PREVALENCE AND PREDICTORS OF ORAL MUCOSITIS IN PATIENTS UNDERGOING RADIOTHERAPY FOR HEAD AND NECK CARCINOMAS AT THE KENYATTA NATIONAL HOSPITAL

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UNIVERSITY OF NAIROBI

STUDENT'S DECLARATION

This is my original work which has not been presented for a degree award at any other university.

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ACCRONYMS / ABBREVIATIONS

DNA:	Deoxyribo Nucleic Acid
EGF:	Epidermal Growth Factor
ENT:	Ear Nose and Throat
FGF:	Fibroblast Growth factor
5FU:	5- Florouracil
GCSF:	Granulocyte Colony Stimulating Factor
HSV:	Herpes Simplex Virus
IL:	Inter Leukine
IgA:	Immunoglobulin A
KNH:	Kenyatta National Hospital
MND :	Metastatic Neck Disease
NF-κβ:	Nuclear Factor – κβ
NCI-CTC:	National Cancer Institute – Common Terminology Criteria
NGT :	Nasogastric Tube
PROMS :	Patient Reported Oral Mucositis Symptom Scale
PEG:	Percutaneous Endoscopic Gastrostomy
QOL:	Quality of life
TPN :	Total Parentral Nutrition
TNF α:	Tumour Necrosis factor α
WHO:	World Health Organisation

ABSTRACT

Background

Oral mucositis is a common and significant acute complication of radiotherapy and chemotherapy but there is limited data on its overall impact, prevalence and risk factors in our setting.

Objective

To determine the prevalence and predictors of oral mucositis in patients with head and neck carcinomas, undergoing radiotherapy at the Kenyatta National Hospital.

Study Setting and Population

The study was carried out at the Kenyatta National Hospital radiotherapy clinic, the ENT (Ear, Nose and Throat) ward and the adult oncology ward. The study sample consisted of 72 patients undergoing radiotherapy for head and neck carcinomas.

Study Design and Methodology

This was a prospective cross sectional study. Pre-treatment demographic and clinical data were collected and the patient's oral cavity was also examined. Participants were re-evaluated at the end of 2, 4 and 6 weeks, during which any oral lesions were graded using the NCI-CTC (National Cancer Institute – Common Terminology Criteria) grading scale.

Results

All the 72(100%) patients developed mucositis by the second week of treatment. A total of 51 patients (70.8%) developed grade 3 mucositis by the 2^{nd} week of treatment. Patients with oral cavity tumours had the highest risk of developing severe mucositis (p value 0.001), in contrast patients with laryngeal carcinomas had the lowest risk of developing severe mucositis ($p < 0.001$). The presence of oral ulceration pre-treatment was found to increase the risk of developing severe mucositis (p value 0.005) and concurrent chemotherapy increased the odds of developing severe mucositis by 2½ times.

Conclusion and Recommendations

The prevalence of mucositis is high in head and neck carcinoma patients undergoing radiotherapy at KNH. There is need for increasing interventions in management of mucositis, to improve the quality of care offered in our set up.

1.0 CHAPTER ONE: INTRODUCTION

Oral mucositis can be described as an inflammatory process involving the epithelial lining of the oral cavity. The process involves gradual thinning of the oral mucosa and eventual ulceration.[1] It is a common side effect of cancer therapies especially chemoradiotherapy.

Oral mucositis leads to severe oral pain which impacts negatively on the successful treatment of head and neck cancer. It leads to reduced oral intake which affects the nutrition of head and neck cancer patients and it eventually increases the use of resources in management of cancer[2] e.g. by an increased need for P.E.G (Percutaneous Endoscopic Gastrostomy) tube placement in patients who develop mucositis. [3, 4]

1.1Background

1.1.1 Pathogenesis of Oral Mucositis

Understanding the pathogenesis of oral mucositis is of paramount importance in assessment of patients with oral mucositis and in grading oral mucositis lesions.

Oral mucositis has been found to typically occur 7- 14 days after radiotherapy or chemotherapy initiation. It has been found to last up to 2-3 weeks after completion of treatment.[1]

Oral mucositis was initially thought to only involve the epithelial lining. Once the patient is exposed to radiotherapy or chemotherapy there is damage to the basal layer of the epithelium. As the superficial cell layers of the epithelium are lost during exfoliation, the epithelium becomes thinner and thinner since no new cells will be formed by the damaged basal layer. This results in erythema and in eventual ulceration.

Current evidence suggests that mucositis not only involves changes in the epithelium but also within the submucosa.[5] It has been shown that submucosal blood vessels and connective tissue are damaged by irradiation prior to changes seen in the epithelium[6]. Platelets also play a role in the pathogenesis of oral mucositis, if platelet aggregation is inhibited, severity of mucositis reduces.[7]

More importantly it has been found that oral mucositis pathogenesis involves various proinflamatory cytokines and when these cytokines are blocked there is associated reduction in oral inflammation.[6, 8, 9]

Sonis divided mucositis into 5 stages to simplify its understanding[5], however, even with these stages it should be remembered that oral mucositis is a dynamic process.

Sonis 5 Stages:

a) Initiation
b) Primary damage response
c) Signal amplification
d) Ulceration
e) Healing

With radiotherapy there is a gradual overlap of these stages but with chemotherapy the stages occur in quick succession.

1.1.2 Initiation

Radiation and chemotherapy cause basal cell injury by causing DNA (Deoxyribo Nucleic Acid) strand breaks. There is also production of Reactive Oxygen Species with introduction of chemotherapy and radiotherapy. The Reactive Oxygen Species directly injure cells, tissues and blood vessels.[10, 11]

1.1.3 Primary Damage Response

The DNA strand breaks and Reactive Oxygen Species cause activation of various transcription factors such as nuclear factor κ-β (NFκ-β). Activation of NFκ-β leads to activation of various genes involved in the production of proinflamatory cytokines such as IL-6 (Interleukin-6), IL-1β (Interleukin-1β) and TNF-α (Tumor Necrosis Factor-α)[12].

These cytokines once produced lead to tissue injury and eventual apoptosis. The cell membrane is also hydrolyzed by chemoradiotherapy; this activates the ceramide pathway and also leads to apoptosis[13, 14].

1.1.4 Signal Amplification

Via a positive feedback loop, proinflamatory cytokines produced during the initial processes cause further tissue damage. TNFα has also been shown to activate the ceramide and caspase pathways hence leading to apoptosis and tissue damage.[12] TNFα also activates NF-κβ, which via positive feedback results in increased production of TNFα, IL-1β and IL-6. Proinflamatory cytokines produced then cause further mucosal damage and further mucosal damage again leads to production of more proinflamatory cytokines. These proinflamatory cytokines also activate matrix metalloproteinase which causes direct tissue injury.[15]

1.1.5 Ulceration

All the changes mentioned above eventually lead to mucosal ulceration. This results in severe oral pain which is experienced by the patient.

Ulceration of the mucosa serves as a port of entry for colonizing bacteria and other microbes from the mouth into the systemic circulation[16] .This can lead to life threatening sepsis especially since most patients are usually severely neutropenic.

Colonizing micro-organisms invade the submucosal tissues. This activates macrophages leading to release of proinflamatory cytokines which further cause tissue damage.

1.1.6 Healing

Healing has been shown to occur within 2-3 weeks after cessation of treatment. The process of healing involves epithelial proliferation and differentiation mediated by a signal from the extracellular matrix. In addition there is normalization of white cell count and local microbial flora.

It is important to note that despite the fact that the mucosa appears to return to normal at this stage, certain changes such as angiogenesis remain. This increases the risk of development of oral mucositis with subsequent exposure to chemotherapy or radiotherapy[10, 11]

1.2 Stages of Oral Mucositis[17]

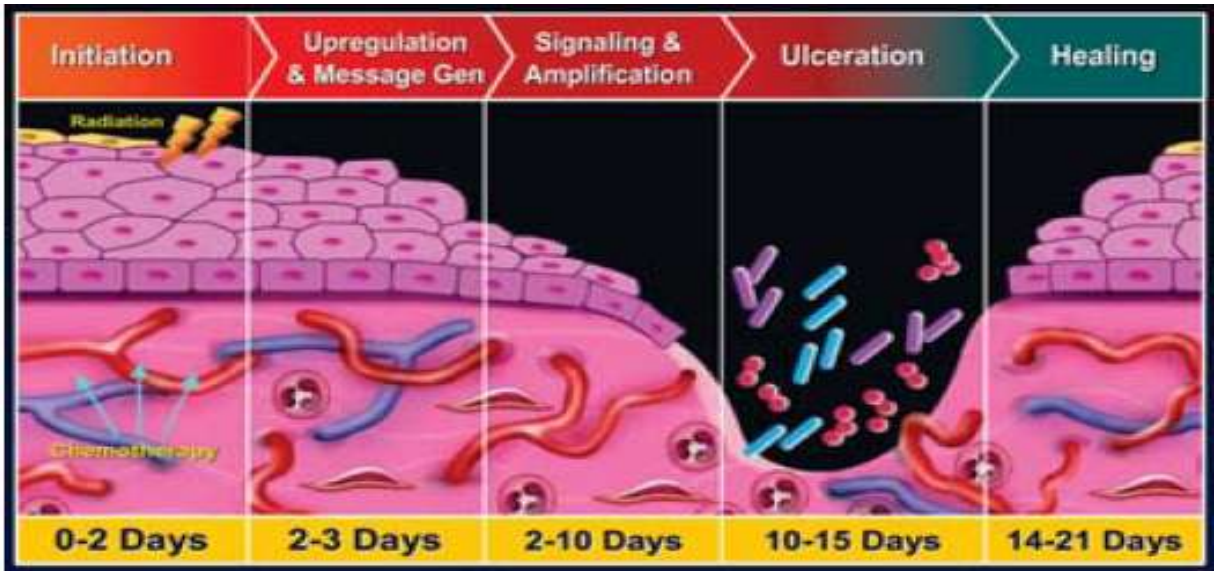

Figure 1: Stages of oral Mucositis

1.3 Grading of Oral Mucositis

There is no universally accepted grading system for oral mucositis. The system used varies from researcher to researcher. This inconsistency is a limitation when assessing the evidence of effectiveness of interventions across different studies on oral mucositis.

Commonly used grading scales include the World Health Organization (WHO) and National Cancer Institute – Common Terminology Criteria (NCI-CTC) scales. The NCI-CTC system separates scores for clinical appearance e.g. erythema and ulceration and scores of function e.g. pain and ability to eat liquids and solids. In contrast the WHO system combines both elements in a single score. The NCI-CTC system is therefore preferred in most scientific studies; the latest version of NCI-CTC is version 4.0. It is generally recommended that each institution should have a standard protocol for oral mucositis assessment for effective patient management. The assessments should be carried out frequently with the patients self reporting forming an integral part of the assessment.

For patients self reporting various tools have been used one being the Patient Reported Oral Mucositis Symptom (PROMS) Scale. PROMS has been found to have good corelation with other clinical indicators of oral mucositis [18,19]. It consists of a 10 item visual analogue scale covering symptoms frequently experienced by patients with mucositis.

Table 1: Grading Scales for Mucositis

GRADE	1	2	3	4	5
NCI-CTC v.4.0 CLINICAL CRITERIA	Erythema of mucosa	Patchy ulcerations or pseudo membranes	Confluent ulcerations or pseudo membranes, bleeding with minor trauma	Tissue necrosis, significant spontaneous bleeding, life threatening consequences	Death related to toxicity
NCI-CTC v.4.0 FUNCTIONAL CRITERIA	Minimal symptoms, normal diet	Symptomatic but can eat and swallow modified diet	Symptomatic and unable to adequately aliment and hydrate orally	Symptoms associated with life threatening consequences	Death related to toxicity
WHO	Oral soreness, erythema	Oral erythema, ulcers, solid diet tolerated	Oral ulcers, liquid diet only	Oral alimentation impossible	—

1.4 Risk Factors for Oral Mucositis

There is little evidence to support the various risk factors for mucositis[2]. Some of the risk factors that have been reported in literature include: radiotherapy regime, dose and schedule, and chemotherapy regime, dose and schedule. Hyperfractionated regimens and concomitant chemotherapy have been found to increase the risk, severity and duration of mucositis.[20, 21]

Dodd et al identified a vast number of patient's and treatment related risk factors for development of oral mucositis.[22] Some of these risk factors are shown in the following table.

Table 2: Patient's and treatment related risk factors for development of Oral Mucositis

PATIENT RELATED	TREATMENT RELATED
Gender(more in female)	Radiotherapy : dose, schedule
Age > 65yrs and < 20yrs	Chemotherapy: agent, dose, schedule
Inadequate oral health and hygiene practices	Myelosuppresion
Periodontal disease	Neutropenia
Microbial Flora	Reduced IgA secretion
Chronic low grade mouth infections	Infection with bacteria, viruses, fungi
Salivary gland secretory dysfunction	Use of Opiates, antihypertensives antihistamines, diuretics and sedatives
Inborn inability to metabolize Chemotherapeutic agents effectively.	Protein caloric malnutrition and dehydration
Exposure to oral stressors : alcohol and smoking	Xerostomia
Ill fitting dental prosthesis	Impairment of renal or Hepatic function

1.5 Treatment and Prevention:

There are different protocols in various institutions for treatment and prevention of oral mucositis. Some of these interventions include the following:

- Use of validated tools to regularly assess the oral cavity during the course of treatment Such as: PROMS, Oral mucositis weekly questionnaire and Oral mucositis Index.
- Use of a soft toothbrush
- Dental care by professionals throughout the course of treatment
- Analgesics e.g. morphine
- Use of benzydamine for prevention of mucositis[23]
- Topical antimicrobials e.g. polymixin, tobramycin and amphotericin B, chlorhexidine oral rinses[24]
- Anti inflammatory agents: misoprostol, prednisolone
- Salivary function modifiers : pilocarpine[25]
- Cryotherapy[26]
- Growth factors : GCSF, EGF, FGF
- Low level laser therapy[27]

2.0 CHAPTER TWO: LITERATURE REVIEW

Oral mucositis is a common and significant acute complication of radiotherapy and chemotherapy. Oral mucositis has been found in most studies to occur in virtually all patients undergoing radiotherapy or chemoradiotherapy for Head and Neck Cancer.

Janjan et al[28] conducted a descriptive study to explore the quality and intensity of pain associated with radiotherapy induced oral mucositis. Daily pain diaries were completed by 14 patients undergoing radiotherapy for a newly diagnosed head and neck cancer. All patients developed painful mucositis usually during second to third week of radiotherapy. Despite the use of analgesics pain was rated as moderate or severe on 37% of the treatment days. Some of the limitations of this study were the small sample size which gives the study less power. There was also lack of a standardized criterion for grading mucositis, this can lead to high individual variability among patients and makes it difficult to compare outcomes for example with other studies on mucositis.

Ohrn et al[29] studied oral status and experiences in 41 patients during the course of chemotherapy and radiotherapy for head and neck cancer treatment. Patient reported outcomes were graded using a Visual Analogue Scale (VAS) which evaluated items such as pain, changes in taste and the viscosity of saliva. Mucositis was graded clinically by two examiners using the Oral Mucositis Index. Patients were evaluated regularly at 10 Gray increases of radiotherapy and once a week during chemotherapy. It was found that once radiotherapy was initiated, patients developed higher score in the VAS over time. In addition patients who had been on neoadjuvant chemotherapy were found to have higher baseline scores of mucositis. The overall incidence of mucositis was 100% by the end of treatment. From this study Ohrn recommended utilizing both clinical assessment and patient reported outcomes when assessing mucositis.

Trotti et al[2] conducted a systemic literature review to study mucositis incidence severity and associated outcomes in patients with Head and Neck Cancer receiving radiotherapy with or without chemotherapy. Thirty three studies met the inclusion criteria with a total of 6,181 patients. The overall incidence of mucositis was found to be 80%. He found that majority of the patients: 25-45% had grade 3-4 oral mucositis which limited or prevented alimentation and significantly decreased the patient's QOL. In this study it was found that patients with mucositis had increased hospitalizations and feeding tube placement compared to patients without oral mucositis. Trotti concluded that mucositis occurs frequently and severely but its

overall impact on treatment outcomes has not been adequately investigated. In this study two reviewers screened both abstracts and full papers to select studies for inclusion in the review, however the author did not state whether the reviewers performed the selection independently yet this can introduce a selection bias in such a study. The author also did not state how the papers were assessed for validity or how the reviewers performed the validity tests.

Montserrat et al[30] conducted a nationwide cross-sectional survey. Data regarding 450 head and neck cancer patients was collected via chart reviews from 154 medical and radiation oncologists. Information collected included patient characteristics, treatment received and highest recorded grade of mucositis during radiation therapy. The grade of mucositis was based on the investigators judgment on whether it was mild, moderate or severe mucositis. From this study 83% of patients undergoing radiotherapy for head and neck cancer developed oral mucositis, with 29% developing severe mucositis. In this study it was concluded that patients with nasopharyngeal carcinoma or oropharyngeal carcinoma were more likely to develop severe oral mucositis. A radiotherapy dose of more than 50 Gray was also found to cause oral mucositis. Patients with oral mucositis were found to most likely have also received concomitant chemotherapy. It was also found in this study that patients with oral mucositis had a fourfold chance of unplanned breaks in treatment compared to those without mucositis and had higher rates of hospital admissions. The results of this study are comparable to the study by Trotti et al[2] where the prevalence of mucositis was 80%. Unlike what has been reported in other studies older patients were found to have a lower risk of mucositis, however, it was not reported what the cumulative radiation dose in these patients was. Other limitations noted in this study was the lack of a standard grading scale for mucositis and that the assessment was done by different clinicians each with their own judgment of the degree of mucositis in each patient. There could also have been a selection bias in this study since medical records were not randomly selected.

Linda et al[31] conducted a prospective study mainly focusing on the patient reported outcomes on mucositis among head and neck cancer patients, 191 patients were recruited in this study. The study results were based on patient reported outcomes where a standard questionnaire, the Oral Mucositis Weekly Questionnaire was filled by the participants. In addition the study assessed the quality of life of these patients during their treatment using various quality of life assessment questionnaires. Contrary to the findings of Montseratt et al[30] the risk of oral mucositis was similar in patients with oropharyngeal cancer (99%) and in patients with cancer of the larynx or hypopharynx (98%). It was also found that QOL scores decreased

from 85.1% at baseline to 69 % at week 6 corresponding with peak mucositis severity. One limitation of this study was the failure to utilize clinical assessment to complement the patient reported outcomes. According to findings reported by Ohrn et al[29] patient reported outcomes have a high individual variability and some patients had a tendency to under report their symptoms making it less accurate.

Barbara et al[32] conducted a prospective longitudinal multicentre non-interventional study of mucositis related morbidity and resource utilization in head and neck cancer patients receiving radiotherapy with or without chemotherapy. A total of 75 patients were enrolled from 6 centers. Mouth and throat soreness was reported by the participants using the Oral Mucositis Weekly Questionnaire. Resource utilization due to effects of mucositis was also assessed by interviews and recorded in patient charts. From this study 76% of the patients developed oral mucositis. Pain and functional impairment because of mouth and throat soreness increased during the course of therapy, despite the use of opioid analgesics in 85% of the patients. She found that 51% of the patients had feeding tube placements and 37% of the patients were hospitalized, with 30% of the admissions being due to mucositis. It was concluded that mucositis related pain and functional impairment is associated with increased use of costly health resource. Just like in the study by Linda et al[31], one limitation was that the patients were not assessed clinically and the findings were based primarily on the patient reported outcomes. Another limitation observed is that even with most patients reporting severe pain while on opioid analgesics, their compliance was not evaluated.

Bhide et al[33] studied the effects of chemotherapy and radiotherapy on the oral and pharyngeal mucosa. Patients were evaluated clinically using the Common Terminology Criteria grading scale. The incidence of grade 3 dysphagia was found to be between 60-70% for pharyngeal mucosa receiving a radiation dose of 50Gy and 60Gy respectively. He also found that the length of pharyngeal mucosa receiving doses close to the prescription dose correlates with grade 3 dysphagia. A limitation of this study was the failure to use patient reported outcomes to complement the clinical assessment of mucositis. The disadvantage of such an approach is that clinical examination may underestimate the degree of mucositis if the area affected is not visible on examination for example in the hypopharyngeal wall. It is recommended that patient reported outcomes and clinical assessment be utilized together to complement each other.

Ourania et al[34] studies oral mucositis in 135 Head and Neck Cancer patients. He assessed severity of oral mucositis during the course of radiotherapy, in patients who had received antiviral and antifungal treatment. Oral mucositis was scored weekly and patients self evaluated their symptoms of pain and xerostomia. Systemic antifungals and antivirals were administered during chemoradiotherapy upon presumptive diagnosis of candidiasis and herpetic infection and the drugs were continued to the end of radiotherapy. The incidence of mucositis was found to be 57% but thereafter reduced to 33% ($P<0.001$), at the end of radiotherapy. The findings of lower incidence of mucositis in this study compared to other studies discussed above demonstrated the important role of these infections in the pathogenesis of mucositis. The limitation of this study was the lack of verification of the fungal status before and after treatment and the verification of the viral status in only 47% of the patients.

Karthika et al[35] studied the changes in the quality and quantity of oral epithelial cells as a result of mucositis during the course of chemoradiotherapy for head and neck cancer. He followed 30 patients throughout the course of treatment and they were compared to age and sex matched healthy individuals. The study involved WHO clinical scoring, collection of oral washings and preparation of buccal smears for both the study and control groups. Oral mucositis was assessed at a cellular level by determining the oral mucosal cell viability and their level of maturation during the course of chemoradiotherapy. Mucositis occurred in all patients by week 3 of treatment. The study group showed higher percentages of viable buccal epithelial cells in oral washings when compared to controls. These changes preceded changes in WHO grading system making cellular assay more sensitive for detection of mucositis compared to the WHO grading system.

Yokota T et al [36] performed a retrospective study of 14 patients with advanced head and neck cancer undergoing chemoradiotherapy and cetuximab therapy. Data was obtained from medical records in a single institution. Prophylactic Percutaneous Endoscopic Gastrostomy (P.E.G) tubes were considered before chemoradiotherapy initiation because severe mucositis is a common complication. Prophylactic PEG tube insertion was performed in 11 patients. Grade 3 mucositis occurred in 85.7% of the patients. Some of the limitations of this study include the small sample size which may not be used to draw a meaningful conclusion and the fact that mucositis was graded by different clinicians which creates inconsistencies due to individual variability of patient assessment. In this study the author did not discuss how patient selection was done to avoid selection bias.

Table 3: Prevalence of reported OM associated with head and neck Cancer radiotherapy in selected clinical studies

LEAD AUTHOR	YEAR	SAMPLE SIZE	STUDY TYPE	PREVALENCE
Karthika et al	2015	30	Case control study	100%
Yokota et al	2015	14	Retrospective cross Sectional study	85.7%
Orania et al	2011	135	Prospective cross Sectional study	57%
Bhide et al	2010	60	Prospective cross Sectional study	34- 43%
Barbara et al	2009	75	Prospective longitudinal multicenter non-interventional study	76%
Linda et al	2008	241	Prospective cross Sectional study	98-99%
Montserrat et al	2005	450	Retrospective cross Sectional study	83%
Trotti et al	2003	6181	Systemic literature review	80-100%
Ohrn et al	2001	41	Prospective cross Sectional study	100%
Janjan et al	1989	14	Randomized Clinical Trial	100%

2.1 Study Justification

Despite the fact that oral mucositis is often described as one of the most common and significant acute complication of radiotherapy and chemotherapy [16],there is limited data on its overall impact, prevalence and risk factors in our setting.

Understanding the impact of oral mucositis in our setting will aid in coming up with protocols for its management and more importantly it will help to come up with preventative strategies which will improve the care of Head and Neck cancer patients in our setup.

2.2 Research Question

What is the prevalence and what are the predictors of oral mucositis, in patients with head and neck carcinomas, who are undergoing radiotherapy with or without chemotherapy at KNH?

2.3 Aims & Objectives

2.3.1 Broad Objective

To determine the prevalence and predictors of oral mucositis in Head and Neck Carcinoma patients, undergoing radiotherapy with or without chemotherapy at the Kenyatta National Hospital

2.3.2 Specific Objectives

(a) To determine the prevalence of mucositis.

(b) To determine the risk factors for development of mucositis.

3.0 CHAPTER THREE: RESEARCH METHODOLOGY:

3.1 Study design

This was a prospective cross sectional study.

3.2 Variables

The dependent variable was the prevalence of mucositis. The independent variables were the risk factors for development of mucositis. The prevalence of mucositis and the risk factors for development of mucositis were the focus of this study.

3.3 Study area

The study was conducted at Kenyatta National Hospital (KNH) at the radiotherapy out-patient clinic, the ENT (Ear, Nose and Throat) ward and the adult oncology ward in KNH. Kenyatta National Hospital is a National teaching and referral hospital in Nairobi, Kenya.

3.4 Target population

The study target population comprised of 80 patients undergoing radiotherapy for head and neck cancer at the radiotherapy out-patient clinic, in-patients from the ENT ward and the adult oncology ward in KNH. The study period was 4 months, from January 2016 to April 2016. The target population was computed from patient records of a monthly average of 20-25 patients.

3.5 Inclusion Criteria

a) Histologic diagnosis of Head and Neck Carcinomas of any of the following sites: Nasopharynx, oropharynx, hypopharynx, larynx, oral cavity and metastatic neck disease of unknown origin
b) Patients scheduled to undergo radiotherapy with or without chemotherapy as the primary mode of management or as post-operative management

3 .6 Exclusion Criteria

a) History of previous irradiation to the head and neck
b) Patients who were HIV (Human Immunodeficiency Virus) positive.
c) Patients on palliative chemoradiotherapy.
d) Patients who failed to consent for the study.

3.7 Sampling procedure & sample size determination

3.7.1 Sampling procedure

The sampling frame consisted of patients being managed at the radiotherapy out-patient clinic and in patients from the ENT ward and the adult oncology ward in KNH for head and neck cancer. The sample selection was done by consecutive sampling.

3.7.2 Sample Size Determination

Assumptions

The study sample was determined based on the concept of sample size for a prevalence survey with finite population correction because the target population was less than ten thousand. The first assumption was the margin of error that will be 5% to improve the reliability and validity of the results (95% confidence interval). The second assumption relates to the proportion of the patients with the desired characteristics which is unknown and in such a case 50% is proposed to ensure maximum sample size.

3.7. 3 Sample size calculation

n The sample size is determined by the Yamane (1967:886) formula to yield a representative sample for proportions considering the assumptions mentioned above

$n = N/ (1+ N*e^2)$

Where

n is the sample size

N is the total target population

e is the desired level of precision (5%)

Required sample

$n = 80/ (1+ (80*0.05^2))$

=66

A sample of 72 patients was used inclusive of 10% attrition to improve on reliability and validity of findings**.**

3.8 Recruitment, consenting and Data Collection Procedure

The principal investigator recruited patients from the radiotherapy outpatient clinic, ward 5c and ward GF-D. The patients all underwent conventional radiotherapy at a cumulative dose of at least 50Gy using the Theratron Equinox (cobalt 60) machine.

For each identified sample patient, the following was done:

1) Explanation of the study to the patient and obtaining of consent.

2) Demographic and medical history taking and examination.

3.9 Obtaining Informed Consent

The principal investigator introduced herself to the participants and explained the purpose of her study. The participants were then given time to read through the participant information sheet and the consent form. Their concerns and questions were addressed before the consent was signed. Thereafter, the study participants, parents or legal guardians for those below the age of 18, were asked to sign the consent forms if they agreed to participate in the study.

The participant information sheet and the consent forms for those who were unable to read English were translated to Kiswahili. For those who could not read at all, the principal investigator went through the documents in a Language that they understand before consent was obtained.

If the patient, parent or legal representative could not sign the consent because of illiteracy, a thumb print was obtained from such a patient or parent. An independent/impartial witness, who was present during the consent process and signing the consent form, will attest that the written information was accurately explained to participants and will also attest that consent had been given freely. This is an independent nurse or another independent witness who also understands the language that was used during this process.

3.10 Data Collection Procedure

Pre-treatment demographic and clinical data was collected by the principal investigator using questionnaires that contained closed and open ended questions (See appendix 3). All patients had laboratory results of full blood count, liver function tests and renal function tests which are routinely done as pre treatment work up. The principal investigator reviewed the laboratory test results and any abnormalities were noted. The principal investigator then carried out an examination of patient's oral cavity at baseline (pre- treatment). At the completion of 2, 4 and 6 weeks of treatment, information on resource utilization was collected by the principal

investigator (see appendix 3). The oral cavity of each patient was reexamined at the end of 2, 4 and 6 weeks and any lesions graded by the principal investigator. Grading of the oral lesions was done using the NCI-CTC version 4.0 grading scale (see appendix 4)

Either the clinical or functional criteria was used in grading the oral lesions in patients who were able to take orally pre-treatment. However, only the clinical criteria was utilized when the patient was not able to take orally pre- treatment and had an alternative feeding route such as nasogastric tube or gastrostomy tube.

3.11 Quality Control

Quality control was a continuous process throughout the study to maximize validity and reliability of the findings of the study. Some of the measures taken include the following:

- Only the principal investigator evaluated the patients throughout the course of treatment.
- A standard grading scale (NCI-CTC version 4.0) was used for all the patients.
- All the patients underwent conventional radiotherapy at a cumulative dose of at least 50 Gy and above.

3.12 Validity and Reliability of Research Instrument

The questionnaires were presented to the University for validation by the supervisors and research panellists before data collection.

Cronbach's alpha coefficient was used to test reliability. The test splits all the answers to a given question into two section or groups then the scores obtained are summed up. The researcher worked out the correlation between the two (a 'split-half test). An alpha (α) score of 0.70 or higher was considered satisfactory and ascertains reliability.

3.13 Data management

At the end of each interview, data collection tools were cross checked for completeness and any missing entries corrected. The quantitative and qualitative data collected was coded and any inconsistencies and outliers rectified. This involved reading through the data and developing codes that draw similar connections between categories and themes. Data was analyzed using SPSS (Statistical Package for the Social Sciences) version 21 as per the specific research questions. Relationship between the independent variables and the dependent variable was established using Chi-square tests of association and Logistic linear regression since the responses were categorical. Findings were presented in the form of text, charts, graphs and tables. All data was stored under lock and key and with password

protected files under the custody of the principal investigator to prevent any illicit access to the data. Use of coded data was done to ensure maximum confidentiality. At the end of the study, the raw data was destroyed and deleted from any existing hard copies by paper shredding and formatting and deleted from any soft copy storage devices including computers, flash discs and hard disks.

3.14 Logistical and Ethical considerations

Approval to conduct the research was obtained from KNH and University Of Nairobi Ethics and Research committee (P541/08/2015). Permission to conduct research was also sought from the relevant authorities at the clinics and wards. Respondents gave consent to participate and were informed that it is voluntary. They were also informed of their right to accept or withdraw or refuse to participate. The researcher gave full information about what the research entails and ensured participants were competent to give consent. Full consent and explanation is given in Appendix I. The questionnaires were administered after duly obtaining consent from the participants. Participants' privacy was highly maintained by ensuring that they were not exposed to public when filling questionnaires. The researcher ensured the anonymity of respondents by concealing their identity and keeping research data confidential for research purposes only. All concerns causing any sort of discomfort to respondents was resolved immediately and mitigation strategies put in place. Participants found to have other ENT diseases apart from mucositis were referred to the ENT clinic at KNH for treatment and follow up free of charge. Patients incurred no extra financial costs and there was no monetary gain by the primary investigator from this study. There was no penalty for declining to participate in the study.

3.15 Dissemination and application of results

The results of this study will be submitted to the University of Nairobi in form of a thesis. The findings will also be shared with various stakeholders through presentation in meetings, seminars, conferences and other scientific forums. The findings will be published in reputable journals and periodical publications for the benefit of the medical fraternity, the study subjects and general population.

4.0 CHAPTER FOUR: RESULTS

Data collection for this study was carried out during the months of January 2016 to April 2016. A total of 72 patients were recruited from the radiotherapy out-patient clinic, the adult oncology ward and the ENT ward. A total of 59 (82%) patients were receiving treatment as out patients, while 13(18%) were in patients.

4.1 Demographic Characteristics:

4.1.1 Age Distribution:

The mean age of the patients recruited for this study was 47.7 years (SD+/- 18.6), with a range of 10-77 years. The most frequent age group was 41- 60 years (34.7%) while the least frequent age group was less than 20 years (11.1%). Paediatric patients recruited were few since the most common head and neck malignancies in this age group were not included in this study.

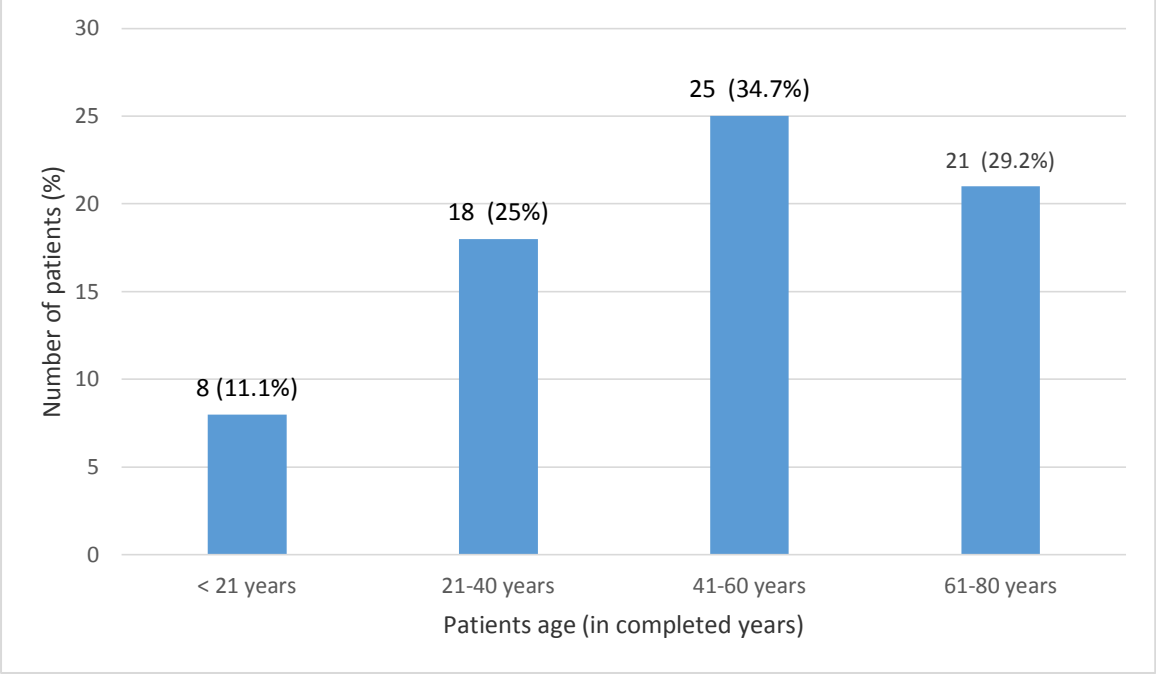

Figure 2: Age distribution of patients with head and neck carcinomas undergoing radiotherapy at KNH

4.1.2 Sex Distribution

The proportion of male patients recruited was higher (60%) than that of female patients (40%) with a male to female ratio of 1.5: 1

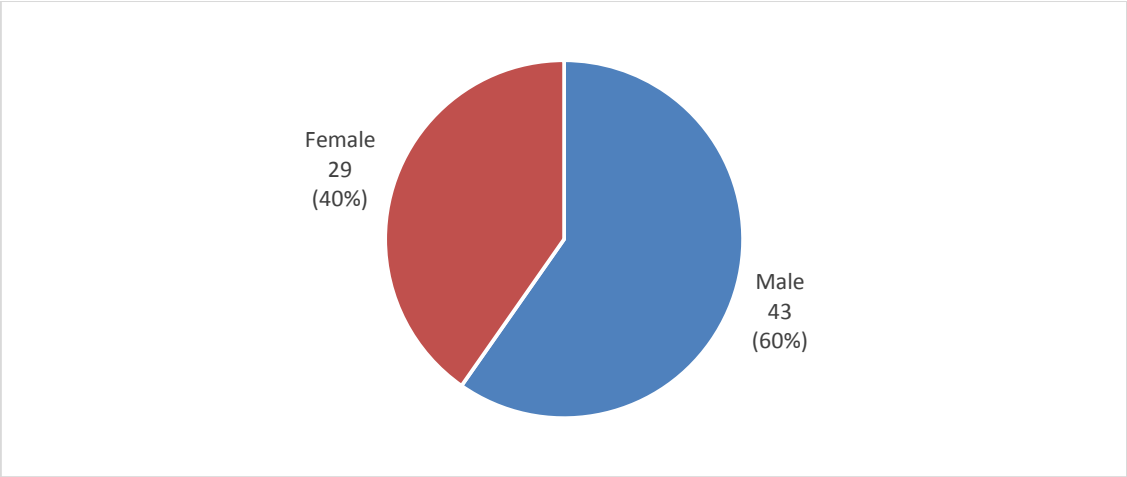

Figure 3: Sex Distribution of patients with head and neck carcinomas undergoing radiotherapy at KNH

4.2 Distribution of Tumours by Primary Sites

The commonest tumour primary site in these patients was oral cavity with 33 patients (45.8%). There was 1(1.4%) patient found to have Metastatic neck disease secondary to an orbital primary (Squamous Cell carcinoma). The primary tumour had been cured, however she was later found to have metastatic neck disease so she subsequently underwent neck dissection and post operative radiotherapy to the neck. Majority of the patients recruited had stage 3(32%) and stage 4 disease (57%)

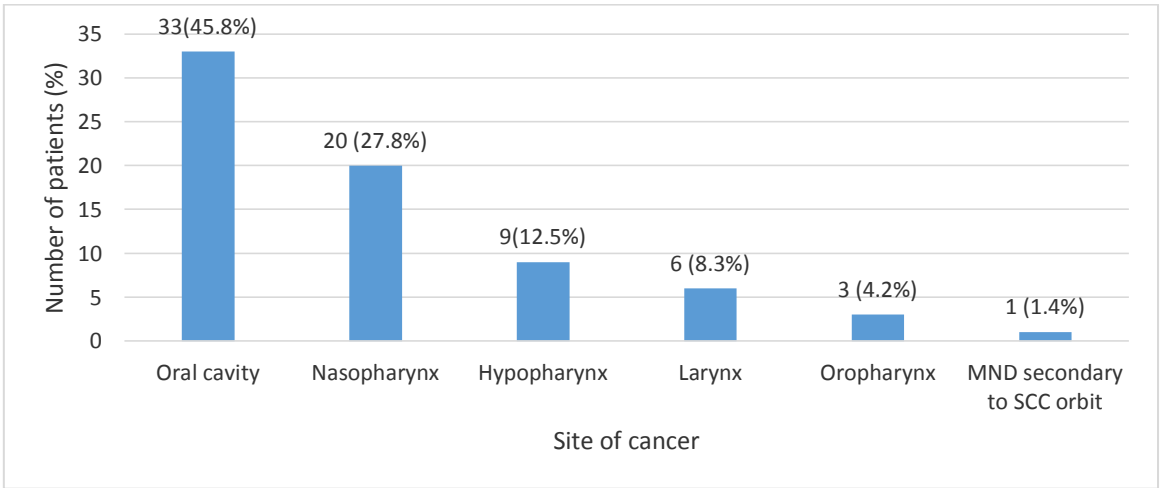

Figure 4: Primary sites for head and neck carcinomas in patients undergoing radiotherapy at KNH

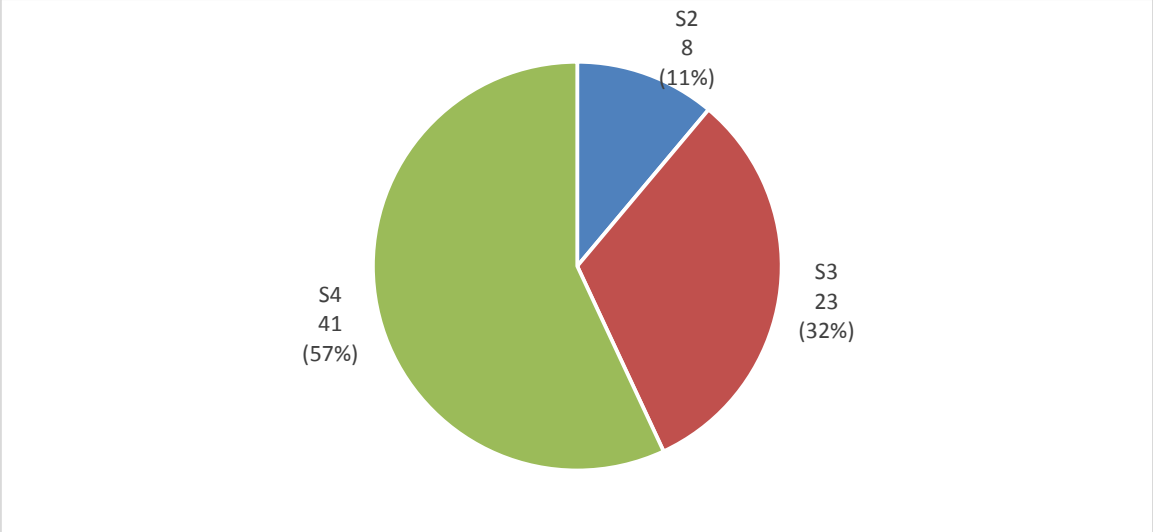

Figure 5: Staging of head and neck carcinomas in patients undergoing radiotherapy at KNH

4.3 Prevalence of Mucositis

All the 72(100%) patients developed mucositis by the second week of treatment at a cumulative radiotherapy dose of 20 Gy. One patient with cancer of the larynx improved on treatment and did not have mucositis at 4 weeks and 6 weeks; hence the prevalence of mucositis was later 98%. Majority of the patients, 51(70.8%) developed grade 3 mucositis by the 2nd week of treatment. The mucositis scores increased over time from grade 3 to grade 4 in 4(5%) patients who had cancers of the oral cavity. The mucositis score improved after treatment in 11(15%) patients.

Table 4: Overall grades of mucositis at 2,4,6 weeks

	Week 2		Week 4		Week 6	
Classification	**n**	**%**	**n**	**%**	**n**	**%**
1	5	6.9	4	5.5	7	9.7
2	15	20.8	16	22.2	16	22.2
3	51	70.8	48	66.7	36	50
4	1	1.4	2	2.8	2	2.8
Not assessed	0	0	2	2.8	11	15.3

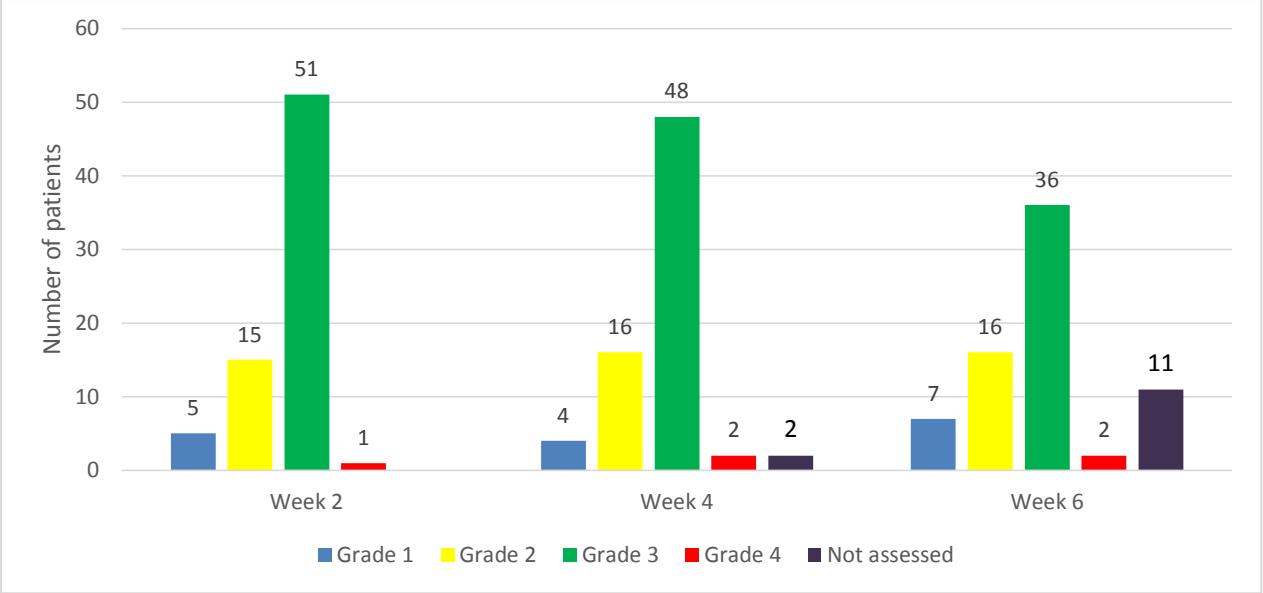

Figure 6: Overall Grades of mucositis at 2,4,6 weeks

Patients with cancers of the oral cavity had the worst overall grade of mucositis, with 93.9% of these patients developing grade 3 mucositis by the second week; this was statistically significant with a p value of 0.001. Patients with cancer of the larynx had the least overall grade of mucositis with 50% of the patients having grade 1 mucositis at 2 weeks of treatment with a p value of <0.001.Only 1 patient with cancer of the larynx had grade 3 mucositis at 2 weeks, this patient was also a known patient with Chronic Lymphocytic Leukemia(CLL).

Table 5: Site of Cancer and grades of mucositis at 2 weeks

	MUCOSITIS GRADING				
	1	**2**	**3**	**4**	**P value**
SITE					
Oral cavity	1(3.0)	1(3.0)	31(93.9)	0	**0.001**
Hypopharynx	0(0.0)	0(0.0)	8(88.9)	1(11.1)	**0.016**
Nasopharynx	1(5.0)	10(50.0)	9(45.0)	0	**0.002**
Larynx	3(50.0)	2(33.3)	1(16.7)	0	**<0.001**
MND	0(0.0)	1(100.0)	0(0.0)	0	0.278
Oropharynx	0(0.0)	1(33.3)	2(66.7)	0	0.918

4.4 Risk Factors for Mucositis

4.4.1 Demographic Characteristics and Mucositis

In this study there was no statistically significant association between age and gender and the development of mucositis. Age and gender did not increase or decrease the risk of developing mucositis.

Table 6: Patient demographic characteristics and grades of mucositis at 2 weeks

	Mucositis grades				
Age	**1**	**2**	**3**	**4**	**P value**
< 20 years	0(0.0)	1(12.5)	7(87.5)	0(0.0)	0.262
21-40 years	0(0.0)	5(27.8)	12(66.7)	1(5.6)	
41-60 years	1(4.0)	6(24.0)	18(72.0)	0(0.0)	
61-80 years	4(19.0)	3(14.3)	14(66.7)	0(0.0)	
Sex					
Male	4(9.3)	11(25.6)	27(62.8)	1(2.3)	0.301
Female	1(3.4)	4(13.8)	24(82.8)	0(0.0)	

4.4.2 Stage of Tumour and Mucositis

There was no statistically significant association found between stage of the primary tumour and the development of mucositis in this study, as shown below

Table 7: Stage of cancer and mucositis grade at 2 weeks

	GRADES OF MUCOSITIS				
STAGE OF TUMOUR	1	2	3	4	**P value**
Stage 2	0(0.0)	4(50.0)	4(50.0)	0(0.0)	0.174
Stage 3	2(8.7)	6(26.1)	14(60.9)	1(4.3)	0.362
Stage 4	3(7.3)	5(12.2)	33(80.5)	0(0.0)	0.111

4.4.3 Previous Surgery and Mucositis

14(19.4%) of patients had a history of previous surgery; however these patients did not show any statistically significant higher grades of mucositis with a p value of 0.637. Previous surgery was found not to increase or decrease the risk of developing mucositis.

4.4.4 Neutropenia and Mucositis

In this study 5 (6.9%) of the patients had low neutrophil count, however these patients did not show any statistically significant higher grades of mucositis with a p value of 0.916

Table 8: Previous Surgery/ low Neutrophil count and grades of Mucositis at 2 weeks

RISK FACTORS	**MUCOSITIS GRADE AT 2 WEEKS**				
Low neutrophil count	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**P value**
Yes	0(0.0)	1(20.0)	4(80.0)	0(0.0)	0.916
No	5(7.5)	14(20.9)	47(70.1)	1(1.5)	
Previous surgery					
Yes	2(14.3)	3(21.4)	9(64.3)	0(0.0)	0.637
No	3(5.2)	12(20.7)	42(72.4)	1(1.7)	

4.4.5 Alcohol Intake and Cigarette Smoking:

With regard to alcohol intake and smoking as risk factors for development of severe mucositis, patients were divided into 3 categories .Those that had prior history of taking alcohol or history of smoking, but had stopped at the time of treatment were put in the "former" category. Those that were taking alcohol or were smoking during treatment were put in the "current" category. Those that had never taken alcohol and had never smoked were put in the "never" category. When the analyzed as risk factors for developing severe mucositis, none of these three categories was found to be statistically significant, with a p value of 0.764 with history of alcohol exposure and 0.314 with history of smoking.

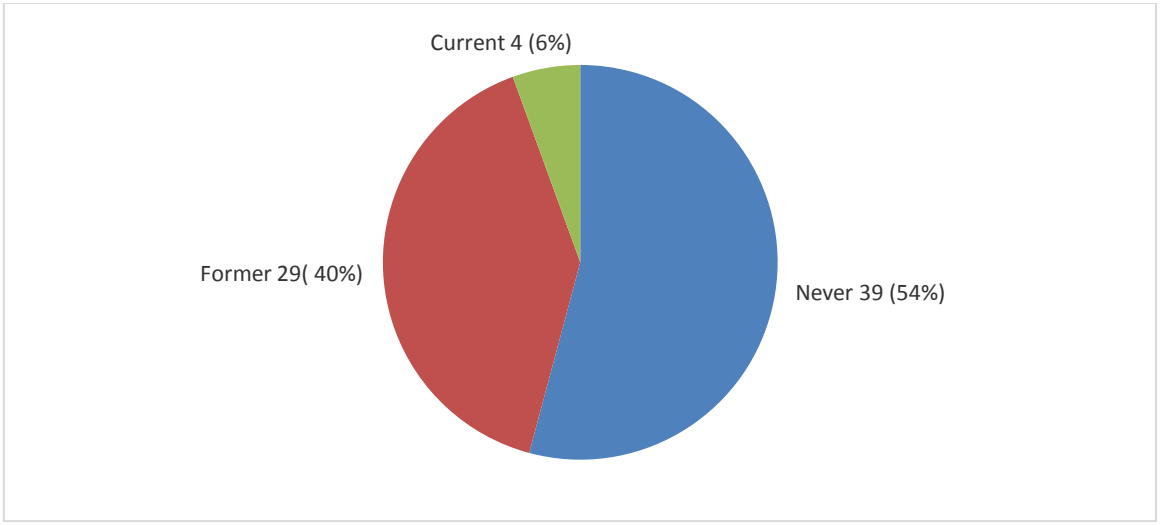

Figure 7: Distribution of Smoking exposure in Patients

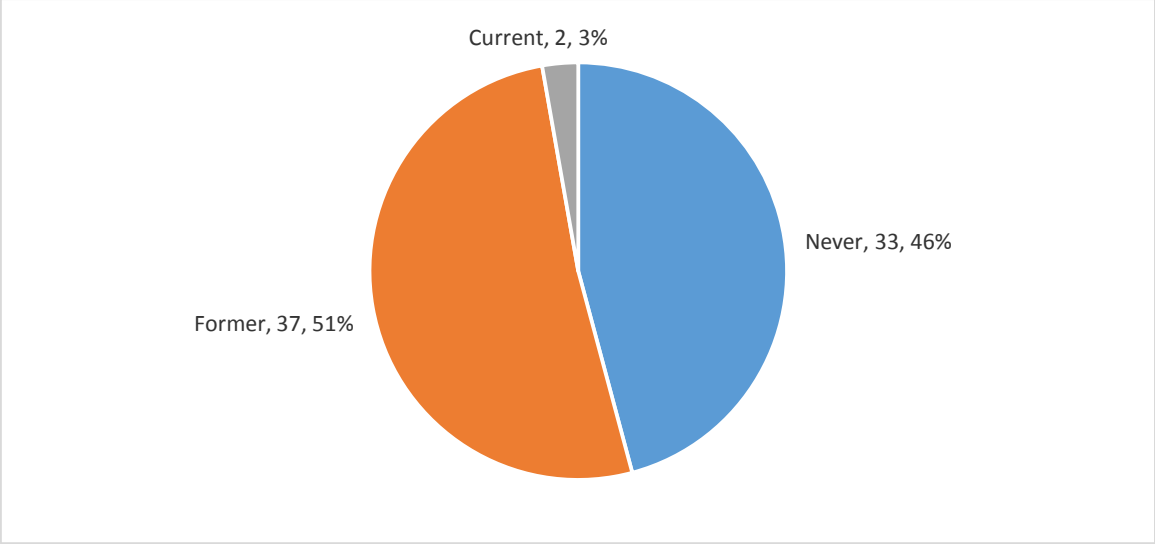

Figure 8: Distribution of Alcohol exposure in patients

Table 9: Alcohol exposure /Smoking exposure and grades of mucositis at 2 weeks

	GRADES OF MUCOSITIS				
Alcohol exposure	1	2	3	4	P value
Never	3(9.1)	5(15.2)	24(72.7)	1(3.0)	0.764
Former	2(5.4)	9(24.3)	26(70.3)	0(0.0)	
Current	0(0.0)	1(50.0)	1(50.0)	0(0.0)	
Smoking exposure					
Never	1(2.6)	7(17.9)	30(76.9)	1(2.6)	0.314
Former	4(13.8)	8(27.6)	17(58.6)	0(0.0)	
Current	0(0.0)	0(0.0)	4(100.0)	0(0.0)	

4.5 Concurrent Chemotherapy and Mucositis

The chemotherapy regimen administered to these patients was found to be standard with the patients receiving cisplatin alone at a dose of 50 – 75mg/m² or cisplatin in combination with paclitaxel at a dose of 175mg/m². This was administered for 3 to 6 cycles.

The number of patients who underwent radiotherapy with concurrent chemotherapy was 24(33%), at 2 weeks of treatment none of these patients had grade 1 mucositis however, 5(20.8%) had grade 2 mucositis and 19(79.2%) had grade 3 mucositis. In comparison, 20(28%) patients were put on radiotherapy alone with no chemotherapy, 2(10%) of these patients had grade 1 mucositis, 6(30%) had grade 2 mucositis and 12 (60%) had grade 3 mucositis. A total of 28(39%) patients had been on neoadjuvant chemotherapy, 21(75%) patients in this group developed severe mucositis.

Although the administration of concurrent chemotherapy was not statistically significant (p value 0.171) the odds of developing mucositis in this group was 2½ times higher than in patients who were on radiotherapy alone. In comparison, the odds of developing mucositis in patients who had been on neoadjuvant chemotherapy was 1.2 times higher than in patients who had not been on neoadjuvant chemotherapy.

Table 10: Chemotheapy and grade of mucositis at 2 weeks

Neoadjuvant chemotherapy	***Grade 3 or 4 Mucositis***	
	YES	NO
YES	21	7
NO	31	13
P value	0.679	
Odds ratio	**1.2581**	
95% confidence interval	0.4303-3.6785	

Table 11: Chemotherapy and grade of mucositis at 2 weeks

Concurrent chemotherapy	***Grade 3 or 4 Mucositis***	
	YES	NO
YES	19	5
NO	12	8
P value	0.171	
Odds ratio	**2.533**	
95% confidence interval	0.6695 – 9.5856	

4.6 State of the Oral Cavity and Mucositis

In the initial assessment prior to starting treatment, 15.3% of patients had normal oral cavities, 33.3% of patients were partially edentulous, 47.2% of patients had ulcerations in the oral cavity and 70.8% had dental carries. These findings were overlapping e.g. a patient would have both dental carries and would have oral ulcerations. Presence of oral ulcerations was associated with higher grades of mucositis with a p value 0.005.

Figure 9: State of the oral cavity pre-treatment

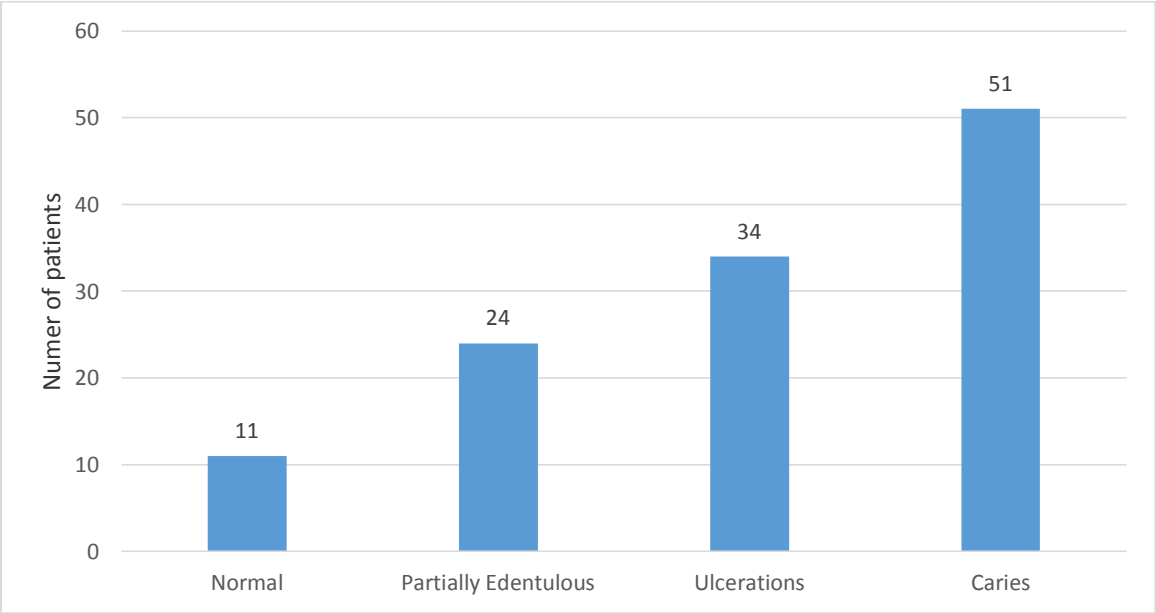

Table 12: State of the oral cavity pre-treatment and gradesof mucositis at 2 weeks

	Mucositis grading				
	1	**2**	**3**	**4**	**P value**
Dental caries					
No	2(9.5)	7(33.3)	12(57.1)	0(0.0)	0.295
Yes	3(5.9)	8(15.7)	39(76.5)	1(2.0)	
Oral ulcers					
No	5(13.2)	12(31.6)	21(55.3)	0(0.0)	
Yes	0(0.0)	3(8.8)	30(88.2)	1(2.9)	**0.005**

4.7 Oral Hygiene Practices and Mucositis

In this study it was found that only 19(26.4%) visited a dentist prior to starting radiotherapy. This was not found to be statistically significant in this study and did not decrease the risk of developing severe mucositis.

Total of 19(26.4%) patients did not practice oral hygiene. This was not found to be statistically significant with a p value 0.495. A total of 24 patients cleaned their teeth once a day while 29 cleaned teeth 2 times or more in a day.

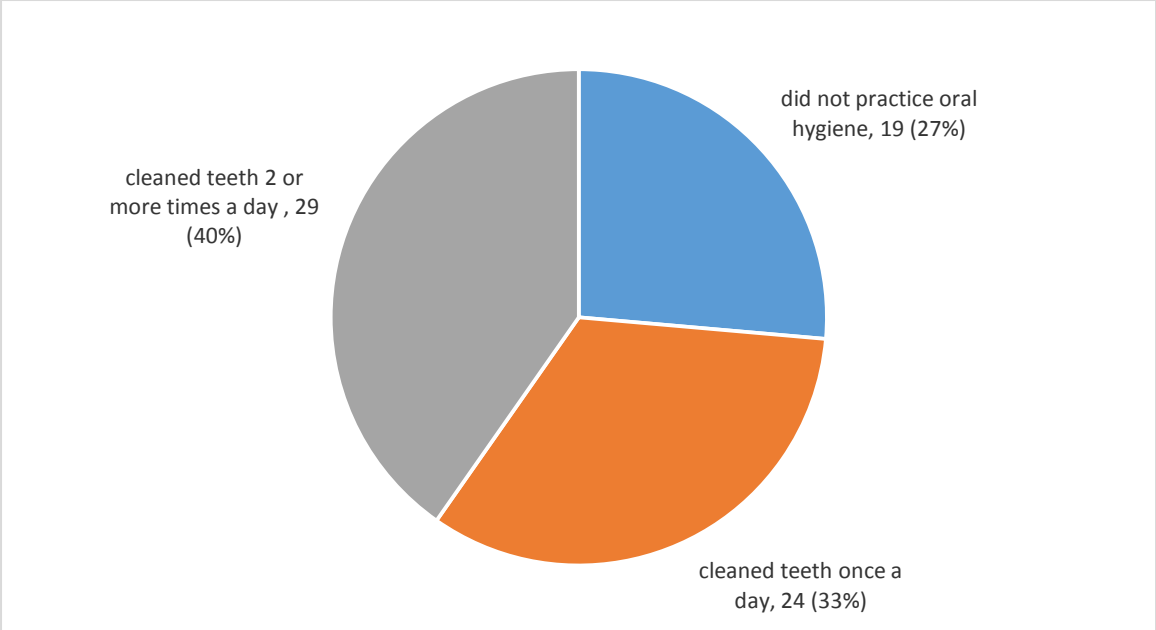

Figure 10: Distribution of oral hygiene practices

4.8 Feeding Routes at Various Stages of Treatment

Prior to starting radiotherapy 69 (96%) patients were on oral feeding, 2 (3%) patients were on Nasogastric Tube (NGT) feeding and 1 (1%) patient was on gastrostomy tube feeding. A total of 6 (8%) patients were put on NG tube feeding and 2 (3%) patients were put on TPN due to severe mucositis

Table 13: Feeding route over time

	Pre Treatment	2 Weeks	4 Weeks	6 Weeks
Oral feeding	69	67	61	56
NGT feeding	2	3	8	4
Gastrostomy Tube feeding	1	1	1	1
TPN	-	1	1	1

4.9 Other Outcomes of Mucositis:

By the 2nd week of treatment 90.3% of the patients were on analgesics due to oral pain, at the same time 83.6% of the patients visited a doctor due to oral pain. In total 5 patients had treatment interruptions, 4 of them due to severe mucositis and 1 due to lobar pneumonia.

Table 14: Treatment Interruptions

SITE OF TUMOUR	REASON	DURATION
Oral Cavity	Severe Mucositis	2 weeks
Hypopharynx	Severe Mucositis	1 week
Hypopharynx	Severe Mucositis	2 weeks
Nasopharyngeal	Severe Mucositis	1 week
Larynx	Lobar pneumonia in a patient with CLL	2 weeks

4.9 Patient Mortality

During the study 10 (13.9%) of the patient died before completion of treatment, these were patients with stage 3 and 4 disease. 6 patients had oral cavity tumours, 2 patients had nasopharyngeal tumours, 1 patient had hypopharyngeal cancer, 1 had cancer of the larynx and was a known patient with CLL. The probable cause of death in this group was the advanced stage of their disease and severe pneumonia in the patient with CLL and cancer of the larynx.

5.0 CHAPTER FIVE: DISCUSSION

Oral mucositis in head and neck cancer patients undergoing radiotherapy has often been described in literature as the most significant acute complication associated with radiotherapy and chemotherapy. The results of this study will give some insight on the magnitude of oral mucositis in head and neck cancer in our facility and will pave way for future research on the management of oral mucositis.

In this study a total of 72 head and neck cancer patients undergoing conventional radiotherapy with or without chemotherapy were recruited. The mean age of these patients was 47.7 years, with the most frequent age group being 40-60 years. There were more male than female patients with a ratio of 1.5:1.

5.1 Prevalence of Mucositis

The prevalence of mucositis was found to be 100% with all the patients developing some degree of mucositis by the second week of treatment at a cumulative dose of 20Gy. One patient with cancer of the larynx improved on treatment and did not have mucositis at 4 weeks and 6 weeks; hence the prevalence of mucositis was later 98%. These findings are similar to those by Ohrn et al[29], Karthika et al[35] and Janjan et al[28]. In all these studies the prevalence of mucositis was also reported to be 100%. Some studies have reported lower prevalence rates such as by Trotti et al[2], Montserrat et al[30], Barbara et al[32] and Ourania et al[34] where the prevalence was found to be 80%, 83%, 76% and 57% respectively. In the study by Barbara et al[32] 45% of the sample patients received Intensity Modulated Radiation Therapy (IMRT). This is a form of targeted therapy which delivers precise radiotherapy doses to the tumour while minimizing damage to the surrounding tissues. This could account for the lower prevalence of 76% in this study. In the study by Ourania et al[34] systemic antifungals were administered in 70% of the sample patients upon clinical, presumptive diagnosis of candidiasis. At the same time systemic antivirals were administered to 71% of the patients upon clinical, presumptive diagnosis of herpertic infection. This could account for the lower prevalence of 57% in this study.

In this study it was found that none of the patients had stage 1 disease, majority (89%) had stage 3 or 4 disease. This can be explained by the fact that most of the patients in our set up present late. In one study done by Onyango et al[37] in KNH he found that 2% of the patients

with head and neck cancer presented with stage 1 disease, while 70% of the patients presented with stage 3 or 4 disease.

In this study the distribution of tumours by primary site was such that oral cavity tumours were the highest in number (45.8%) followed by tumours of the nasopharynx (27.8%). This distribution is influenced by various factors and does not reflect the distribution of head and neck malignancies in our set up. At the time this study was being conducted there was only 1 radiotherapy machine working to its full capacity. Due to this limitation, certain patients were given priority to start treatment such as those who had active bleeding from the tumour, young children, those at risk of upper airway obstruction and those who had a longer radiotherapy waiting time. These factors therefore influence the distribution of patients undergoing radiotherapy at any particular time.

Patients with oral cavity tumours had the worst overall grades of mucositis, with 93.9% of these patients developing grade 3 mucositis by the second week; this was statistically significant with a p value of 0.001. The high prevalence of mucositis in this group can be explained by effects of irradiation being worse with pre existing damage to the epithelium. Patients with laryngeal cancer had the least overall grades of mucositis, with 50% of the patients having grade 1 mucositis at 2weeks of treatment with a p value of <0.001. In the study by Montserrat et al[30], the highest grades of mucositis were reported in oropharyngeal, nasopharyngeal and oral cavity tumours. Patients with oral cavity tumours also had higher grades of mucositis in this study, similar to what Montserrat[30] found. There were very few patients with oropharyngeal tumours (4%) recruited in this study compared to 26.4% of patients in the study by Montserrat[30]. A larger sample size would be needed to determine the severity of mucositis in this group. Lower grades of mucositis were also reported in patients with cancer of the larynx by Montserrat[30] which is similar to the findings in this study. In contrast to other studies, Linda et al[31] found no difference in severity of mucosistis in patients with oral cavity and oropharyngeal tumours when compared with patients with laryngeal tumours, however this study by Linda[31] was based solely on patient reported outcomes with no clinical evaluation done to confirm the findings.

Majority of the patients (70.8%) developed grade 3 mucositis by the 2nd week of treatment. The mucositis scores increased over time from grade 3 to grade 4 in 4(5%) patients who had cancers of the oral cavity. The mucositis score improved after treatment in 11(15%) patients. In 57 (80%) of the patients the mucositis grade remained constant despite treatment. These

findings are similar to those by Barbara et al[32] who reported persistent mouth and throat soreness in 85% of the patients despite the use of analgesics. Linda[31] also reported that mouth and throat soreness severity over the course of radiotherapy was identical.

5.2 Risk Factors for Mucositis

The risk factors for development of oral mucositis have not been well defined in literature especially those relating to patient related characteristics[2]. Not all risk factors were evaluated, however it was noted the site with the highest risk of severe mucositis was the oral cavity with 93.9% of these patients developing grade 3 mucositis by the second week; this was statistically significant with a p value of 0.001. The site with the lowest risk of severe mucositis was the larynx with 50% of the patients having grade 1 mucositis at 2weeks of treatment with a p value of <0.001. These findings are supported by the fact that presence of oral ulcerations prior to starting radiotherapy was associated with higher risk of developing severe oral mucositis with a p value of 0.005.

The number of patients who underwent radiotherapy with concurrent chemotherapy was 24(33%) while 28 (39%) had neoadjuvant chemotherapy. In contrast, 20(28%) of the patients were put on radiotherapy alone with no chemotherapy. Although the administration of concurrent chemotherapy was not statistically significant (p value 0.171) the odds of developing mucositis in this group was 2½ times higher than in patients who were on radiotherapy alone. In comparison, the odds of developing mucositis in patients who had been on neoadjuvant chemotherapy was 1.2 times higher than in patients who had not been on neoadjuvant chemotherapy. Similar to what was found in this study, Ohrn et al [29] reported higher baseline scores of mucositis in patients who had received neoadjuvant chemotherapy. Montserrat et al [30] also found that concurrent chemotherapy increased the chances of developing severe mucositis.

A larger sample size of patients may be required to compare the effects of chemotherapy on mucositis, this can allow comparison of similar groups of patients who are on chemotherapy, which was not possible in this study.

In this study age, gender, low neutrophil count and poor oral hygiene were not found to be statistically significant as risk factors for the development of mucositis. It was observed that only 26.4% of patients in this study had been seen by a dentist prior to commencing radiotherapy, however this was also not found to be statistically significant in this study.

5.3 Outcomes of Mucositis

90.3% of patients were on analgesics by the second week of treatment and 83.6% had been seen by a doctor due to oral pain. Oral mucositis affects the quality of life in these patients due to severe pain experienced as a result of mucositis. It was noted that there was no regular follow up of patients on radiotherapy during the course of their treatment, with patients being reviwed only when they complained of mouth soreness. This meant that there were delays in initiating treatment for mucositis in majority of the patients in this study.

Despite the severity and effects of mucosistis, interventions in its management were not adequate with only 6 (8%) patients being put on NGT feeding and 2 (3%) patients being put on TPN. This is contrary to what has been reported in studies such as by Trotti et al[2], Montserrat et al[30] and Linda et al[31] all who reported increased hospital admissions and feeding tube placement for patients who developed oral mucositis. Barbara et al[32] in particular studied mucositis related morbidity and resource utilization and found that out of a total of 75 patients recruited from 6 centers, 51% of patients had feeding tube placement and 30% of admissions in these patients were due to oral mucositis.

5.4 Study Limitations

- Patient reported outcomes were not assessed in this study this can under estimate the grade of mucositis if only clinical evaluation is used.
- Not all risk factors of mucositis could be evaluated adequately.

6.0 CHAPTER SIX: CONCLUSION

The prevalence of mucositis in patients undergoing radiotherapy for head and neck cancer is high (100%) in KNH. Patients with cancers of the oral cavity were found to have the highest risk of severe mucositis (p value 0.001) in contrast; patients with laryngeal cancer had the lowest risk of severe mucositis (p value <0.001). Presence of oral ulcers was found to be a risk factor for developing severe mucositis (p value 0.005) and the administration of concurrent chemotherapy increased the odds of developing severe mucositis by 2½ times.

6.1 Recommendations

With the high burden of oral mucositis in our setup there is need for us to improve the care of head and neck cancer patients undergoing radiotherapy by:

1. Increasing resource allocation for cancer management in our set up such as by having more oncologists, oncology nurses and nutritionist who will identify patients at risk of complications early enough and initiate timely interventions.
2. Patient undergoing radiotherapy for head and neck cancer should be scheduled to be seen regularly in various clinics by the oncologist or head and neck specialists to improve quality of care.
3. Treatment protocols for mucositis can aid in better management of patients with mucositis. It would be important to evaluate what our current interventions are for this significant complication to identify what needs to be done better.
4. Validated tools such as the oral mucositis weekly questionnaire should be interpreted to swahili so as to evaluate what the patient reported outcomes are. This will also aid in diagnosis and follow up of the patient throughout the course of treatment, since most of our patients are managed as out patients.

REFERENCES

1. Spencer W. Redding, Transfer of advances in science in dental education, Journal of dental education 2005; 69:8.
2. Trotti A, Bellam LA, Epstein JB et al, Mucositis incidence, severity and associated outcomes in patients receiving radiotherapy with or without chemotherapy : a systemic literature review, Radiotherapy Oncology 2003;66: 253-262.
3. Elting HS, Cowsley C, Chambers M et al, The burden of cancer therapy, clinical and economic outcomes of chemotherapy based mucositis, Cancer 2003; 98:1531-1539.
4. Goda M, Jinnouch O, Takaoka T et al, Efficacy of PEG on unplanned treatment interruption and nutritional status in patients undergoing chemoradiotherapy for advanced head and neck cancer, Journal of medical investigation 2015; 62 : 173-176.
5. Sonis ST, Devita VT, Hellman S et al, Oral Complications of cancer therapy, Principles and practices of oncology 1993; 4 : 2385.
6. Sonis ST, Peterson RL, Edwards LJ et al, Defining mechanisms of action of IL-11 on the progression of radiation induced oral mucositis in hamsters, Oral Oncology 2000; 36:373-381.
7. Wang J, Albertson CM, Zheng LT et al ,Short term inhibition of ADP- Induced platelet aggregation by dopidogrel ameliorates radiation induced toxicity in rat intestines, Journal of Thrombosis and Haemostasis 2002; 87:122-128.
8. Hall PD, Benko H, Hogan KR et al, The influence of serum TNF α and IL-6 concentrations on non- hematologic toxicity and hematologic recovery in patients with acute myeloid leukemia, Experimental Hematology 1995; 23: 1256-1260.
9. Epstein JB, Silverman S, Paggiarino DA et al, Bezydamine Hydrochloride for prophylaxis of radiation induced oral mucositis; results from a multicentre, randomized double blinded, placebo controlled clinical trial, Cancer 2001; 92: 875-885.
10. Sonis ST, Elting LS, Keefe D et al, Perspective on cancer therapy induced mucosal injury. Cancer 2004; suppl. 100(9): 1995-2025.
11. Sonis ST, The pathobiology of mucositis, Nature Reviews Cancer 2004; 4:279-84.
12. Sonis ST, The biological role of NF-κβ in disease and its potential involvement in mucosal injury associated with anti-neoplastic therapy, Oral Biology and Medicine 2002;13:300-309.

13. Maddens S, Charruyer A, Berger S et al, Kit signaling inhibits the sphingomyelin-ceramide pathway through PLC gamma1: implication in stem cell factor radioprotective effect, Blood 2002; 100: 1294-301.
14. Chmura SJ, Nodzenski E, Beckett MA et al, Loss of ceramide production confers resistance to radiation induced apoptosis, Cancer Research 1997; 57: 1270-1275.
15. Bamba S, Andoh A, Yasui H et al, Matrix metalloproteinase 3 secretion from human colonic subepithelial fibroblasts, role of IL-17, Journal of Gastroenterology 2003; 38: 548-554.
16. Engels MA, Pini A, Yamshika Y et al, Inactivation of Pac and rmKB genes reduces the release of TNF-α, IL-6 and IL-8 by Streptococcus mutans in monocytic dental pulp and periodontal ligament cells, Infection Immunology 2003; 71: 5169-77.
17. Margaret M, Laura M, Current trends in managing oral mucositis, Clinical Journal of Oncology Nursing 2005;9: 5.
18. Kushner JA, Lawrence HP, Soval I et al, Development and validation of a patient reported oral mucositis symptom (PROM) scale, Journal of the Canadian Dental Association 2008; 74(1):59.
19. Ann MG, Andrew J, Asbjorn J et al, Assessment of cancer therapy induced oral mucositis using PROM experience questionnaire, Public Library Of Science ONE 9(3);e 91733.
20. Fu KK , Pakaj TF, Trotti A et al, A Radiation Oncology Group (RTOG) phase III randomized study to compare hyperfractionation and two variants of accelerated fractionation to standard fractionation radiotherapy for head and neck squamous cell carcinoma : first report of RTOG 9003, International Journal of Radiation Oncology Biology and Physics 2000; 48: 7-16.
21. Ghosh S, Rao PB, Kumar PR et al , Concurrent chemoradiotherapy with weekly cisplatin for treatment of head and neck cancer : an institutional study on acute toxicity and response to treatment, Asian Pacific journal of cancer prevention 2015; 16 : 7331-7335.
22. Dodd MJ, Paul SM, Laison P, Risk factors for chemotherapy induced oral mucositis, Cancer Investigation 1999; 17:278.
23. Sheiban KM, Mafi AR, Moghaddam S et al, Efficacy of benzydamine oral rinse in prevention and management of radiation induced oral mucositis : a double blind placebo controlled randomized clinical trial, Asian Pacific Journal of Cancer Prevention 2015; 11: 22-27.

24. Mallick S, Benson R, Rath GK, Radiation induced oral mucositis : a review of current literature on prevention and management, European Archives of Otorhinolaryngology 2015: 1-9.
25. Lauren JR, Makala BP, Asif S , Prevention and management of radiation induced dermatitis, mucositis and xerostomia, American Journal of Health System Pharmacy 2013 ; 70 : 1025-1032
26. Douglas EP, Kerstin O, Joanne B et al, Systemic review of oral cryotherapy for management of oral mucosistis caused by cancer therapy, Support Care Cancer 2013; 21: 327-332.
27. Otonleit AF, Silva GB, Morais MO et al, Effect of low level laser therapy on chemoradiotherapy induced oral mucositis and salivary inflammatory mediators in head and neck cancer patients, Laser in Surgery and Medicine 2015 ; 47 : 296-305.
28. Janjan N, Wessman DE, Byhardt BW, Assessment of pain during head and neck cancer irradiation, Journal of pain Symptom Management 1989; 4(2): 90-95.
29. Ohrn O, Ylva- Britt, Per-olow et al, Oral status during radiotherapy and chemotherapy: a descriptive study of patient's experiences and occurrence of oral complications, Support cancer care 2001; 9: 247-257.
30. Montserrat L, Gery D, May H et al, Oral mucositis in patients undergoing radiation therapy for Head and Neck Carcinoma, Cancer 2006;106: 329-36.
31. Linda S, Dorothy M, Keep MD et al, Patient reported measurements of oral mucositis in head and neck cancer patients treated with radiotherapy with or without chemotherapy, Cancer 2008;113:2704-2713.
32. Barbara A, Jennifer L, John I et al, Mucositis related morbidity and resource utilization in head and neck cancer patients receiving radiation therapy with or without chemotherapy, Journal of pain and symptom management 2009; 38:522-532.
33. Bhide SA, Gulliford S, Fowler J et al, characteristics of response of oral and pharyngeal mucosa in patients receiving chemotherapy and intensity modulated radiotherapy for head and neck cancer, Radiotherapy Oncology 2010; 97: 86-91.
34. Ourania NG, Vassilis K, Anastacia SL et al, Oral mucositis, pain and xerostomia in 135 head and neck cancer patients receiving radiotherapy with or without chemotherapy, The Open Cancer Journal 2011; 4:7-17.
35. Karthika N, Chemoradiotherapy induced oral mucositis during IMRT for head and neck cancer- An assessment, Medicina oral pathologia Oral cirugia Bucal 2015; 10 :4317.

36. Yokota T, Onoe T, Ogawa H et al, Distinctive mucositis and feeding tube dependency in Cetuximab and radiotherapy for head and neck cancer, Japanese Journal of Clinical Oncology 2015;45(2):183-188.

37. Onyango JF, Macharia IM, Delays in diagnosis, referral and management of head and neck cancer presenting at Kenyatta National Hospital, East African Medical Journal 2006; 83(4):85-91

APPENDICES

Appendix I: General Patient Information and Consent Form

Study number _____

Study title: -PREVALENCE AND PREDICTORS OF ORAL MUCOSITIS IN PATIENTS UNDERGOING RADIOTHERAPY FOR HEAD AND NECK CANCER AT THE KENYATTA NATIONAL HOSPITAL

Principal Investigator: Dr Josephine Njeri Kimani (Postgraduate student in Ear Nose and Throat Surgery, University of Nairobi)

Supervisors: - **Dr. Peter Mugwe**

-Dr.Catherine Irungu

Introduction

Participation in this study is voluntary. We aim to find out the prevalence and risk factors for development of oral mucositis in patients undergoing radiotherapy for head and neck cancer at the Kenyatta National Hospital.

Mucositis can be described as changes in the lining of the mouth which occur as a result of cancer treatment. It is one of the commonest immediate side effects of radiotherapy and chemotherapy. Failure to recognize and treat mucositis early can lead to a poor quality of life and a poor treatment outcome.

In our set up there is unfortunately very limited information about this condition in our head and neck cancer patients. The aim of this study is to find out how common this condition is and to identify some of the underlying conditions that make one susceptible to development of mucositis. The information we obtain from this study will help us in the future to improve the care we give to our head and neck cancer patients by identifying patients at risk early enough and also by coming up with treatment strategies for this condition.

What is involved in this study?

Once consent is granted, the principal investigator will take a medical history from you and an examination of your mouth will be performed. The principal investigator will record her findings in various documents. The principal investigator will follow up on your progress once you start treatment and at the completion of 2 weeks, 4 weeks and 6 weeks of your treatment she will take additional medical history and will re-examine you to check for any changes in the mouth.

Are there any risks involved?

There are no risks involved.

Will I be penalized for not participating?

No, participation in this study is voluntary you will receive the same attention and treatment as those who choose to participate.

What benefits will I get if I participate?

There is no direct benefit from participation in this study but the Information obtained from this study will help us understand more about this disease and be able to help more patients in the future.

What about confidentiality?

All the information we obtain from you will be kept confidential.

How much will it cost me?

No extra cost will be incurred

What are my rights as a participant?

Participation in the study is voluntary. Once inducted in the study, you can choose to discontinue at any time.

What do you do with the information you get?

The information will help us improve the care of our patients undergoing chemoradiotherapy and like any other scientific information, we will seek to share our findings with other doctors in Kenya and the rest of the world.

Are you satisfied with the information given?

If yes and you are willing to participate, please fill in and sign the consent below.

If you have any questions or need further clarifications about the study contact

The principal investigator:

Dr Josephine Kimani

Resident in ENT Head and Neck Surgery,

Phone number 0729-683000, e-mail address: njeriwanjahi@gmail.com

Supervisors:

- Dr. Peter Mugwe, MBCHB, MMED (ENT)

  Consultant ENT Surgeon, senior lecturer University of Nairobi

  email : pmugwe@yahoo.com

  Phone number : 0722513778

- Dr. Catherine Irungu, MBCHB, MMED (ENT)

  Consultant ENT Surgeon, lecturer University of Nairobi

  e-mail : catherineirungu@uonbi.ac.ke

  Phone number : 0722385710

If you have any questions on your rights as a participant contact the *Kenyatta National Hospital Ethics and Research Committee (KNH-ERC)* by calling *2726300 Ext. 44355.*

CONSENT FOR THE STUDY

Participation in this study is voluntary

I……..……..……..

study no…… of …… do hereby consent to be included in this study on the prevalence and risk factors for development of oral mucositis. The nature of the study has been fully explained to me by Dr…… I have not been promised any material gain to participate.

Signed (or thumb print)……. Date…….

I Dr.....confirm that I have explained to the patient the nature of the study. Date.....signed.....

CONSENT BY PATIENT'S PARENTS/GUARDIAN:

Participation of your child in this study is voluntary

I.....

Study number……..of.....hereby give consent for..... (Name of child) to be included in this study, on the prevalence and risk factors for development of oral mucositis. The nature of the study has been fully explained to me by Dr…… I have not been promised any material gain to participate.

Signed…….

Date……

I Dr.....confirm that I have explained to the patient the nature of the study. Date.....signed.....

Appendix II: Fomu ya Maelezo Kuhusu Utafiti

Nambari ya utafiti _____

Kiini cha utafiti: - Kutathmini ni idadi gani ya wagongwa walio katika matibabu ya saratani ya viungo vya kichwa na shingo wanaathiriwa na vidonda vya mdomo na ni kipi kinachosababisha vidonda hivyo

Mtafiti mkuu: Dkt Josephine Kimani (Mwanafunzi wa uzamili katika Chuo Kikuu cha Nairobi anayesoma kuhitimu kama daktari wa Maskio, Mapua na Koo).

Wasimamizi: -Dkt. Peter Mugwe

-Dkt. Catherine Irungu

Maelozo zaidi kuhusu utafiti

- Kushiriki kwa utafiti huu ni kwa hiari yako
- Lengo la utafiti huu ni Kutathmini ni idadi gani ya wagonjwa walio katika matibabu ya saratani ya viungo vya kichwa na shingo wanaathiriwa na vidonda vya mdomo na ni kipi kinachosababisha vidonda hivyo
- Je hivi vidonda ni vipi? Vidonda hivi vya mdomo ni aina moja ya magonjwa yanayosababishwa na madhara ya mionzi inayotumika kutibu saratani ya viungo vya kichwa na shingo. Ugonjwa huu husababisha kudhoofika kwa maisha ya walioadhiriwa. Utafiti uliofanywa hapa kwetu kuhusu ugonjwa huu hautoshi, kwa hivyo tungetaka kuongeza ujuzi wetu kuhusu ugonjwa huu ili tuweze kuwasaidia wagonjwa wengine siku za usoni.
- Unapokubali kushiriki kwa utafiti huu, utaulizwa maswali mbalimbali kuhusu ugonjwa ulionao na jinsi matibabu unayopata yanakuathiri kwa mdomo wako na koo lako. Baada ya wiki mbili za matibabu yako, mtafiti mkuu atawasiliana nawe ili aweze kujua jinsi unavyoendelea na ili aweze kujua kama kuna mabadiliko yeyote unahisi mdomoni tangu uanze matibabu. Mtafiti mkuu pia atawasiliana nawe baada ya wiki nne na baada ya wiki sita za matibabu yako.
- Madhara: -Hakuna madhara au gharama yoyote yatakayotokana na kushiriki kwako au mtoto wako katika utafiti huu.

- Kushiriki ni kwa hiari yako na hautashurutishwa kwa njia yoyote. Una haki ya kukataa kushiriki au kutamatisha ushirikiano wako wakati wowote bila kuhujumiwa.
- Hakuna malipo yoyote utakayopata ila shukrani kwa kukubali kushiriki katika utafiti huu. Ujuzi tutakaopata kwa utafiti huu utaweza kusaidia wagonjwa wengine siku za usoni.
- Habari yote utakayotoa kukuhusu itawekwa kwa siri. Jina lako au la mtoto wako halitachapishwa popote bila idhini yako. Hata hivyo, majibu tutakayopata tutayajadili bila kutoa kitambulisho chako au cha mtoto wako kwa mtu yeyote.

Ikiwa una swali ama ungetaka kupata maelezo zaidi kuhusu utafiti huu, wasiliana na :

Mtafiti Mkuu

Dkt Josephine Kimani

Nambari ya simu 0729-683000

Barua pepe: njeriwanjahi@gmail.com

Wasimamizi:

- Dkt. Peter Mugwe, MBCHB, MMED (ENT)

  Nambari ya simu : 0722513778

  Barua pepe: pmugwe@yahoo.com

- Dkt. Catherine Irungu, MBCHB, MMED (ENT)

  Nambari ya simu : 0722385710

  Barua pepe: catherineirungu@uonbi.ac.ke

Ikiwa unaswali kuhusu haki zako katika utafiti huu wasiliana na *Kenyatta National Hospital Ethics and Research Committee (KNH-ERC)* Nambari ya simu *2726300 Ext. 44355.*

KIBALI CHA UTAFITI

Kushiriki kwako katika utafiti huu ni kwa hiari yako. Mimi ……..… wa …….. nambari ya utafiti…… nimekubali kuhusishwa katika utafiti huu unaoangalia ugonjwa wa vidonda vya mdomo kwa walio katika matibabu ya saratani. Nimekubali baada ya kusoma na kufahamishwa na Dkt.…… hakuna malipo nitapewa.

Sahihi…….Tarehe…….

Mimi Dkt ……. Nadhibitisha kuwa nimemwelezea mgonjwa yote yanayohusika na utafiti huu. Tarehe…….

KIBALI CHA UTAFITI CHA WATOTO

Kushiriki kwa mtoto wako katika utafiti huu ni kwa hiari yako. Mimi ……..…… ……..

mzazi/msimamizi wa …….. nambari ya utafiti…… nimekubali mtoto wangu kuhusishwa katika utafiti huu unaoangalia ugonjwa wa vidonda vya mdomo kwa walio katika matibabu ya saratani. Nimekubali baada ya kusoma na kufahamishwa na Dkt.…… hakuna malipo nitapewa.

Sahihi……. (mzazi/ msimamizi)
Tarehe…….
Mimi Dkt ……. Nadhibitisha kuwa nimemwelezea mgonjwa yote yanayohusika na utafiti huu. Tarehe…….

Appendix III: Demographic and Clinical Data

***STUDY NUMBER*:**

AGE:

SEX Male ☐ *Female* ☐

SITE OF PRIMARY TUMOUR:

TNM STAGING OF TUMOUR :

MANAGEMENT MODALITY

Prior surgery Yes ☐ No ☐

If yes, type of surgical intervention:

Radiotherapy Alone

Dose

Schedule

Chemotherapy + Radiotherapy: Agent

Dose

Schedule

PRE-TREATMENT NEUTROPHIL COUNT:

PRE-TREATMENT LIVER FUNCTION TESTS:

PRE-TREATMENT UREA AND CREATININE:

ALCOHOL EXPOSURE: NEVER ☐ FORMER ☐ CURRENT ☐

SMOKING EXPOSURE: NEVER ☐ FORMER ☐ CURRENT ☐

PRE-TREATMENT FEEDING ROUTE:

Oral feeding ☐

Nasogastric tube feeding ☐

Gastrostomy tube feeding ☐

Percutaneous Endoscopic Gastrostomy (P.E.G) tube ☐

STATE OF ORAL CAVITY PRE-TREATMENT:

Normal:

Adentulous:

Ulcerations:

Dental carries:

ORAL HYGIENE PRACTICES:

Number of times per day you brush/ clean your teeth?

What is used to clean/ brush your teeth?

Any visit prior to treatment for professional dental care?

RESOURCE UTILIZATION INFORMATION

STUDY NUMBER*:*

TREATMENT DURATION:

TOTAL NUMBER OF GRAYS RECEIVED:

USE OF ANALGESICS *IN THE LAST 2 WEEKS*

YES ☐

NO ☐

IF YES NSAID ☐

OPIOD ☐

ANY VISIT TO A DOCTOR DUE TO *ORAL PAIN*

YES ☐

NO ☐

ANY HOSPITALIZATIONS

YES ☐ REASONS

NO ☐

ANY FEEDING TUBE PLACEMENTS

YES ☐

NO ☐

TYPE OF FEEDING TUBE

WHEN WAS IT PLACED?

ANY USE OF TPN

YES ☐

NO ☐

ANY INTERRUPTION OF TREATMENT

YES ☐ DURATION: REASON:

NO ☐

Appendix IV: NCI – CTC VERSION 4.0 GRADING SCALE

GRADE	**1**	**2**	**3**	**4**	**5**
NCI-CTC v.4.0 CLINICAL CRITERIA	Erythema of mucosa	Patchy ulcerations or pseudo membranes(< OR = 1.5cm and non contiguous)	Confluent ulcerations or pseudo membranes (>1.5cm), bleeding with minor trauma	Tissue necrosis, significant spontaneous bleeding, life threatening consequences	Death related to toxicity
NCI-CTC v.4.0 FUNCTIONAL CRITERIA	Minimal symptoms, normal diet	Symptomatic but can eat and swallow modified diet	Symptomatic and unable to adequately aliment and hydrate orally	Symptoms associated with life threatening consequences	Death related to toxicity

Appendix V: KNH/ERC Letter of Approval

UNIVERSITY OF NAIROBI
COLLEGE OF HEALTH SCIENCES
P O BOX 19676 Code 00202
Telegrams: varsity
(254-020) 2726300 Ext 44355

KNH-UON ERC
Email: uonknh_erc@uonbi.ac.ke
Website: http://www.erc.uonbi.ac.ke
Facebook: https://www.facebook.com/uonknh.erc
Twitter: @UONKNH_ERC https://twitter.com/UONKNH_ERC

KENYATTA NATIONAL HOSPITAL
P O BOX 20723 Code 00202
Tel: 726300-9
Fax: 725272
Telegrams: MEDSUP, Nairobi

Ref: KNH-ERC/A/495

9th December, 2015

KENYATTA NATIONAL HOSPITAL APPROVED 09 DEC 2015 KNH/UoN-ERC P.O. Box 20723-00202 Nairobi

Dr. Josephine Njeri Kimani
Reg. No. H58/68421/2011
Dept. of Surgery
School of Medicine
College of Health Sciences
University of Nairobi

Dear Dr. Kimani,

Revised research proposal: Prevalence and Predictors of Oral Mucositis in Patients Undergoing Radiotherapy for Head and Neck Cancer at the Kenyatta National Hospital (P541/08/2015)

This is to inform you that the KNH- UoN Ethics & Research Committee (KNH-UoN ERC) has reviewed and **approved** your above proposal. The approval periods are 9th December 2015 – 8th December 2016.

This approval is subject to compliance with the following requirements:

a) Only approved documents (informed consents, study instruments, advertising materials etc) will be used.
b) All changes (amendments, deviations, violations etc) are submitted for review and approval by KNH-UoN ERC before implementation.
c) Death and life threatening problems and serious adverse events (SAEs) or unexpected adverse events whether related or unrelated to the study must be reported to the KNH-UoN ERC within 72 hours of notification.
d) Any changes, anticipated or otherwise that may increase the risks or affect safety or welfare of study participants and others or affect the integrity of the research must be reported to KNH- UoN ERC within 72 hours.
e) Submission of a request for renewal of approval at least 60 days prior to expiry of the approval period. (*Attach a comprehensive progress report to support the renewal*).
f) Clearance for export of biological specimens must be obtained from KNH- UoN ERC for each batch of shipment.
g) Submission of an *executive summary* report within 90 days upon completion of the study.

This information will form part of the data base that will be consulted in future when processing related research studies so as to minimize chances of study duplication and/ or plagiarism.

Protect to discover

For more details consult the KNH- UoN ERC website **http://www.erc.uonbi.ac.ke**

Yours sincerely,

PROF. M.L. CHINDIA
SECRETARY, KNH-UoN ERC

c.c. The Principal, College of Health Sciences, UoN
The Deputy Director, CS, KNH
The Chair, KNH-UoN ERC
The Assistant Director, Health Information, KNH
The Dean, School of Medicine, UoN
Supervisors: Dr. Peter Mugwe, Dr. Catherine Irungu