5-year prevalence of 1.36 per 100,000 while in Tanzania, lung cancer is ranked number 11 out of all cancer cases with 5 year prevalence of 1.62 per 100,000 (1).

1.2.3 Risk factors.

Risk factors associated with lung cancer can be grouped into environmental, lifestyle and genetic, all this play a part in the carcinogenesis and patient capacity to respond to the cancer.

Globally, smoking is the most common and studied risk factor associated with lung cancer.

In a systematic review and meta-analysis done by O'Keeffe LM et el it showed that current smoking was associated with an age-adjusted Relative Risk of lung cancer of 7.48 in women and 8.78 in men compared with non-smoking (9).

The risk of smoking-related lung cancer increased according to the number of cigarettes smoked per day in both sexes (9). In addition data from 89 cohorts, and 38244 cases of lung cancer, reported that there is higher risk of lung cancer in former smokers as compared with never smokers (9).

In a pooled analysis by Berthiller J et al, of three case-control studies conducted in Tunisia, Morocco and Algeria it also showed there was an increased risk of lung cancer from smoking cannabis (OR 2.4; 95% CI: 1.6 –3.8) (10). Report from Study by Sasco AJ et al , showed that environmental risk factors such as, coal or wood burning in the house was associated with increased risk of lung cancer (RR=2.0; 95% CI=1.1-3.6) for men and women (11).

Treatment of breast cancer and Hodgkin lymphoma with radiotherapy is also known to increases the risk of second primary lung cancer (12). This increase in risk appears to be more pronounced in current smokers. But with improved radiotherapy techniques, dose to normal tissues has greatly reduced hence reduced risk of developing second lung cancers (12)(13).

Genetic has been shown to play some role in development of lung cancer. This was demonstrated in a meta-analysis of 17 observational cohort and 28 case-control studies conducted by Matakidou A et al, which revealed that the risk was greatest in relatives of patients diagnosed with lung cancer at a young age and in those with multiple affected family members with relative risk 1.8, 95% CI 1.6-2.0 (14). Many studies have reported mutation of genes including KRAS,EGFR, B- RAF, HER- 2, PIK3CA and gene rearrangements involving the ALK, RET and ROS1. KRAS mutation is the most common among these mutations and is present in approximately 25% of lung adenocarcinoma patients (15).

In study by Paez JG, et al reported that EGFR mutations was observed in 15% of white patients with lung cancer and 40% of the Asians (16).

It was also demonstrated in study by Dayaram T, et al that patients with EGFR activating mutations responded well to tyrosine kinase inhibitors (17).

In addition approximately in 5% of patients with lung adenocarcinoma, gene rearrangement involving ALK is observed and these patients have been shown to draw benefit from ALK kinase inhibitors (17).

1.2.4 Clinico - pathological presentation.

1.2.4.1 Clinical manifestation.

A study by Spiro SG et al, reported that Lung cancer is one of the most lethal cancer due to late diagnosis. Most often is insidious, with no symptoms until the cancer is at advanced stage. About 7-10% of lung cancer cases are asymptomatic, the diagnosis is through a coincidental finding on chest radiograph. The study also reported that at initial diagnosis, 20% of the patients will present with localized disease, 25% with regional metastasis and 55% of patient will have distant metastasis (18).

The clinical presentation of lung cancer is caused by primary tumor, locoregional spread, metastatic disease, or ectopic hormone production. Another study by Al Jahdali H. 2008, showed that 27% of the patients presented with primary tumor at the time of diagnosis, 34% had nonspecific systemic symptoms which was suggestive of metastases including; anorexia, weight loss and fatigue, and 32% had symptoms specific to a metastatic site (19).

Study by Corner J et al 2005, reported that cough is the most common presenting symptom of lung cancer in 45-75% of the patients (20). The other respiratory symptoms include chest pain (27-47%), dyspnea (37-47%) and hemoptysis (27-57%). The study also revealed that patients with hemoptysis seek medical advice earlier than others hence earlier diagnosis (20).

Symptoms due to Primary Tumor.

Lung cancer can be located either in the central or in peripheral of the lung lobes. The tumors that are located centrally are generally squamous cell carcinomas and produce cough, dyspnea, atelectasis, post obstructive pneumonia, wheezing, and hemoptysis (18). Tumors that are located in the peripheral of the lung are mostly adenocarcinoma or large cell carcinomas and usually present with cough, dyspnea and chest pains due to pleural effusion and are usually diagnosed late (18).

Loco-regional spread Symptoms.

Patients with loco-regional spread presents with symptoms like superior vena cava obstruction, paralysis of the recurrent laryngeal nerve, and phrenic nerve palsy, which causes hoarseness and paralysis of the diaphragm. Other symptoms are Horner syndrome which is due to pressure on the sympathetic plexus, dysphagia caused by compression of the esophagus (18). If the tumor extends to the superior sulcus (Pancoast tumors) it leads to compression of the brachial plexus roots resulting in neuropathic pain in the upper extremity (18).

Signs and symptoms of Metastatic disease.

According to Spiro SG et al 2007 study, metastasis to the liver accounts for 66%, and the symptoms include weakness, weight loss, anorexia, and hepatomegaly. 25% of lung cancer spreads to the bone in which patients' presents with pain, fractures and elevated alkaline

phosphatase. 15- 20% of patients present with lymphadenopathy, while 5% present with brain metastasis: headaches, seizures, nausea and vomiting, mental status changes (18).

1.2.4.2 Pathological features.

WHO classified Lung cancer into two main histological types according to their appearance into Small Cell Lung Cancer (SCLC), which accounts 15%, and Non–Small Cell Lung Cancer (NSCLC), which accounts for 85%. Further, NSCLC is sub classified into adenocarcinoma (40%) squamous cell carcinoma (25%) and large cell carcinoma 10-15 % (21).

Adenocarcinoma is the most common histologic subtype of lung cancer in men and women. It accounts for 40 % of the NSCLC and is further sub classified into; Colloid, Mucinous, Lepidic, Acinar, Papillary, Micropapillary, Fetal (21). In the US, adenocarcinoma represents nearly 50% of all cases of lung cancer. Adenocarcinoma has a higher predilection for distant metastasis compared to squamous cell histology (21).

According to Travis WD et al, small cell lung cancer forms 14% of lung cancers and it typically presents as a perihilar mass and is very aggressive (22). Small cell lung cancer has a strong association with smoking history and commonly causes paraneoplastic syndromes. Other histologic subtypes of lung cancer include; large cell 3%, Adenosquamous 1-2 % and carcinoid tumors 1-2 % (22).

1.2.5 Treatment modalities for Lung cancer.

The main treatment modalities used in the management of lung cancer include surgery, radiation therapy, and systemic therapy. The employment of these modalities depends on the patient performance status, stage and histological type at diagnosis. Early stages are treated with surgery or radiotherapy alone and more advanced diseases are treated with combined modalities. Each country has its own customized treatment protocols for lung cancer.

1.2.6 Overall survival rates.

Lung cancer is the leading cause of cancer death worldwide, with lowest survival rates, along with liver and pancreatic cancer. The overall two-year survival rate of those diagnosed with lung

cancer is 25%. At five years, survival rate drops to 15%. Worldwide statistics shows that women have higher survival rate than men across all ages (23).

In Europe, Lung cancer has the highest mortality of about 20% of total cancer deaths. The overall 5-year survival for lung cancer in Europe is about 13% since diagnosis and it decreases with advanced age. The 5 –year survival rate for men is 11.2% and 13.9% for women (24).

A study by Holmberg L et al, conducted between 2001 and 2004 showed that 5- year survival rate for lung cancer in England was 6.5% for male and 8.4% for female while that of Sweden was 11.3% male and 15% for female (25).

In study done in Brazil it reported that the overall survival for patients with lung cancer was 19.0 months (95%CI 16.2 - 21.8). The median survival was highest for stage I at 99.7 months and lowest for metastatic disease at 12.2 months (26).

Patients with lung cancer who are diagnosed with a localized stage have a good prognosis. Unfortunately, most patients are diagnosed with advanced or distant disease. Jeremić et al in his study which was looking for independent prognosticators in patients with lung cancer found out that; female sex, good Karnofsky performance score (KPS), less pronounced weight loss, squamous histology, and lower stage independently predicted better overall survival and progression-free survival. However, age did not influence overall survival or progression-free survival (27).

A study done by Yoshihisa Shimada et el found out that vascular invasion location was a statistically significant predictor of prognosis and potential recurrence patterns for lung cancer (28). A Korean study conducted between 2001 and 2016 by Jun Hyeok Lim et al revealed that gender is an independent prognostic factor in small -cell lung cancer (29).

1.3 Problem Statement.

There are few studies about lung cancer conducted in East Africa, both in Tanzania, Kenya and Uganda. However, there is no study about lung cancer that has been done in ORCI that looks at

clinico- pathological characteristics, treatment modalities and survival of patients with lung cancer despite being attended at ORCI.

1.4 Rationale of the Study.

The findings of this study will help to compare treatment outcome of lung cancer to other parts of the world and will help in understanding the predictors of survival. Therefore, this study will form the baseline for more studies on lung cancer in Tanzania and East Africa.

1.5 Research Questions.

1. What are the clinic-pathological characteristics and treatment modalities for patients with lung cancer treated at ORCI from January 2014 to December 2018?
2. What is the overall survival rate and predictors of survival of patients with lung cancer treated at ORCI from January 2014 to December 2018?

1.6 Objectives.

1.6.1 Broad objectives.

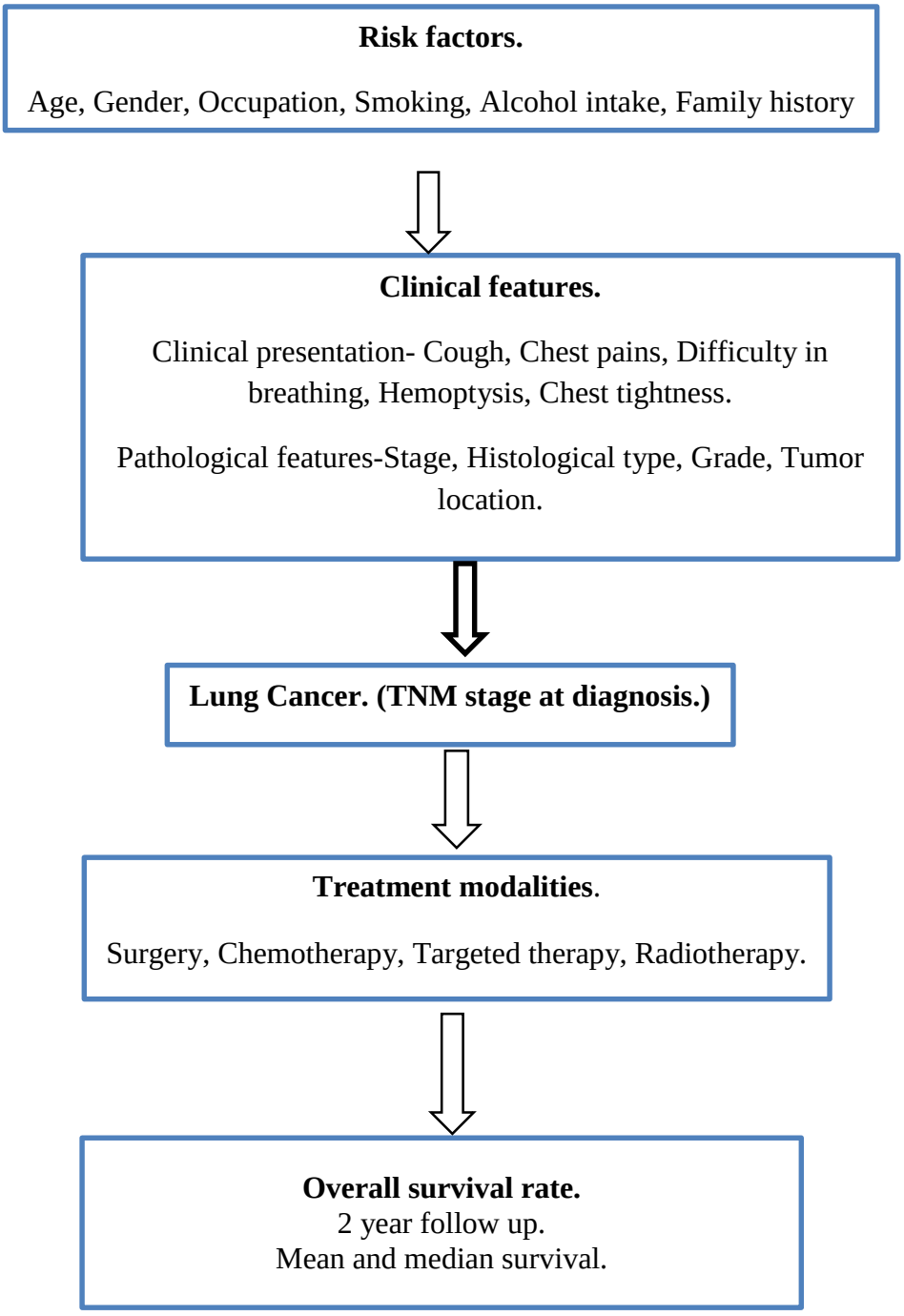
1. To determine the Clinico-Pathological characteristics, Treatment Modalities and Overall Survival rate of patients with lung cancer treated at ORCI from January 2014 to December 2018.

1.6.2 Specific Objectives.

1. To determine the social demographic characteristics and risk factors of patient with lung cancer treated at ORCI from 2014 to 2018.
2. To determine the Clinico-pathological characteristics and treatment modalities of patients with Lung cancer treated at ORCI from 2014 to 2018.
3. To determine 2 years overall survival rate among patients with lung cancer treated at ORCI from 2014 to 2018.
4. To determine the predictors of overall survival rate of patients with lung cancer treated at ORCI from 2014 to 2018.

1.7 Conceptual Framework.

Figure 1: showing conceptual framework.



The figure above shows the relationships of various factors in the study on lung cancer at ORCI, Tanzania. The social-demographic factors, e.g. age, gender, smoking, alcohol intake and family history have been associated with increased risk of developing lung cancer. Males have increased chance of having lung cancer than females. Lung cancer is common in elderly population. Clinical presentation has been shown to have a reciprocal relationship with the pathological types, stages, and grade of tumor cells. The tumor characteristics and lung cancer stage have a significant role in the choice of treatment. The treatment outcomes were evaluated in terms of overall survival (whether dead or alive).

CHAPTER TWO

: MATERIAL AND METHODS.

2.1 Study design.

This was a retrospective hospital-based analytical study.

2.2 Study setting.

This study was conducted at the Ocean Road Cancer Institute (ORCI), which is located in Dar-es Salaam, Tanzania. ORCI is a cancer treatment, research and academic facility in Tanzania. The institute is affiliated with the Muhimbili University of Health and Allied Sciences (MUHAS), and Muhimbili National Hospital (MNH). ORCI offers both inpatient and outpatient services, including chemotherapy, radiation therapy, imaging and laboratory services, palliative care and cancer screening services. It plays a major role in the country's National Cancer Registry and the National Cancer Control Strategy. It receives patients with a histologically confirmed diagnosis from MNH through tumor board meetings, as well as from other hospitals from within and outside the country. Estimates from the Hospital based cancer registry shows that there is an approximately 18 cases of lung cancer per annum at ORCI.

2.3 Target population.

All patients with lung cancer in Tanzania.

2.4 Study population.

All patients with lung cancer attended at ORCI from January 2014 to December 2018

2.5 Eligibility criteria.

2.5.1 Inclusion criteria.

All patients with histologically confirmed lung cancer, with complete medical charts.

2.5.2 Exclusion criteria.

Patients who have history of other previous cancers before developing lung cancer.

2.6 Sample size.

Owing to the reality of lung cancer cases treated at ORCI, all patients with lung cancer treated between, January 2014 and December 2018 were included in the this study.

2.7 Study variables.

2.7.1 Independent variables.

Risk factors such as; Age, Sex, Alcohol, Smoking and family history were documented.

Clinical presentation: - chronic cough, chest pains, hemoptysis, weight loss, Difficult in breathing and chest tightness were assessed.

Pathological features: - TNM Stage, Histological type, Tumor grade and Tumor location

Treatment modalities: -Surgery, Chemotherapy, Radiotherapy and targeted therapy. ORCI uses Tanzania National Cancer treatment Guideline for management of all cancer types. The management guideline for limited stage SCLC I-III is concurrent chemo - radiotherapy. The radiation regimen given includes; 45 Gy in 30 fractions given twice daily over 3 weeks or 66 Gy in 33 fractions given once daily. Prophylactic cranial irradiation of 25 Gy in 10 fractions is recommended after completion of chemoradiation. The chemotherapy that is used is Cisplatin/Carboplatin, Etoposide. Chemotherapy is the recommended modality for Extensive stage IV. The first line chemotherapy includes; Cisplatin/ Carboplatin, Etoposide or cisplatin plus irinotecan or cyclophosphamide, doxorubicin, vincristine. The second line chemotherapy includes; Etoposide/ Topotecan / Paclitaxel. The patients who responds to chemotherapy are recommended to get chest radiotherapy to residual disease and prophylactic cranial irradiation. According to the guideline recommendations, surgery is the mainstay curative treatment for early stage and locally advanced NSCLC. The surgical resection may be either Lobectomy, Wedge or Pneumonectomy with Lymphadenectomy. Patients with advance features like positive margin, positive nodes, and higher stage after resection are given adjuvant radiotherapy. For the higher stage NSCLC which is not operable or patients who are not fit for surgery chemo - radiotherapy can be used. The radiation doses that are used include; 60 Gy in 30 fractions with chemotherapy or 66 Gy in 33 fractions without chemotherapy. The chemotherapy that is used include; Cisplatin and Etoposide/vinorelbine or Cisplatin and Gemcitabine/docetaxel or Carboplatin and paclitaxel.

2.7.2 Dependent variables.

Median and two years overall survival were assessed.

2.8 Data collection.

A structured Data extraction form with four sections was used to collect data. The first section covers the social demographics like age at diagnosis, gender, occupation, history of alcohol intake and smoking, history of cancer in the family and patient presenting signs and symptoms and duration like cough, chest pain, hemoptysis, weight loss, difficulty in breathing and chest tightness.

The second section involved tumor characteristics such as Histological types-SCLC and NSCLC, TNM Stage, I, II, III, IV and Tumor grade I, II, III, and tumor location whether right or left lobes.

The third section consisted of treatment received e.g. type of surgery done if any, site and dosage of radiotherapy, cycles and regimen of chemotherapy and targeted therapy given. The last part extracted information about patients survival status whether alive, death or lost on follow up.

The research assistants helped the principal investigator during data collections. Before the commencement of the data collections, the principal investigator trained two research assistants on how to collect data, what to collect while maintaining confidentiality of the patients' medical records. All patients who attended the ORCI from January 2014 to December 2018 with a diagnosis of Lung cancer were traced from the ORCI hospital cancer registry. Then the research assistants retrieved the information and fill in the data extraction form. The principal investigator cross checked for completeness and accuracy on a daily basis during data collection.

In cases where survival data was missing in the medical charts, the investigators called patient or guardian. The investigators introduced themselves and explained the aim of the call and the purpose of the study. The investigators also assured the recipient (patient or guardian) that there are no risks associated with this study. Then the investigator asked for verbal consent from the recipient. Recipients who gave consent were asked the where about of the named patient. If the patient was alive, he/she was asked about their current health status and ask them not to miss

the scheduled clinics. In cases where the patient was deceased, the investigators consoled with the recipient (guardian) and thanked them for consenting to share the information and once more assure them of confidentiality. In cases where the owners of the phone numbers were not reached, the patients were censored lost to follow up.

2.9 Validity and reliability of the Data extraction form.

The Data extraction form was made by the principal investigator and reviewed by the panel of senior consultant at the department of clinical oncology for assuring that the form covers the scope of the study. After being reviewed by the panelists, then a pilot of 10 patients was conducted to check for the reliability of the data extraction form.

2.10 Data Analysis.

The data extraction forms were conscientiously reviewed for completeness and consistency. Raw data was entered into SPSS (IBM) version 23. To demystify the analysis, all string variables such as gender and clinical features variable were assigned a number code that were entered into SPSS whereas the numerical variable were entered as they are. Continuous variables were summarized by means, medians, standard deviation and range while categorical variables were summarized by frequencies and percentages. Kaplan Meier curves were used to identify and compare overall survival for the study period by the log-rank test. Significance was defined as the P-value of less than 0.05.

Table 1: Specific objectives and methods of Analysis.

Specific objective.	**Analysis plan**
To determine the social demographic characteristics of patients with lung cancer treated at ORCI from January 2014 to December 2018.	Frequency and percentage.
To determine the risk factors associated with developing lung cancer in patients treated at ORCI from January 2014 to December 2018.	Frequency and percentage.
To determine the clinical and pathological characteristics of patients with lung cancer	Frequency and percentage.

treated at ORCI from January 2014 to December 2018.	
To determine the various treatment modalities applied for patients with Lung cancer at ORCI from January 2014 to December 2018.	Frequency and percentage.
To determine the 2 years overall survival rate and its predictors among patients with Lung cancer treated at ORCI from January 2014 to December 2018.	Kaplan Meier curves was used to describe the survival of patients with lung cancer for the study period. The log-rank test was used to test the difference in survival times between different groups. Cox regression was used in the multivariate analysis to assess for possible confounders.

2.11 Ethical Considerations.

2.11.1 Ethical clearance.

Before conducting study, Ethical clearance was obtained from the Muhimbili University of Health and allied sciences (MUHAS) Research Ethics and Publication Committee and from the Ocean Road Cancer Institute (ORCI) to permit access to the patient's medical information from the ORCI medical registry. To reduce the potential risks of disclosure of protected patient medical information, efforts were made to ensure and assure patient's confidentiality is preserved by ensuring that the patient's identity was not revealed and that the waiver requested did not cause any adverse effects to the rights and welfares of the patients.

2.11.2 Consent Process.

Since this study was a retrospective hospital-based study review of available patient's medical charts in the hospital setting, a waiver of informed consent was obtained from the MUHAS Research Ethics and Publication Committee which assisted in accessing patients' medical charts without obtaining consent from individual participants (patients).

CHAPTER THREE

3. RESULTS.

There were 97 patients with lung cancer cases recorded, between January 2014 and December 2018. Seven of the medical charts reviewed did not have histology results hence they were excluded from the study. Eleven patients had other primary site cancer with metastasis to the lungs.-Therefore 79 patients were included in the final analysis.

3.1 Social Demographic.

Table 2: Social Demographic Characteristics of study population (N=79)

Variable	Frequency	Percent
Age of Patients		
<40	8	10.1
41-50	19	24.1
51-60	17	21.5
>60	35	44.3
Age Mean (range)		**56.85 (23-86)**
Gender		
Female	33	41.8
Male	46	58.2
Occupation		
Peasant	29	36.7
Businessman/woman	15	19.0
Civil servant	17	21.5
Teacher	6	7.6
Police officer	6	7.6
Miners	4	5.1
Student	2	2.5
Smoking status		
Yes	33	41.8
No	37	46.8
Unknown	9	11.4
Alcohol consumption		
Yes	33	41.8
No	35	44.3
Unknown	11	13.9

Family History of lung Cancer		
Yes	14	17.7
No	47	59.5
Unknown	16	20.3
Other sites	2	2.5

The mean age of the study population was **56.85 years** (range 23-85years). About two thirds of the patients were more than **50** years while one third were less than **50 years**. Male to female ratio was 1.4:1. **36.7%** of the patients were peasant farmers while only **2.5%** of the patients were students**.** There were two students with lung cancer with mean age of **24.50 years (SD 2.121). 41.8%** of the patients were smokers while **46.8%** were non-smokers**. 17.7%** of the patients had family history of lung cancer. **41.8%** of the patients had history of alcohol consumption (Table 2).

Table 3: The clinical presentations and performance status (N=79)

Variable	***Response***	***Frequency***	***Percent.***
Cough	Yes	67	84.8
Chest pain	Yes	58	73.4
Hemoptysis	Yes	27	34.2
Weight loss	Yes	47	59.5
Difficulty in breathing	Yes	33	42.3
Chest tightness	Yes	13	16.5
Performance status (ECOG)	<2	56	70.9
	>2	23	29.1
Treated for pulmonary tuberculosis.	Yes	31	39.2

3.2 Clinical presentation.

Most common symptoms were cough (84.6%) and chest pain (73.4%) and the least common symptom was chest tightness (16.5%).

About two thirds (70.9%) of patients had ECOG performance status less than 2. **39.2%** of the patients were treated for pulmonary tuberculosis initially. (Table 3.)

Duration of symptom presentation.

Table 4: Duration of presenting symptoms.

Variable	Symptom duration	Frequency (%)
Cough duration.	<3 months	5(7.4)
	3 - 6 months	16(23.9)
	>6 months	46(68.7)
Chest pain duration.	<3 months	11(19.0)
	3 - 6 months	15(25.8)
	>6 months	32(55.2)
Hemoptysis duration.	<3 months	19(70.4)
	3 - 6 months	7(25.9)
	>6 months	1(3.7)
Weight loss duration.	<3 months	36(76.6)
	3 - 6 months	11(23.4)
Difficulty in breathing duration.	<3 months	26(78.8)
	3 - 6 months	4(12.1)
	>6 months	3(9.1)
Chest tightness duration.	<3 months	12(92.3)
	3 - 6 months	1(7.7)

At the time of presentation **68.7%** (46 patients out of 67) presented with chronic cough of more than 6 months. 32 out of 58 patients (**55.2 %)** presented with chronic chest pains of more than 6 months. Majority of the patients with hemoptysis **(70.4%)** reported of symptom of less than 3 months also majority **(76.6%)** of the patient reported of weight loss of less than 3 months prior to presentation in hospital. (Table 4 above).

3.3 Pathological characteristics.

Table 5: The Pathological Characteristics (N=79)

Histological type		**Frequency.**	**Percent.**
NSCLC	Adenocarcinoma	54	68.4
	Squamous cell carcinoma	17	21.6
	Large cell	2	2.5
SCLC		6	7.6
Tumor Location			
Right lung		44	55.7
Left lung		35	44.3
Tumor grade			
I (Well differentiated)		2	2.5
II (Moderately differentiated)		20	25.3
III (Poorly differentiated)		34	43.0
Not mentioned		23	29.1

Majority of the patients presented with NSCLC **(92.4%)** while SCLC was diagnosed in only (**7.6%)** patients. The most common histologic subtype among patients with NSCLC was adenocarcinoma **(68.4%).**) The mean age for SCLC at diagnosis was **51.00 ±21.30** years while for NSCLC was **57.33 ±13.436** years**.**

There were more lung tumors located on the right lung than the left lung, **55.7%** versus 44.3% respectively. The commonest tumor grade was grade III (poorly differentiated) **(43%)**.
(Table 5.)

Figure 2: The percentages of different stages at diagnosis

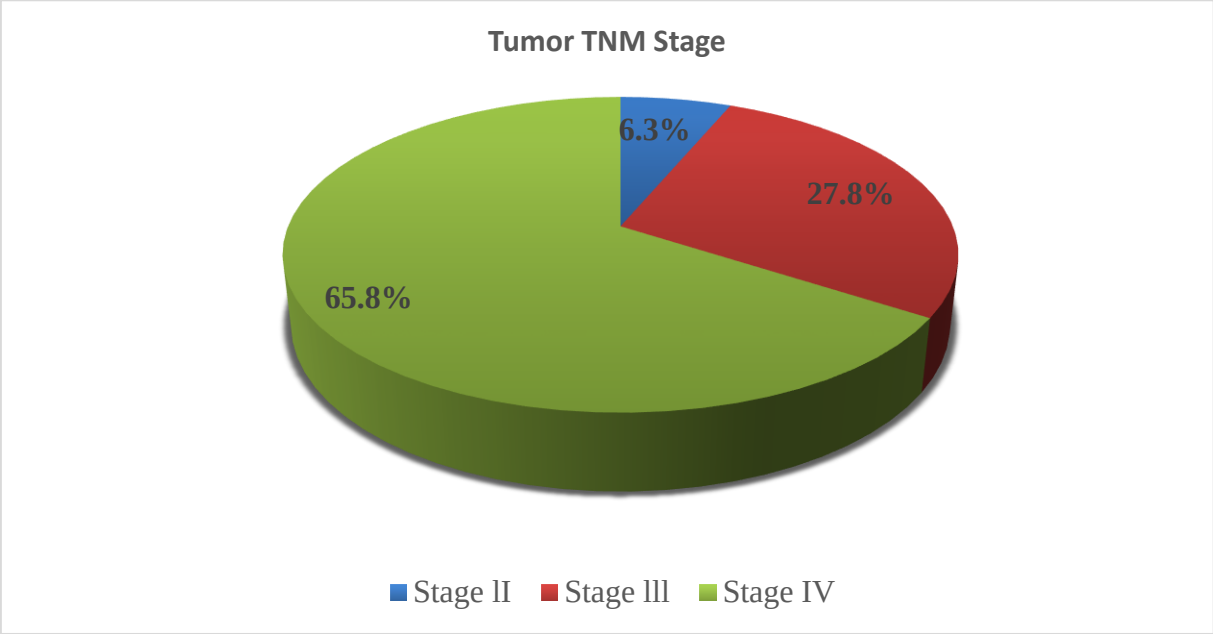


Figure 2 above show that majority of the patients (65.8 %) presented with stage IV disease.

Table 6 Percentage of different metastatic sites verses histological types in lung cancer at diagnosis

Metastatic site	Response.	NSCLC		SCLC		□2	p
		n	%	n	%		
Bone	Yes	16	21.9	2	33.3	0.385	0.535
	No	57	78.1	4	66.7		
Liver	Yes	17	23.3	1	16.7	-	1.000
	No	56	76.7	5	83.3		
Brain	Yes	10	13.7	0	0.0	0.956	0.328
	No	63	86.3	6	100		
Contralateral Lung plus effusion	Yes	26	35.6	3	50.0	-	0.665
	No	47	64.4	3	50.0		

The commonest site for metastatic lung cancer was contralateral lung with pleural effusion for both NSCLC **35.6%** and SCLC **50%.** None of the patients with SCLC had brain metastasis. (Table 6).

3.4 Treatment modalities.

3.4.1 Surgery.

Table 7 Percentage of surgeries done verses histological types (N=79)

	Histological types.				**Total**	**χ^2**	**p**
	NSCLC (n-73)		**SCLC (n-6)**				
Surgery	N	%	N	%			
NO	60	82.2	5	83.3	65		1.000*
Lobectomy	5	6.8	0	0	5		
Open Biopsy only	8	11.0	1	16.7	9		

** P-value was calculated using exact Fishers test*

Patients were treated with different modalities. The mean age of the patient who underwent surgery was 55.50 ±13.69 years while those who did not receive surgery was 57.14 ±14.26 years p >0.4. Five patients (6.8 %) of 73 who had NSCLC received lobectomy while eight patients (11.0%) of 73 patients with NSCLC, only biopsy was done due to high disease burden. Open biopsy was done in only one patient (16.7%) of 6 patients who had SCLC. (Table 7).

3.4.2 Chemotherapy.

Table 8. Percentage of chemotherapy regimens prescribed verses the histological types (N=79)

Chemotherapy regimens	**NSCLC**	**SCLC**
Platinum/Taxane	51(72.9)	2 (33.3)
Platinum/etoposide.	11(15.7)	4 (66.7)
Platinum/gemcitabine	6 (8.6)	0
Platinum/premetexed	2 (2.8)	0

76 (96.2 %) of total 79 patients received chemotherapy during the course of treatment. Some patients received more than one chemotherapy regimen. Two third of SCLC patients received platinum/etoposide regimen. **72.9%** of NSCLC patients received platinum/taxane regimen. (Table 8).

Table 9: Mean Number of chemotherapy cycles by histological types (N=79)

Histological types.	N	Mean	Std. Deviation	Std. Error Mean
NSCLC	70	4.80	1.733	.207
SCLC	6	6.00	.000	.000

$T(74) = -1.69, p=.096$

The table above shows that 70 patients with NSCLC received a mean of 4.8 cycles of chemotherapy while 6 patients with SCLC received a mean of 6 cycles of chemotherapy however the difference was not statistically significant (Table 9).

3.4.3 Radiotherapy.

Table 10: Radiotherapy given to patients with lung cancer treated at ORCI (N=79)

Variable	Frequency	Percent
Radiotherapy		
Yes	27	34.2
No	52	65.8
Radiation intent		
Curative	9	33.3
Palliative	18	66.7
Curative intent(dose & fraction		
45Gy in 30 fractions	1	11.1
60Gy in 30 fractions	8	88.9
Palliative intent.		
8 Gy single fraction	4	22.2
20 Gy in 5 fractions	4	22.2
30 Gy in 10 fractions	10	55.6
Palliative intent (site radiated)		
Brain	8	44.4
Bone	7	38.9
Lung and chest wall	3	16.7

One third (34.2%) of the patients received radiotherapy. Of the patients who received radiotherapy only 9 **(33.3%)** of 27 were treated with curative intent while 18 (**66.6%)** of 27 received palliative dose. All the 9 patients treated with curative intent had NSCLC. For the patients who were treated with curative intent majority **88. 9%** received a dose of 60Gy in 30 fractions. Patients who had metastatic lung cancer were treated with palliative intent to specific site of metastasis, which included brain **44.4%,** bone **38.9%,** lungs and chest wall **16.7%.** (Table 10).

Table 11: Percentage of palliative metastatic sites radiation verses histological types

Palliative radiotherapy (Site radiated) Verse Histological type. Cross tabulation					
			Histological type.		Total
			NSCLC	SCLC	
Site radiated	Brain	Count	9	0	9
		%)	100.0%	0.0%	100.0%
	Bone	Count	6	0	6
		%	100.0%	0.0%	100.0%
	Lung and Chest wall.	Count	2	1	3
		%	66.7%	33.3%	100.0%
Total		Count	17	1	18
		%	94.4%	5.6%	100.0%

A total of 18 patients received palliative radiotherapy. Majority **94.4%** of the patients who received palliative radiotherapy had NSCLC. All patients who had brain metastasis received whole brain radiotherapy (WBRT) and had NSCLC. Also all patients who received palliative radiotherapy to the bone had NSCLC.

3.4.4 Targeted therapy.

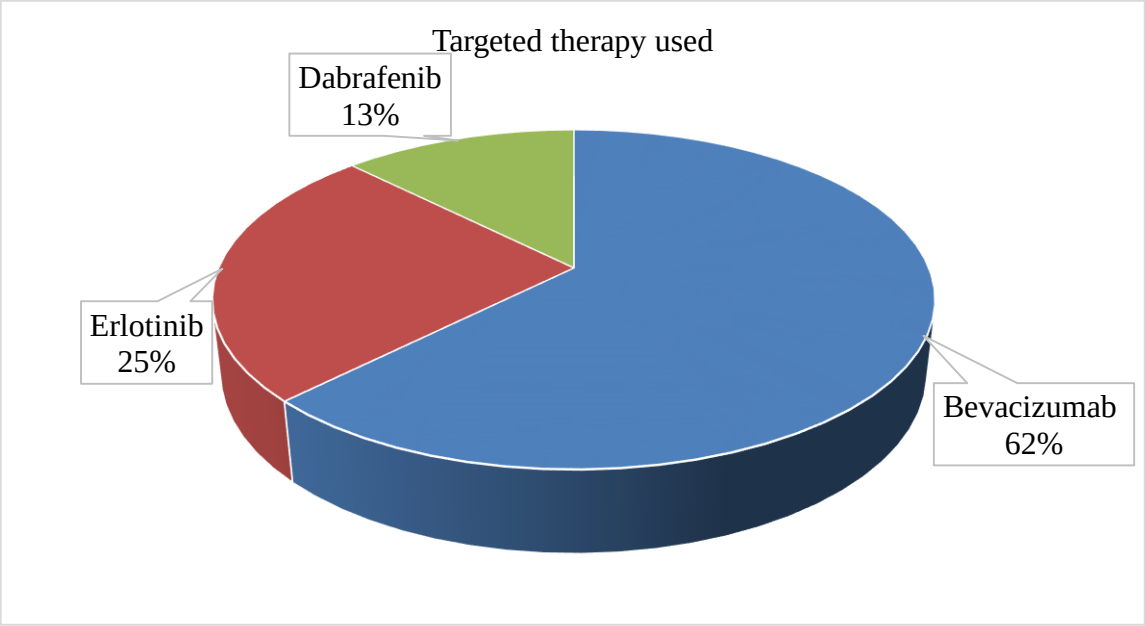
Table 12: Percentage and type of targeted therapy prescribed to patients with lung cancer verses histological type

Treatment	**Pathological type**				**Total**	**χ^2**	**p**
	NSCLC		**SCLC**				
Targeted therapy	N	%	N	%			
No	66	91.67	6	8.33	72	0.63	0.427
Yes	7	100.00	0	0.00	7		

** P-value was calculated using exact Fishers test*

A total of 7 patients received targeted therapy and all of them had NSCLC. All the 6 patients with SCLC did not receive targeted therapy.

Figure 3 percentage of types of targeted therapy used



Bevacizumab was the most commonly 62% prescribed drug. Other agents used were Erlotinib, and Dabrafenib.

In all patients who received targeted therapy, it was given as second line treatment based on clinical predictors and not on mutation results.

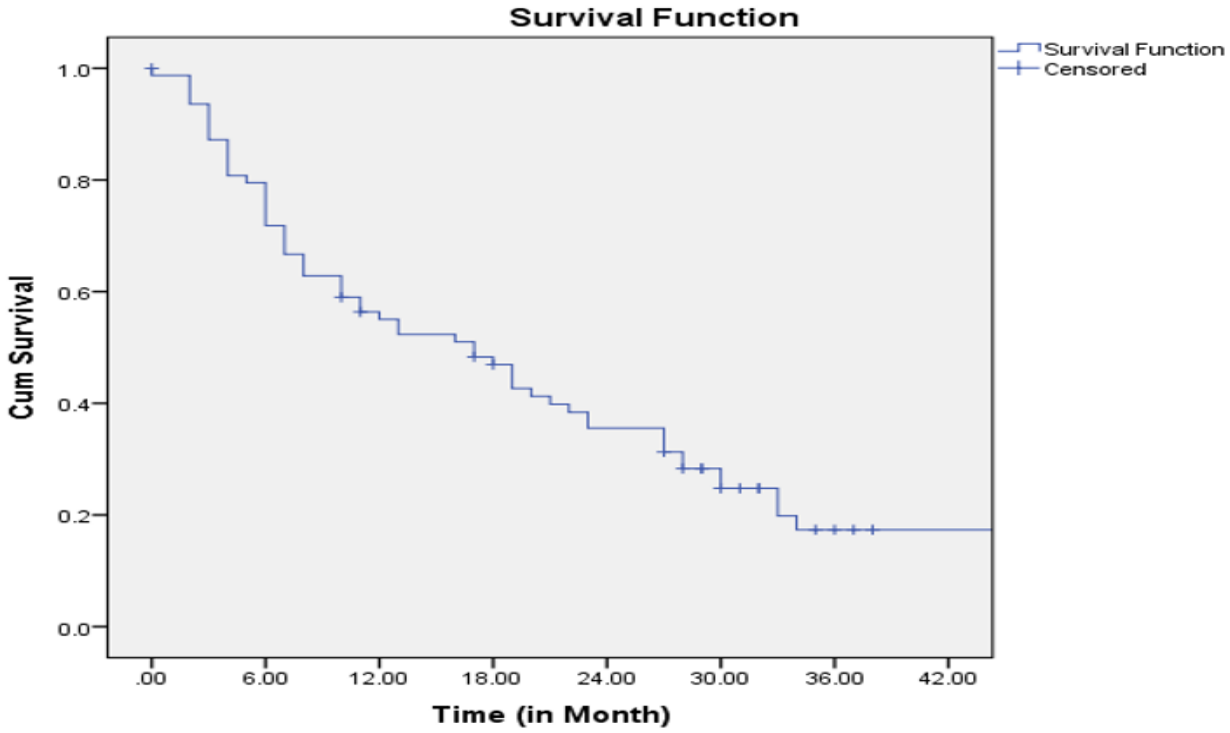
3.5 Overall survival rate

Table 13: Overall Survival rate of patients with lung cancer treated at ORCI (N=79)

Overall survival rate		**95% Confidence Interval**	
		Lower bound	**Upper bound**
Mean	10.142	8.259	12.025
Median	8.000	5.16	10.84

From this study the mean overall survival rate was **10.14 months** and the median overall survival was **8 months** with the 95% confidence interval. (Table 13)

Figure 4. Kaplan Meier survival curve showing the overall survival of patients with lung cancer



The figure 3 above shows that the 2 year overall survival was **37%.**

Table 14: Univariate analysis (Kaplan Meier) of predictors of survival of patients with lung cancer treated at ORCI

Risk factor	MST	95% CI		Log Rank (X^2)	p-value
		LB	UB		
Targeted therapy					
No	19.943	15.777	24.109	2.39	0.122
Yes	24.714	14.307	35.121		
Radiotherapy					
No	19.360	14.759	23.96	0.77	0.381
Yes	22.971	15.676	30.265		
Chemotherapy					

Yes	21.778	17.489	26.068	10.68	0.001*
No	4.000	1.737	6.263		
Surgery					
Yes	36.839	25.048	48.63	8.10	0.004*
No	16.212	13.202	19.223		
Age category					
<=60	21.968	16.781	27.155	0.26	0.610
>60	19.374	12.948	25.801		
Tumor Grade					
II	35.912	25.4	46.423	15.13	0.001*
III	17.717	12.838	22.596		
Not mentioned	12.571	8.786	16.356		
Weight loss					
Yes	17.573	12.49	22.656	3.84	0.050*
No	25.352	18.917	31.786		
Metastatic Site.					
Bone					
Yes	11.929	7.97	15.887	7.83	0.005*
No	23.756	18.653	28.859		
Liver					
Yes	12.456	7.847	17.064	6.68	0.010*
No	23.868	18.753	28.983		
Brain					
Yes	10.200	4.009	16.391	4.12	0.042*
No	22.357	17.841	26.873		
Contralateral lung with effusion.					
Yes	13.384	9.837	16.93	7.12	0.008*
No	24.718	19.042	30.394		

*** Significant at P < .05, *p value calculated by Log rank test, MST – Mean Survival time*

Univariate analysis identified the following factors that may predict survival in patients with lung cancer: tumor grade <0.001, weight loss <0.05, bone metastasis<0.005, liver metastasis<0.010, brain metastasis<0.042, contralateral lung<0.008, chemotherapy<0.001, surgery<0.004. (Table 14).

Table 15: Cox regression analysis of multivalent predictors of survival of patients with lung cancer

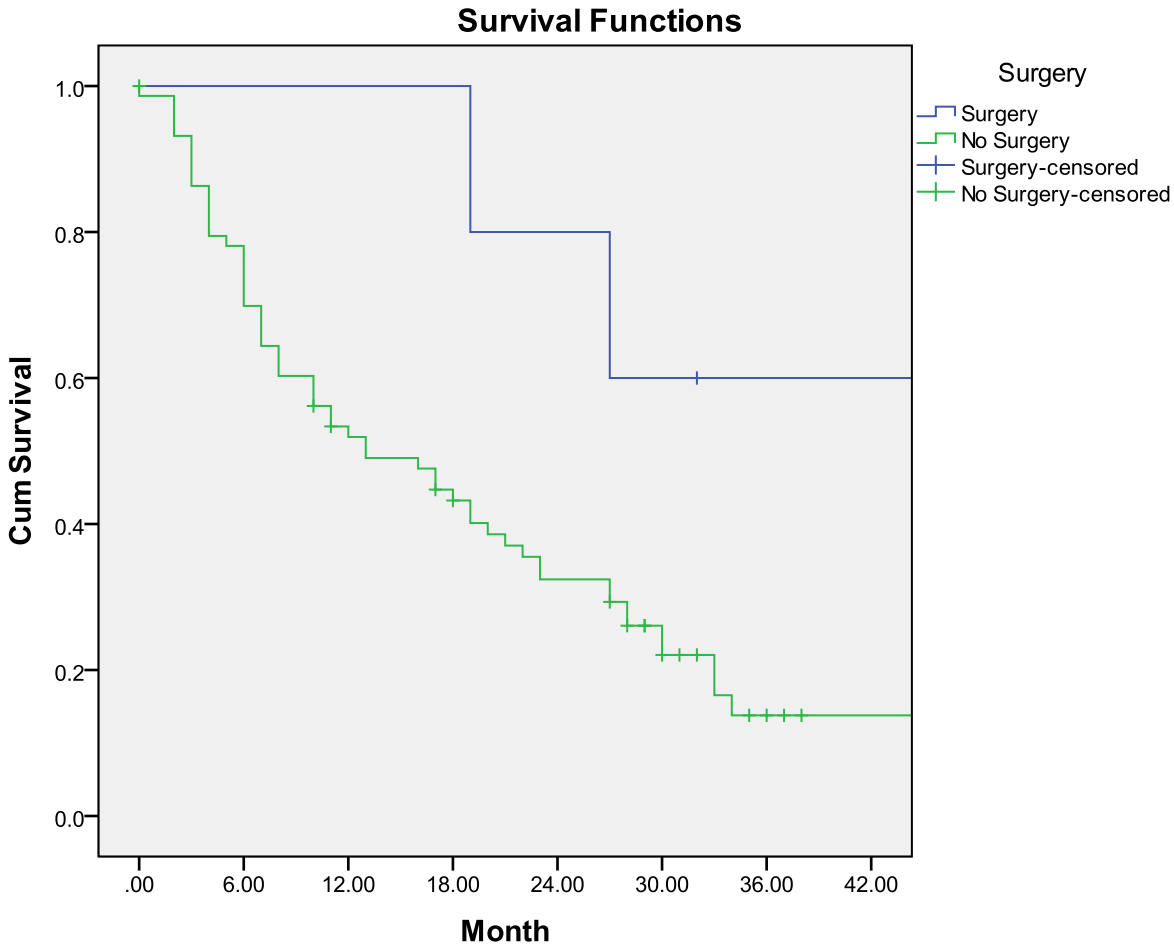
Risk factor	B	Wald (X^2)	AOR	95.0% CI		p-value
				Lower	Upper	
Tumor TNM Stage						
stage IV	ref	1.14	-	-	-	0.565
stage II	-13.56	0.00	0.000	0.000	-	0.980
stage III	-0.98	1.14	0.377	0.063	2.259	0.286
Tumor Grade						
Grade III	ref	4.43				0.109
grade I	-0.30	0.05	0.742	0.049	11.203	0.830
grade II	1.64	3.04	5.163	0.814	32.733	0.081
Treatment given						
Surgery	-2.24	5.35	0.107	0.016	0.711	0.041*
Chemotherapy	-4.10	5.70	0.017	0.001	0.480	0.017*
Targeted therapy	-1.08	0.61	0.340	0.023	5.112	0.435
Radiotherapy	-1.68	4.56	0.186	0.040	0.872	0.033*
Histological type.						
small cell	ref	4.41				0.110
adenocarcinoma	-2.76	2.94	0.063	0.003	1.486	0.087
Squamous Cell Carcinoma	-3.77	4.22	0.023	0.001	0.843	0.040*
Performance Status (ECOG)						
3	ref	12.83				0.002*
2	-1.61	7.00	0.201	0.061	0.659	0.008*

Metastatic diseases		.				.
lung	0.02	0.00	1.017	0.255	4.063	0.980
liver	-1.07	2.21	0.344	0.084	1.405	0.137
bone	2.17	7.35	8.734	1.824	41.826	0.007*
brain	1.71	3.68	5.534	0.963	31.789	0.055
Family history of lung cancer	-1.42	3.15	0.243	0.051	1.158	0.076
Tumor Location						
Left lung	ref					
Right lung	0.76	1.90	2.147	0.724	6.369	0.168
weight loss	0.13	0.05	1.140	0.362	3.595	0.823

** Significant at p≤ 0.05 level*

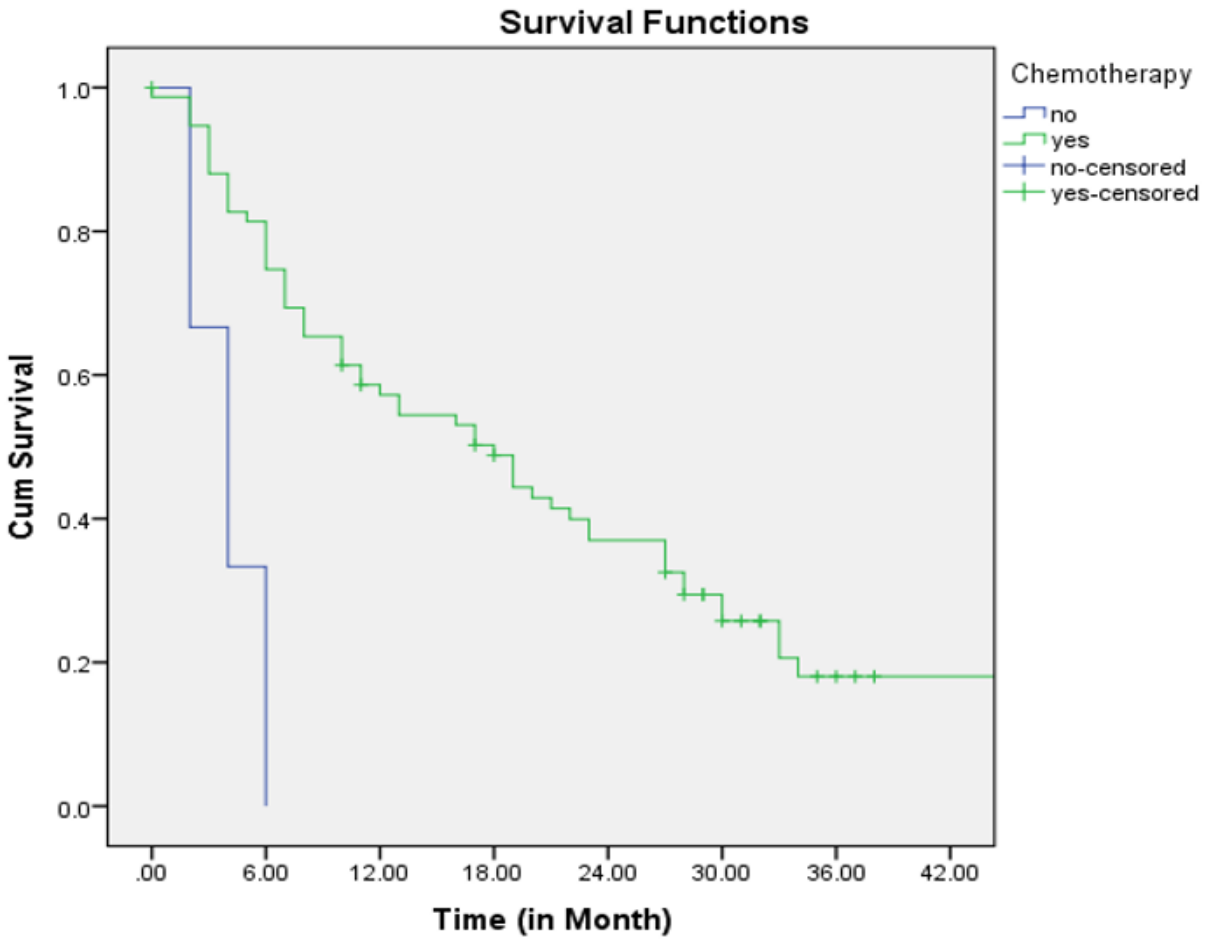
On multivariate analysis this study found four independent factors that may improve survival of patients with lung cancer: treatment with surgery (p=0.041), chemotherapy (p=0.017) Radiotherapy (p=0.033), performance status<2 (0.008). The study also identified two independent predictors that reduce overall survival: performance status >2 (p< 0.002) and metastasis to bone (p < 0.007). (Table 15).

Figure 5: Kaplan Meier Survival curve showing how surgery influenced survival in patients with lung cancer



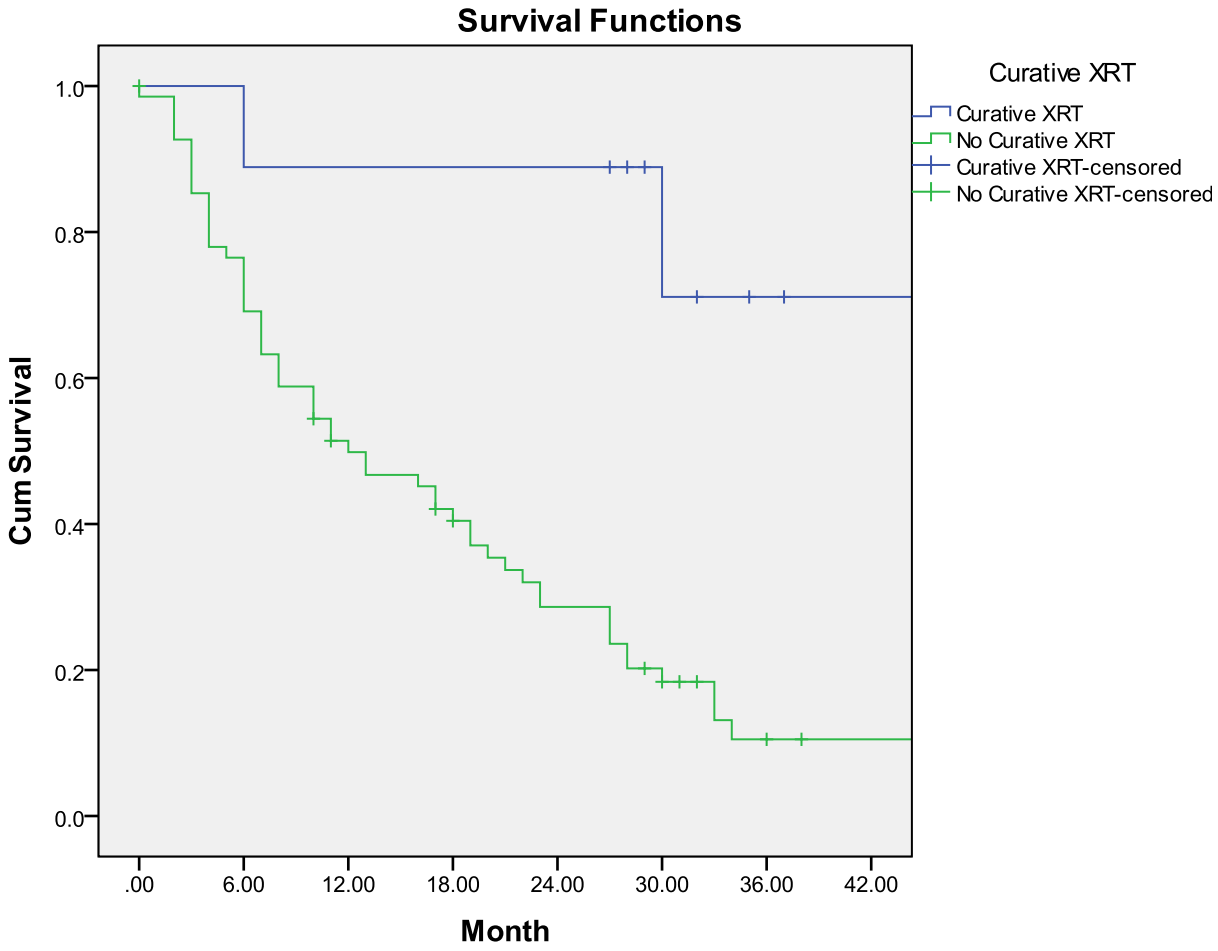
The figure 5 above shows that there is statistically significant survival benefit between patients with lung cancer treated with surgery verses those without surgery p value < 0.041.

Figure 6: Kaplan Meier Survival curve showing how treatment with chemotherapy influenced survival in patients with lung cancer



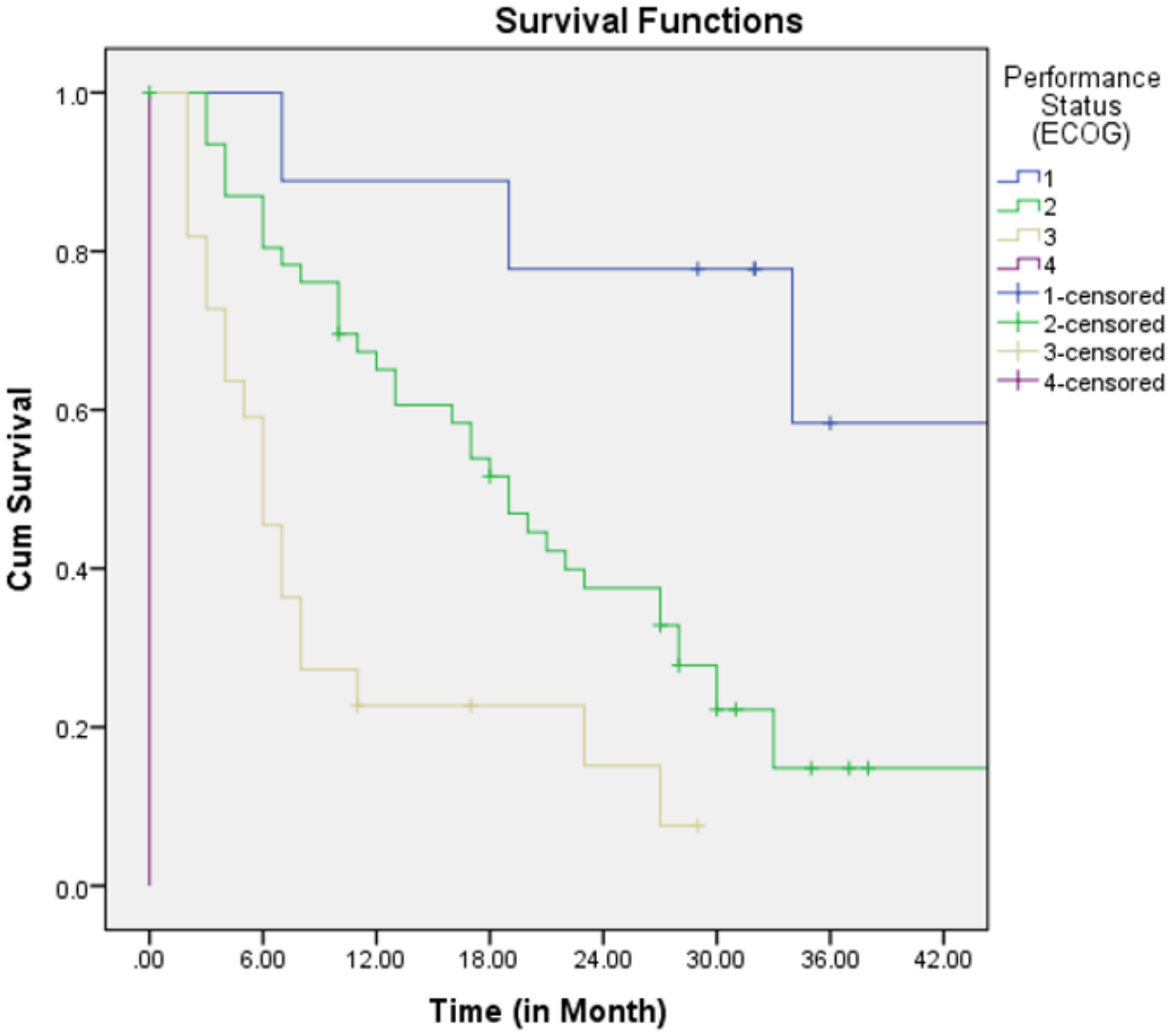
The figure 6 above shows that there is statistically significant survival benefit between patients with lung cancer who were treated with chemotherapy verses those not treated with p value < 0.017.

Figure 7: Kaplan Meier Survival curve showing how treatment with radiotherapy influenced survival in patients with lung cancer



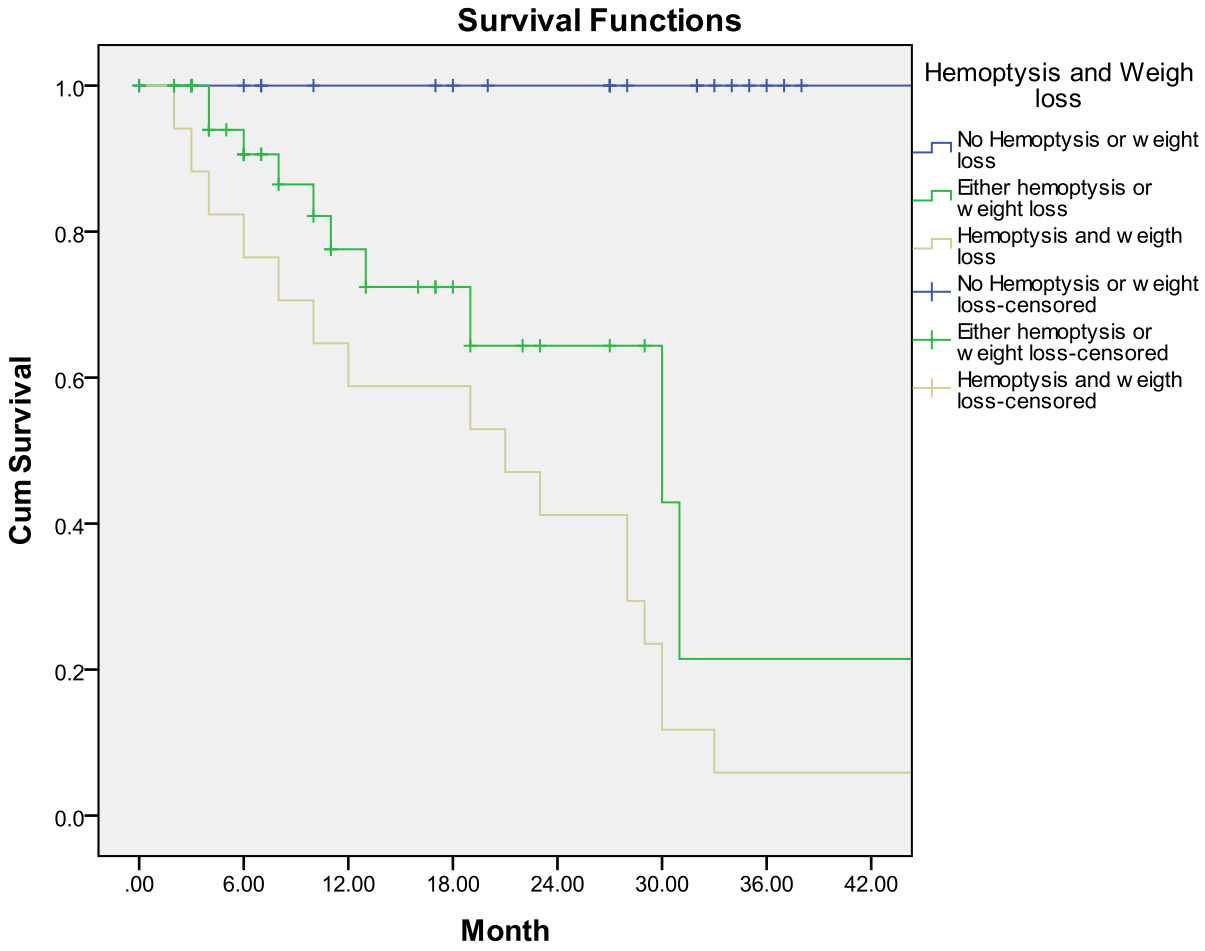
The figure 7 above shows that there is statistically significant survival benefit between patients with lung cancer who were treated with curative radiotherapy verses those not treated with p value < 0.033.

Figure 8: Kaplan Meier Survival curve showing how performance status influenced survival in patients with lung cancer



The figure 8 above shows that there is statistically significant survival benefit for patients with lung cancer who had ECOG of <2 verses those who had ECOG of > 2 at diagnosis with p value < 0.008.

Figure 9: Kaplan Meier curves showing how presentation symptoms influenced survival of patients with lung cancer



Majority(two thirds) of patients presented with either weight loss or hemoptysis for less than 3 months and on the other hand most patients who had cough or chest pain or difficulty in breathing had these symptoms for more than 6 months. Patients who had both hemoptysis and weight loss had poor survival compared to those who had one of these symptoms or none of these symptoms (P< 0.000) (Figure 9).

CHAPTER FOUR

4. DISCUSSION

From this study the mean age at the diagnosis of lung cancer was **56.85 years** with range of (23-86) years and the gender distribution showed that lung cancer affected more males than females with male to female ratio of 1.4:1.These results are comparable with most of the lung cancer studies. In a study by Singh Malik et el in India, which analyzed 434 pathological confirmed lung cancer , reported that the median age at diagnosis was **55 years** with a range of 23- 85 years(30). Another Egyptian study which analyzed 99 cases of lung cancer between 2012 and 2014 reported that the mean age at diagnosis was **53.4 years** with range of 30-70 years and a male predominance (M:F ratio: 1.7:1)(31). A Nigerian prospective study that was looking at the challenges of lung cancer treatment in developing countries reported that the age at diagnosis ranged from 30 - 81 years, mean 56.6±21.6 years and male: female ratio of 2.4:1(32). However, on contrary Western studies on lung cancer have shown that, median age at diagnosis is about a decade older than what this study has reported. Study by Blanchon et el in France reported that the mean age of lung cancer development was **64.1 years**(33). Also, study by Cetin. K et el in USA reported that the mean age at diagnosis of lung cancer was **64.2 years**(34). Another study done in china by Huan tang lin et el reported that on average, male patients with lung cancer were older than female **(69.58 ± 12.28 years** in male versus **66.67 ± 13.35 years** in female) and had a lower socioeconomic status(4).

Our study showed that peasant are the commonest affected group. This is contrary to study done in France, that reported farmers as one of the lowest group that develops lung cancer(33). The reasoning for these is that most of the population in Tanzania are peasant farmers without formal employment.

Smoking has been associated with development of most of the lung cancer cases especially squamous cell carcinoma type(4). However, in the last 2 decades adenocarcinoma has surpassed squamous cell carcinoma. And it has been reported that smoking is not associated with development of Adenocarcinoma (35)(36). In our study, we found that **(41.8%)** of the patients had smoked at one point in life while **46.8%** had never smoked. However, some patients

reported of passive smoking from the close family members whom they live with. Our results are comparable with Nigeria study by Ezemba .N et el, which reported that history of smoking was present in 42% of males who had lung cancer(32).

Most of the lung studies have reported that cough is the most common presentation. This was also the case in this study which reported that cough was reported in **(84.8%)** of the study cases**.** Other clinical presentations from this study included: weight loss **(59.5%),** chest pain **(58%),** difficulty in breathing **(42.3%),** hemoptysis **(34.2%)** and chest tightness **(6.5%).** Results from this study are comparable with other lung cancer studies(30)(31) (32)(33) (37)(38) (40).

Results from this study showed that at presentation **70.9%** patients had ECOG performance status ≤2 while **29.1%** had ECOG performance of more than >2. This results are comparable to many other studies which report that majority of the patient have ECOG performance status of less than <2(30)(33).

In this study NSCLC was diagnosed in majority of the patients **(92.4%)** while SCLC was diagnosed in **(7.6%)** patients. Among NSCLC cases, Adenocarcinoma was found to be the commonest histological subtype, accounting for **68.4%** of all lung cancer cases. According to studies over the last 2 decades there has been a shift of histological profile from squamous cell carcinoma towards adenocarcinoma worldwide. Also this study reported that the most common tumor grade was poorly differentiated (**43.0 %)** followed by, moderately differentiated (**25.3%)**, then well-differentiated **2.5%**. This study results are commensurate with other lung cancer studies done worldwide(30) (31) (34(32)(38) (39).

This study reported that most of the patients had primary lung tumor located on the right lung (**55.7%)** while the left lung was **44.3%.** This results are comparable to study done by A Caldarella et el which reported that tumor was more frequently located in right lung than in left lung both in women (53% vs 46%) and in men (58% vs 40%)(40). In another study done in Egypt by Shokrallan H A et el, it was reported that majority of the patients had primary lung cancer in the right lung (77%)(31).

From this study it was shown that at presentation most patients had stage IV disease. It was also shown that the commonest site for metastatic lung cancer was contralateral lung with pleural effusion for both NSCLC **35.6%** and SCLC **50%.** This study results are comparable with series of studies which reported that 50-70% cases of NSCLC and up to two thirds of SCLC usually present in advanced stage(33) (36)(41)(42).

In this study curative surgery rate was only 6.8% which was lower than recommended. This study is comparable to Indian study that showed among patients with NSCLC, only 5.36% patients underwent surgery(30).

However, study done in American reported that the surgical resection in lung cancer across races was lower than previously reported, and African Americans were significantly less likely to undergo surgery compared with whites (44.7% versus 63.4%; $p < 0.0001$). This American study also reported that even in the United States 30-60% of cases of early stage lung cancer do not undergo surgery(43)(44).

Our results showed that **96.2 %** of patients received chemotherapy. Some patients received more than one chemotherapy regimen. All the patients with SCLC received chemotherapy and the most common regimen was platinum/etoposide. About **95.9%** patients with NSCLC received chemotherapy and the common regimen was platinum /taxane. This results are similar to Indian study by Singh Malik et el which reported that chemotherapy was given to 75.47% of NSCLC patients and 100% of SCLC patients and the most common regimen prescribed was combinations of Paclitaxel and Carboplatin for NSCLC and Cisplatin and Etoposide for SCLC(30)

Only 11.4% of patients received curative radiation to the primary site. Our results are not comparable with Indian study by Singh Malik et el which reported that among patients with NSCLC, 39.08% while 36.7% of SCLC patients received radiotherapy to primary site. Majority of the patients (64.7% of NSCLC and 72.2% of SCLC) could receive palliative doses of

radiation(30). There was marked underutilization of this treatment modality partially because during this study period ORCI had only cobalt 60 machines only (Equinox 100 and Equinox 80 radiotherapy machines). In the late 2018, ORCI procured the linear accelerator machine and during this time majority of the patients were treated with curative intent. Generally, guidelines recommend that up to 76% of lung cancer patients should receive radiotherapy at some time point during their treatment. However in actual practice, 36-70% cases actually receive radiotherapy, worldwide(45)

A total of 7 (8.9 %) patients received targeted therapy and all of them had NSCLC. None of the patients with SCLC received targeted therapy. During this study period targeted therapy were not readily available and were costly. Bevacizumab was the most commonly 62% prescribed drug. Other agents used were Erlotinib, and Dabrafenib. In all patients who received targeted therapy, it was given as 2^{nd} line treatment based on clinical predictors and not on mutation results. This results are similar to other studies.(30)

The two year overall survival from this study was **37%** which comparable with other studies(30).From this study the mean overall survival rate was **10.14 months** and the median overall survival was **8 months** with the 95% confidence interval. This reflects the large proportion of advanced stage disease in the study population. Furthermore, many of early stage patients could not complete the expected treatment and hence had lower survival than expected. These results are comparable with Indian study by Singh Malik et el which reported that the median overall survival of patients with NSCLC and SCLC was 12.8 months 95%CI 11.0- 14.7) and 9.1 months (95%CI 6.1-8.8) respectively(30). Another Brazilian study by Luiz Henrique de Lima et el reported that the median overall survival rate was 19.0 months (95% CI 16.2 – 21.8). However, this overall survival was higher than in this study and this could be explained by the fact that Brazil has better health systems than Tanzania.

On multivariate analysis of the index study it was found out that treatment with surgery, chemotherapy use, radiotherapy and ECOG status less than two were independent predictors that could increases overall survival. On the other hand ECOG status more than two, metastasis

to bone and weight loss were negative predictors of survival in patients with lung cancer. These results are comparable to a study done by I RCH, I JHS, I NT, I CGF et el which reported that female patients also had greater survival rates, as well as those with better PS , no weight loss and no history of smoking (26).Also in a larger study of 4669 patients with NSCLC, done by Blanchon et al reported that age, stage, PS, histology and treatment modalities used had a significant impact on survival(33).

CHAPTER FIVE:

5.0 LIMITATION, CONCLUSION AND RECOMMENDATION.

5.1 Study Limitations

This was a retrospective study so some of the medical charts did not have the data that was needed for the study. Some did not have information about tumor grade, history of smoking or alcohol consumption. Some medical charts were not clearly documented thus making data extraction difficult.

Survival information was not found in majority of the medical charts, which prompted calling of the patients or guardians to get the data. However, some of the patients were unreachable through mobile numbers and were censored lost to follow up.

This study results are not a true reflection of the current radiotherapy treatment at ORCI, as much has changed since the commission of the linear accelerator machine in the late 2018. Prior to the commission of the linear accelerator machine radiotherapy of lung cancer was mainly by use of 2 D conventional technique using cobalt 60 machines (Equinox 100 and Equinox 80 radiotherapy machines).

5.2 Conclusion.

Patients treated at Ocean Road Cancer Institute had characteristics and survival rates that is similar to data from international literature. A high proportion of patients were diagnosed at advanced stages and the outcomes remained poor because many of them were not able to receive adequate treatment. Treatment was largely palliative due to advanced stage of the lesion at presentation. Multivariate analysis of patient characteristics found out that treatment with surgery ($p=0.021$), chemotherapy ($p=0.017$), Radiotherapy ($p=0.033$) and ECOG < 2 (0.002) were independent predictors that could increases overall survival. On the other hand ECOG of > 2 ($p< 0.008$), weight loss and metastatic to bone (0.007) were negative predictors of survival in patients with lung cancer who were treated at ORCI between January 2014 and December 2018.

5.3 Recommendation.

1. Majority of the patients were diagnosed at advanced stage therefore another study to find out why most patients are diagnosed at a late stage?
2. Another study needs to be done to compare the survival rate of lung cancer patient's treatment during the 2 D radiotherapy era and 3 D radiotherapy era.
3. Some of the medical charts were poorly documented thus capacity building should be done so as to improve documentation especially on histology reporting and during patient follow up notes.
4. Since surgery improved overall survival, all patients with medically operable early stage lung cancer surgery should be done.

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APPENDINCES.

Appendix I: Lung Cancer Data Collection Form.

SERIAL NO……

Date …….

Reg No: ……...

SECTION 1. Patient Particulars and Demographics.

1. Age: (years)….…….

2. Sex. (Tick where appropriate)

(1) Male

(2) Female

3. Residence: ……..

4. Occupation: (Tick where appropriate)

(1) Peasant (2) Businessman/woman (3) Civil servant (4) Teacher

(5) Police officer (6 Miners

5. Smoking Status: (Tick where appropriate)

(1) Yes (2) No

6. Alcohol Consumption. (Tick where appropriate)

(1) Yes (2) No

7. Family History of lung Cancer: (Tick where appropriate)

(1) Yes (2) No

B. Clinical Characteristics. (Tick where appropriate)

8. Cough. (1)(Yes) (2) (No) if yes duration ……..

9. Chest Pain: (1) (Yes) (2) (No) if yes duration……

10. Hemoptysis (1) (Yes) (2) (No) if yes duration……..

11. Weight Loss (1) (Yes) (2) (No) if yes duration……

12. Difficulty in breathing (1) (Yes) (2) (No) if yes duration……

13. Chest tightness (1) (Yes) (2) (No) if yes duration…….

14. **Performance Status**: **ECOG** (Tick where appropriate)

(1). 0 (2). 1 (3). 2 (4). 3 (5). 4 (6). Not Mentioned.

SECTION B: Tumor Characteristics.

15. Histological Type. (Tick where appropriate).

(1) Adenocarcinoma (2) Squamous cell carcinoma (3) Large cell

(4) Small cell. (5) Others specify.

16. Tumor Location. (Tick where appropriate).

i) Right lung (1) (Yes) (2) (No)

If yes

1. Upper lobe ( )
2. Middle lobe ( )

3. Lower lobe ( )

ii) Left lung (1) (Yes) (2) (No) (Tick where appropriate)

If yes

1. Upper lobe ( )
2. Lower lobe ( )

17. Tumor TNM Stage. (Tick where appropriate).

1 .Stage l

2 .Stage lI

3 .Stage llI

4 .Stage IV

5 .Unknown ……

18. Metastatic site. (Tick where appropriate).

(1) Bone (2) Liver (3) Brain (4) Contralateral lung.

19. Tumor grade. (Tick where appropriate).

1) I (2) II (3) .III (4) .Not mentioned.

SECTION C. Treatment Received.

20. Surgery. (Tick where appropriate)

1 .Yes 2 .No

21. Type of surgery done. (Tick where appropriate)

1 .Lobectomy.

2 .Wedge resection.

3 .Pneumonectomy.

4 .Biopsy only.

5 .Not mentioned.

22. Chemotherapy. (Tick where appropriate)

1 .Yes. 2 .No.

23. Which regimen. (Tick where appropriate).

(1). Carboplatin/paclitaxel (2). Carboplatin/ etoposide (3). Gemcitabine/cisplatin

(4). Cisplatin /paclitaxel. (5). Cisplatin /etoposide. (6). Cisplatin/docetaxel.

(7). Premetrexate/carboplatin. (8). Carboplatin/docetaxel.

24. Cycle (s) given. (Tick where appropriate).

(1). One (2). Two (3). Three (4). Four (5). Five (6). Six

25. Duration

a. Start date of chemotherapy…….

b. Last date of chemotherapy…….

26. **Targeted therapy.** (Tick where appropriate)

(1). Yes **(2). No**

If yes which regimen. (Tick where appropriate).

1. Bevacizumab (2). Cetuxumab 3. Erlotinib (4). Dabrafenib

Number of cycle. (Tick where appropriate)

(1). One (2). Two (3). Three (4). Four (5). Five (6). Six

Duration

a. Start date

b. Last date

27. Radiotherapy. (Tick where appropriate)

1. Yes (2). No

If yes what was the intent. (Tick where appropriate)

1. Curative (2). Palliative

If Curative Intent.

Dose and fraction. (Tick where appropriate).

1. 45 Gy in 30 fractions
2. 60 Gy in 30 fractions
3. 66 Gy in 33 fractions

If palliative intent.

Site radiated. (Tick where appropriate).

1. Brain (2). Bone (3). Liver

Dose and fraction regimen. (Tick where appropriate)

(1). 8 Gy single fraction. (2). 20 Gy in 5 fractions. (3). 30 Gy in 10 fractions.

SECTION D.

28. Survival.

Date of diagnosis: ……

Date of death: ……

Date of last follow up.....

Status at last follow up……

Duration of follow up (month)……

Appendix 2: Phone Call Guide.

Title: Clinico-Pathological Characteristics, Treatment Modalities and Survival of Patients with Lung Cancer at Ocean Road Cancer Institute.

Principle Investigator.

Dr. Omari Ogora Nyangau Fred

Resident Clinical Oncology.

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This phone call guide will be used by the principle investigator and two assistant investigators for the purpose of getting more information about patient survival status when such information is not found in the medical charts.

The following procedure will be followed.

1. The investigator will call the patient or guardian using contact phone numbers provided in the medical charts.

2. Once the recipient (Patient or Guardian) picks up the call, the investigator will introduce himself/herself, then inform the recipient the aim of the call and purpose of the study. The purpose of the study is to determine the Clinico - Pathological Characteristics, Treatment Modalities and Survival of patients with lung cancer who were treated at Ocean Road Cancer Institute as from January 2014 to December 2018. The aim of the call is to get information about a patient (mentioning the name of patient and the last date of clinic visit- for identification) survival status.

3. The investigator will assure the recipient that there are no risks associated with this study and the information given will be treated with high index of confidentiality. The investigator will welcome any questions and clarifications concerning the information given.

4. If the information that is given is clear, the investigator will ask for verbal consent before giving the information. Those recipients who will decline to give verbal consent, their decision will be respected but they will be excluded from the study.

5. For the recipient who consent, they will be given a chance to narrate about patient status- if deceased they will give the date of death. The investigator will console with the guardian and once more assure for confidentiality of the information given. If the patient is alive, the recipient will narrate how the patient is doing currently and give the date for the next visit. The investigator will give information on the importance of regular clinic visits and encourage them not to miss the scheduled clinic visits.

6. For the patient whose phone numbers (contacts) in medical charts that will be unreachable through the calls during the course of data collection (45days) they will be censored lost to follow up.

7. All patients /guardians who will be called for interview will be given contact information for use if they have questions at any time about this study. They may contact the principle investigator whose contact information is provided on the first page. If they have questions regarding their rights as a research participant, or if problems arise which they do not feel they can discuss with the principle Investigator, they can contact.

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