PREVALENCE OF HEARING LOSS AMONG HEAD AND NECK CANCER PATIENTS RECEIVING CHEMOTHERAPY WITH OR WITHOUT RADIATION THERAPY AT ORCI

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By

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Dissertation submitted in (partial) fulfillment of the Requirement for the Degree of Master of Medicine (Otorhinolaryngology) of

Muhimbili University of Health and Allied Sciences

October, 2018

CERTIFICATION

The undersigned certify that they have read and hereby recommend for acceptance of the dissertation entitled **"*Prevalence of hearing loss among head and neck cancer patients receiving chemotherapy with or without radiation therapy at ORCI,"*** in (Partial) fulfillment of the requirements for the degree of Master of Medicine (Otorhinolaryngology) of Muhimbili University of Health and Allied Sciences.

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Date……

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DEDICATION

To my mother Theonestina Kokuramuka Barongo. You taught me to work hard, to endure the endurable, and to always be strong and focus on my goals. Thank you for everything Mom! With love I am dedicating this work to you.

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Abbreviations

ASHA	American Speech language Hearing association
BAK I	Bcl-2 Antagonist/Kille protein I
BAX	Bcl-2 Associated Xprotein
CRT/XRT	Chemo Radiation therapy
CHL	Conductive Hearing Loss
CDDP	Cis-Diamine Dichlo-Platinum
dB	Decibels
DNA	Deoxyribonucleic Acid
EAC	External Auditory Canal
ENT	Ear Nose and Throat
ERK	Extracellular Regulatory kinase
GY	Grays
HL	Hearing loss
KHZ	Kilohertz
LET	Linear Energy Transfer
MNH	Muhimbili National hospital

MUHAS	Muhimbili University of Health and Allied Sciences
MOMP	Mitochondria Outer Membrane Permeabilization
MHL	Mixed hearing loss
NADPH	Nicotinamide adenine di nucliotide phosphates
NO	Nitrogen oxide
ORCI	Ocean Road Cancer Institute
ORL	OtoRhinoLaryngology
POGT	Pediatric Oncology Group Toxicity
PTA	Pure Tone Audiometry
PUFA	Poly Unsaturated Fatty Acids
QoF	Quality of life
RT	Radiation Therapy
ROS	Reactive Oxygen Species
SNHL	Sensory Neural Hearing Loss
WHO	World health organization
5 FU	5 Fluorouracil
VDAC I	Voltage Dependent Anion Channel I

Definition of terms

Audiogram is the graph which illustrates hearing ability by showing hearing threshold at various frequencies. Normal hearing threshold is 0 to 25 dB

Chemotherapy: Treatment of diseases by using chemical substances, especially the treatment of cancer by cytotoxic and other drugs.

Head and neck cancers: Group of cancers found in the head and/or neck region. They include cancers of the nose and paranasal sinuses, lips and mouth, salivary glands, pharynx and larynx.

Pure tone audiometry (PTA); is the key hearing test used to identify hearing threshold levels of an individual, enabling determination of the degree, type and configuration of a hearing loss .

Radiotherapy: Treatment of a disease especially cancer by using ionizing radiations

Cumulative dosage: The total amount of a drug or radiation given to the patient over a period of time.

Abstract

Hearing loss affects the quality of life of people in low and middle income countries. Worldwide about 5.3% of people have disabled hearing (WHO, 2012). This population is expected to increase significantly by 2050. (1) It affects all age groups with unequal distribution. (2) Majority of the affected people reside in developing countries. In the past, most cancer patients who survived through treatment with various chemotherapeutic regimes considered themselves serendipitous to be free from this devastating disease. Nevertheless, the outcome of adverse reactions of chemotherapy and/with radiation in relation to the Quality of life (QoF) such as hearing loss was crucial but neglected .(1)

Objective: The aim of this study was to determine the prevalence and patterns of hearing loss among head and neck cancer patients receiving chemotherapy with or without radiation therapy at Ocean road cancer institute in Tanzania.

Materials and methods: This was a descriptive cross sectional hospital based study conducted at ORCI in 2017. 138 cases who had been on treatment for the period of six weeks were recruited in the study. Patient history was taken, age, body surface area, drug dosage and duration of treatment were asked and crosschecked from the patient's file. Otoscopic examination was done prior PTA test. PTA was done in a quiet room, at frequency range of 250HZ to 8000HZ using Amplivox 270 audiometer. Data collection was done by using a special designed questionnaire. Data analysis was done using the Statistical Package for Social Sciences version 20 and a p value of <0.05 was considered significant.

RESULTS

Among 138 patients in the study population, 68(49.3%) were males and 70 (50.7%) were females. Age ranged from 16- 89 years. Mean age was 50.78years with Std deviation of 14.958.Most cases were in the age group of 36-55years 66(47.8%), least cases were above 75years 5(3.6%). Hearing loss was found in 98(71%) cases and was bilateral in most of the patients. Among 98 patients with hearing loss, 93 (95.0%) patients had sensorineural hearing loss which was bilateral with equal severity except for one patient who had unilateral sensorineural hearing loss. 3(3.0%) patients had conductive hearing loss which was bilateral,

and 2(2.0%) patients had mixed hearing loss in which one patient had bilateral and the other one had unilateral mixed hearing loss. The most affected age groups were 56-75years and >75years (80.0%) each, the least affected group was 16-35years (45.5%). Increase in age was associated with increased risk of developing hearing loss(P.value=0.029).Males had higher prevalence of hearing loss (76.5%) than females (65.7%).Gender was not associated with increased risk of developing hearing loss.(P.value =0.164).Conductive and mixed hearing loss were seen only in patients with sinonasal and nasopharyngeal cancer respectively. However, there was no statistical significance on the relationship between the site of the tumor and type hearing loss (P.value=0.23).Treatment modality (chemotherapy alone or chemoradiation therapy) had statistical significant effect on the type of hearing loss (P.value =0.045) but it had no statistically significant effect on severity of hearing loss (Pvalue=0.526). Out of 138 patients, 79 patients used chemotherapy alone which consisted of various drug group combinations. Among these patients, 53(67.0%) developed hearing loss. Use of a single drug group or combined drug groups had no statistical difference on severity of hearing loss (P.value=0.603). High cumulative doses of platinum and taxane compounds were associated with increased severity of hearing loss, this association was statistically significant. (P.values=0.003, 0.021).

Conclusion

Chemotherapy with or without radiotherapy is the main stay in treatment of most malignancies including head and neck cancers, however its ototoxic effect especially hearing loss needs to be checked in order to prevent permanent disability that can occur post treatment.

Audiological follow up in cancer patients before, during and after treatment is the main stay for earlier detection of hearing loss and can help to guide the dosage to be delivered according to the patient's condition, and earlier provision of hearing rehabilitation services.

1.0 INTRODUCTION

1.1 Back ground

Hearing loss (HL), also known as hearing impairment is defined as a partial or total loss of ability to hear. Other terms; deaf and hard of hearing are also used whereby; hard of hearing is used for individuals who may experience mild to severe hearing loss who may benefit from hearing rehabilitation. Deaf is used to describe individuals who have profound hearing loss who cannot benefit from hearing rehabilitation i.e. hearing aids.(1)

This condition may occur in one or both ears. It can be congenital or acquired. Also it can be classified as conductive hearing loss (CHL), sensorineural hearing loss (SNHL), or mixed type where an individual presents with both CHL and SNHL. Severity as per WHO can be mild, moderate or severe HL .(2) There are several causes of hearing loss such as high frequency noise, congenital causes, trauma and infections to the ears, and ototoxic agents.(1)

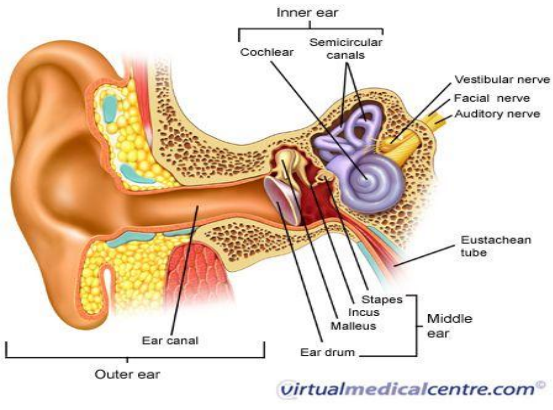
Hearing loss is a public health problem affecting the social economic status of the affected individuals thus needing more attention and efforts to address. Some of the cancer drugs are ototoxic and patients receiving these drugs may end up with hearing loss that further reduces their quality of life, more over patients receiving mixed treatment ie chemotherapy and radiation therapy on the head and neck areas may suffer from mixed type of hearing loss.(3)

1.2 Applied anatomy and physiology of the ear and hearing

Anatomically, the ear has three parts, the outer middle and inner ear.(4) Every part plays a role in the process of hearing. Thus any alteration or disturbances in any of these parts can lead to changes in the quality of hearing.(5) For a sound to be heard the auditory system must carry out three basic tasks. First, to deliver the acoustic stimulus to the receptors, second, it has to convert the stimulus from pressure changes into electrical signals, then thirdly, must process these electrical signals so -that they can efficiently indicate the qualities of the sound source, such as frequency (pitch), amplitude (loudness, volume), and location .(6)

Physiologically hearing mechanism can conveniently be divided into three parts: The outer ear which captures sound waves and performs mid frequencies amplification, ensures vertical direction and coding. This is aided by the structure in which the ear canal is irregular cylindrical shaped with an average diameter of less than 0.8 mm and about 2.5 cm long. It is open at the outside at the pinna which plays an important special focusing role in hearing. The EAC then narrows slightly and widens towards its inner end, at the eardrum.(7) which supports sound vibrations best at the frequencies which the human ears hear most sharply. This resonance amplifies the variations of air pressure that make up sound waves, placing a peak pressure directly at the eardrum. For frequencies between approximately 2 KHz and 5.5 KHz, the sound pressure level at the eardrum is approximately 10 times the pressure of the sound at the auricle. The eardrum acts as an interface between outer and middle ear. Airborne sound waves reach only as far as the eardrum.(7) Here they are converted into mechanical vibrations in the solid materials of the middle ear. Sound waves first set up sympathetic vibrations in the taut membrane of the eardrum, The eardrum passes these vibrations on to the middle ear structure.(7)

The Middle Ear*;* Provides protection, Creates impedance matching by increasing 22 folds as much pressure to be exerted on the cochlear fluids as is exerted by the sound wave against the tympanic membrane.It is a frequency analyser and sound transducer. It contains three small bones known as the Malleus, Incus, and Stapes. These bones form a system of levers which are linked together and driven by the eardrum. Malleus pushing Incus, Incus pushing Stapes. The lever system amplifies the force of sound vibrations. This system moves through a shorter distance but exerts a greater force. In combination the bones double or triple the force of the vibrations at the eardrum.(4,6) Muscles of the middle ear modify the performance of this lever system as an amplifying unit. They act as safety devices to protect the ear against excessively large vibrations from very loud sounds - a sort of automatic volume control.(5,6)



The stirrup passes the vibrations to the "oval window". The size of the oval window compared to that of the eardrum (15 to 30 times smaller) produces the critical amplification needed to match impedances between sound waves in the air and in the cochlear fluid. Apart from the amplification of the bone lever system of the middle ear, this concentration of force amplifies the incoming vibrations of sound about 15 to 30 times.(7,8)

The inner ear*:* In the Cochlea, the mechanical vibration is immediately transformed into hydraulic pressure which imparts movement to the cochlear duct and to the organ of Corti - the "peripheral seat of hearing".(7)

The vestibular and tympaniccanals contain perilymph - a liquid almost identical with spinal fluid. The cochlea duct contains endolymph - a liquid similar to the fluid within cells. The canals are separated by thin membranes: Reissner's membrane and the basilar membrane respectively. The perilymph and endolymph have different chemical compositions and are electrically charged differently, any defect in the membranes that allows the two fluids to mix impairs the process of hearing by impairing proper generation of electric potentials.

The pressure waves in the cochlea exert energy along a route that begins at the oval window and ends abruptly at the membrane-covered round window, where the pressure is dissipated.(8) Hydraulic pressure waves in the cochlea induce a wave-like ripple in the basilar membrane which travels from the taunt towards the loose end. High tones create their greatest crests where the membrane is tight, low tones where the wall is slack. This is because resonant frequency is correlated with tension as in a taunt string. The position of this crest is important because it determines which nerve fibres will send signals to the brain. High frequency tones cause the crest to occur at the base of the cochlea and the lower frequencies towards the apex. Apart from airborne sounds, the basilar membrane also picks up vibrations in the skull from such sources as teeth clicking, for example.(7,8)

The Organ of Corti is a gelatinous mass about 4 cm long and is composed of some 7500 interrelated parts. The Organ of Corti is enclosed in the cochlea. It is filled with fluid, surrounded by other fluid and responds to movements in these fluids induced by sound waves. The fluids filling and surrounding it act as shock absorbers, and so do the springy membranes which support it. It is even isolated from the normal body supply lines, for the faint pulsing of blood through capillary vessels would be detected as background noise.(7,8)

The organ of Corti is shaped like the jam in a jam roll. It spirals around within the cochlea. The basilar membrane supports the organ which contains a mass of cells almost touching the branch endings of the auditory nerve. From these cells sprout fine hairs, (23,500 of them) rising in orderly rows like the bristles of a very soft brush. These hairs are transducers. As the basilar membrane bellies in and out, it pushes and pulls the complex of tissues above it. The hairs' cells of the organ of Corti ride with the basilar membrane. The hairs have their tops embedded in the tectorial membrane and their roots fixed in the hair cells, so the motion of the basilar membrane bends and twists and pull and push the hairs. Under these physical stresses the hairs generate electrical signals which stimulate the auditory nerve. A bundle of about 30,000 individual fibres. Eventually, the electrical signals running through the auditory nerve stimulate the hearing centre of the brain.(5,7)

The fibres are grouped by the frequency of the sound signal they carry, the number of fibres a sound requires gives the brain a gauge of its intensity. Coming from the brain, descending nerve fibres may carry instructions from the brain back to the ear to filter out and thus eliminate some signals which the brain determines are of no importance, and concentrate on others. After passing through the cochlear nucleus, some of the descending nerves from the brain go to the middle ear where they control the muscles used for fending off dangerously loud sound. The nerve fibres carrying sound signals lead to different parts of the auditory cortex depending on the frequencies they carry. The auditory cortex lies in a deep furrow called the Sylvian fossa. The high tones terminate deep within the Sylvian fossa while the low tones end near the outer surface.(8)

1.2.1 Types and causes of hearing loss.

There are main three types of HL. Conductive hearing loss when hearing loss is due to problems with the ear canal, ear drum, or middle ear and its little bones (the malleus, incus, and stapes). Sensoryneural hearing loss (SNHL) when hearing loss is due to problems of the inner ear, also known as nerve-related hearing loss. Mixed conductive and sensory neural hearing loss refers to a combination of conductive and sensorineural hearing loss. This means that there may be damage in the outer or middle ear and in the inner ear (cochlea) or auditory nerve.(2,5,8)

1.2.1.1 Conductive hearing loss and its causes:

Malformation of outer ear, ear canal, or middle ear structures, Fluid in the middle ear from colds, Ear infection (otitis media - an infection of the middle ear in which an accumulation of fluid may interfere with the movement of the eardrum and ossicles, Allergies, Poor Eustachian tube function, Perforated eardrum, Benign tumors, Impacted earwax, Infection in the ear canal, Foreign body in the ear, Otosclerosis where there is abnormal deposition of bony material around the ear osicles.(5)

1.2.1.2 Sensory neural hearing loss and its causes

Exposure to loud noise, Head trauma, Ototoxic agents eg anticancer drugs, Virus or disease, Autoimmune inner ear disease, Congenital causes of hearing loss; genetic and non genetic causes, Aging (presbycusis), Malformation of the inner ear, Meniere's Disease, Otosclerosis a hereditary disorder in which a bony growth forms around a small bone in the middle ear, preventing it from vibrating when stimulated by sound.in some cases bone growth can extend to the cochlear in the inner and cause SNHL.(5,8)

1.2.2 Pathophysiology of hearing loss due to anticancer drugs and radiation therapy

Head and neck cancers are primarily treated by three main modalities: surgery, chemotherapy and radiotherapy administered alone or in combination.(3) Radiotherapy alone is the most common modality of treatment for certain types of head and neck cancers such as Nasopharyngeal carcinoma (9). For loco-regional advanced cancers concurrent chemo-radiotherapy is mainly used .(9,10)

1.2.2.1 Anticancer drugs

The most common ototoxic anticancer drugs are cisplatin and Carboplatin. At ORCI, several chemotherapeutic drugs are offered for various cancers on different sites.eg for brain tumors eg Astrocytoma, adjuvant CRT is given, the common drug offered is Timozolomide given 75mg/m2po qd withTR 59.4GY/33\\/6weeks,3dythen 200mg/m2 every month 4weeks after RT.(11)

In head and neck cancers concurrent CRT for stages 3,4A and 4B;cisplatin 30mg/m2ivdl weekly with concurrent RT 50-70 GY/25-35\ for five to seven weeks. In recurrence and metastas is, any of (5FU+cisplatin,cisplatin+gemcitabine,cisplatin+capecitabine,cisplatin+taxanes) combinations can be used.(11)

Ototoxic mechanisms of cisplatin

Cisplatin (cis-diamminedichloroplatinum II) (CDDP) is a highly effective chemotherapeutic agent used to treat solid tumors, like ovarian tumors, testicular tumors, bladder, non-small cell lung, and head and neck solid tumors.(12)

The mechanism accounting for its antitumor activity is the formation of covalent bonds between the cisplatin platinum (Pt) atom and DNA purine bases in the N7 position, which generate intra- and inter-strand cross-links that have been demonstrated in vitro to trigger apoptotic and necrotic cell death.(13)

The main reported side effects associated with its use are nephrotoxicity, peripheral neurotoxicity and ototoxicity. While nephrotoxicity can be ameliorated by increasing saline hydration as well as mannitol diuresis, there are no approved preventive treatments available for ototoxicity and neurotoxicity.(14)

Recent studies pointed out that the cytostatic/cytotoxic effects of CDDP originate from both nuclear and cytoplasmic signaling pathways. It is known that only ~1% of intracellular CDDP forms covalent bonds with nuclear DNA, but CDDP also exerts prominent cytotoxic effects in enucleated cells (cytoplasts). The exact molecular mechanisms that explain cytotoxic potential of cytoplasmic CDDP are not yet known, but they are believed to involve:.(1) the accumulation of reactive oxygen species

(ROS) and nitric oxide (NO) which exert direct cytotoxic effects by favoring the opening of the permeability transition pore complex (PTPC); (2) the induction of a mitochondrial outer membrane permeabilization (MOMP)-stimulatory signal via BAK1 (pro-apoptotic BCL-2 family member), VDAC1 (PTPC component voltage-dependent anion channel1) and BAX (BAK1 homolog) ; and (3) the activation of a cytoplasmic pool of p53, which is capable to promote the MOMP.(14)

CDDP is chemically inert until one or both of its cis chloro groups are replaced by water molecules. Such a equation reaction takes places in lower proportion in the blood, but mostly occurs spontaneously in the cytoplasm, due to the relative low concentration of chloride ions (~2–10 mM, as compared with ~120 mM in the extracellular space). Once inside the cell, cis-diammine (aqua) chloroplatinum (II) (or monohydrate cisplatin complex) is capable of causing death by at least two different mechanisms: one dependent on p53 and caspases, and one mediated by protein kinesis Both mechanisms have been demonstrated in vivo in rats.(12,14)

In p53 and caspase-dependent apoptosis, exposure to high doses of cisplatin inhibits the activity of some antioxidant enzymes (superoxide dismutase, catalase, glutathione peroxidase and glutathione reductase) and stimulates the activity of others, such as NOX-3 (a nicotinamide adenine dinucleotide phosphate (NADPH)-oxidase isoform that is highly expressed in the cochlea), with a consequent increase in lipid peroxidation, causing high levels of reactive oxygen species (ROS).(12,14)

The superoxide radicals thus generated can develop four cytotoxic actions: (a) interact with nitric oxide (NO) and form peroxynitrite which will nitrosylate proteins, inactivating them ; (b) form hydroxyl free radicals that, after interacting with iron (Fe), can react with polyunsaturated fatty acids (PUFA) of the cell membrane lipid bilayer, generating the reactive aldehyde 4-hydroxynonenal (4-HNE) that triggers calcium influx into the cell, leading to apoptosis (c) inactivate antioxidant enzymes and (d) trigger cytosolic migration of Bax, with consequent activation of the mitochondrial apoptosis signaling pathway, which involves the release of cytochrome c from mitochondria and the activation of caspases 9 and 3.(12,14,15)

In addition to p53 and caspase-dependent apoptosis, cells exposed to cisplatin show over expression of the extracellular regulatory kinase (ERK) 1/2 and nuclear factor κB (NFκB), which stimulate pro inflammatory cytokines, such as tumor necrosis factor α (TNF-α), interleukin (IL)-1β and IL-6. This causes nuclear fragmentation, rearrangement of the actin cytoskeleton and cell death.(12,14)

The cochlea is comprised of many cell types whose susceptibility to the cytotoxic mechanisms of cisplatin varies. Several studies have addressed mechanisms of cisplatin toxicity that operate in particular cells or tissues of the cochlea.(12,14,15)

In type I fibrocytes from the sidewall of the spiral ligament, cisplatin activates big conductance potassium channels. The increased potassium efflux causes a loss of intracellular osmotic pressure and ionic strength. This disrupts the electrochemical gradient of the endolymph, where the concentration of potassium is high and that of calcium is low compared to the surrounding perilymph. These alterations in ion balance trigger pro-apoptotic pathways, leading to cell death(14).

1.2.2.2 Radiotherapy for head and neck cancers

Biological effects of radiation

Radiation therapy works by damaging the DNA in cancer cells weather through direct or indirect effects. The direct effect is when the energy of a photon or a secondary electron ionizes biological macromolecules while the indirect effect is when the photon is absorbed by water molecules in an organism, and some of the water is ionized, and the free radicals that are formed in water indirectly can change biological molecules. Since the radiation cannot distinguish between cancer cells and the normal cells the radiation therapy causes side effects.(16)

Cells and organs of different types have different radio sensitivity, meaning diverse response to radiation. The most radiosensitive cells have special characteristics; a high mitotic rate and therefore will undergo many future mitoses and are primitive in differentiation, e.g basal cells of the oral mucosal membrane. Low radiosensitive cells are highly differentiated and the mature cells will not undergo division, e.g neurons and striated muscle cells.(16)

Types of radiation therapy

Radiotherapy for head and neck can classified as: External-beam radiation therapy internal radiation therapy or brachytherapy;

External-beam radiation therapy; This is the most common type of radiation therapy and the most commonly used at ORCI in which radiations are given from a machine outside the body. External radiation therapy can be administered in various designs, most of which have evolved over the past few decades, it can be 2D RT, 3D Conformal RT, Intensity modulated radiation therapy (IMRT),which is an advanced form of 3D therapy.

Internal radiation therapy or brachytherapy; In which radiation therapy is provided using implants where radioactive material is placed directly into or near the cancer.(17–19)

Radiation dosage and Fractionation

The optima radiation dose for head and neck cancers depends on the size and location of the primary tumor and the neck lymph nodes. In general, primary tumor and gross lympha-denopathy require a total of 70 Gy or more with a daily fraction of 2 Gy. Radiation to low risk neck nodes require a total of 50 Gy or more. For postoperative radiotherapy higher doses (60 to 66 Gy) is required.(18)

Radiation dosage is normally given at small amounts daily in what is called fractionation schedule. Conventional fractionation consists of daily fractions of 1.8 – 2 Gy, five treatments per week. Hyper fractionation schedule delivers two or more small dose fractions on each treatment day and keeps the overall treatment time the same or slightly reduced. Accelerated fractionation schedule is the one in which the overall treatment time is reduced, but the number of dose fractions, total dose and size of dose per fraction is not changed.(18,20)

1.2.2.3 Complications of radiotherapy for head and neck cancers

Regardless of the clinical intent, radiotherapy produces tissue changes that may profoundly affect patients' quality of life later. Toxicities from radiation therapy (RT)

for head and neck cancers are classified as early (acute) or late (delayed) effects based on the time course of their development relative to the radiotherapy.(21)

Acute (Early) complications*:*

Early complications develop during the course of RT or shortly after completing RT (about 2-3 weeks) and usually subside thereafter.(22–24) e.g. Oral and oropharyngeal mucositis, dysphonia and laryngeal edema, MEE and ototoxicity is important.

In the past studies reported SNHL after RT in patients with NPC but did not differentiate between sensory and neural deafness.(13) RT induced SNHL is believed to result from damage on the auditory sensory hair cells in the cochlear .In adults the auditory neural cells are end cells with no ability to undergo cell division, thus they are resistant to direct killing by radiations, however they are said to be susceptible to damage by.(13) high doses of radiation. Eg studies done in Chinchilians showed that degeneration of cochlear nerve fibres occurred after irradiation with 40Gy-50Gy and 60Gy-90Gy; the incident rates were 31% and 62% respectively.(13)

Radiation induced SNHL can be early or late onset. Early onset SNHL occurs within hours to days after completion of therapy and is due to acute radiation induced Cochlear cell apoptosis. Late onset SNHL occurs months to years after completion of RT, this is believed to be due to progressive vascular compromise from radiation induced vasculitis obliterans. It is much interesting that radiation induced vasculitis has no correlation with vestibular dysfunction.(13)

Post radiation SNHL is progressive; this is because the cochlear has finite number of hair cells, which keeps dying until a critical number is reached when an individual experiences hearing loss. Also the effect of initial radiation induced cell injury renders the cells more susceptible to apoptosis following subsequent exposure to insults eg noise and ototoxic medications.(13)

The Role of p53

In the OC-k3 inner ear cell line, Low et al found up-regulation of p53 related genes from microarray studies. Western blotting confirmed up-regulation of p53 at 72hours and phosphorylation at 3, 24, 48 and 72 hours after irradiation. It is now known that p53 can induce apoptosis through 2 mechanisms: one that depends on transactivation of apoptotic-related genes and another that involves translocation of p53 to the mitochondria where it can physically interact with and inactivates pro-survival Bcl-2proteins. The 2 mechanisms most likely do not work independently of each other as transcriptional blockage.(25)

The Role of Reactive Oxygen Species

There has been compelling evidence in animal models, implicating reactive oxygen species (ROS) in the damage associated with non-radiation causes. Although the exact relationship between ROS and other cell death events is still not fully understood, ROS is believed to play a key role in the promotion of apoptosis by affecting mitochondrial permeability, release of cytochrome c and activation of p53 and caspases. In radiation-induced apoptosis in the OC-k3 inner ear cell line, Low et al demonstrated dose-dependent intracellular generation of ROS at 1hour post-irradiation.

Multiple Cell Death Mechanisms

Although the p53-dependent apoptosis is likely to play a key role in radiation-induced cochlear cell death, it is not necessarily the only mechanism involved. A number of different mechanisms leading to cell deaths have been described and may well be also involved in radiation induced ototoxicity. Firstly, necrotic cell death is expected to occur, especially in high radiation doses. Although this is a passive form of cell death which does not encompass activation of any specific cellular programme, ROS can contribute to the death process by affecting lipid peroxidation of the cell membrane.(9,13)

Secondly, p53-independent mechanisms had been described. It had been noted that apoptosis induced by high LET radiation was not affected by cellular p53 gene status. Ionising radiation has been found to induce caspase dependent but p53-independent

cell death in Drosophilia. This may possibly be due to ceramide formation as ceramide has been shown to trigger caspase activation during gamma induced apoptosis of human glioma cells lacking functional p53.(13,25)

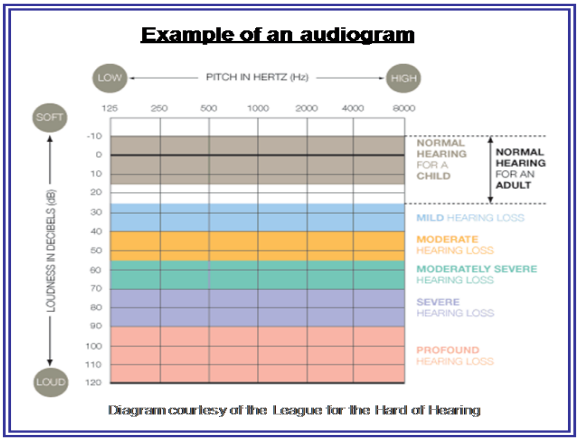
Thirdly, caspase-independent programmed cell death mechanisms had also been described in recent years. Non caspase proteases such as cathepsins, calpains and granzymes are involved, resulting in intra-cellular signaling processes that lead to apoptotic- or necrotic-like morphological forms of programmed cell death. Indeed, leupeptin, a calpain inhibitor, had been shown to protect inner ear cells from aminoglycoside ototoxicity.(13,14)

1.2.3 Management of hearing loss

Investigations;

Mainly Pure tone audiometry is performed, where the type and severity of hearing loss is identified. The results are presented on the audiogram and interpreted as follows according to (WHO, 2008);

0-25db….. Normal hearing,
26-40db….. Mild hearing loss
41-60db…… Moderate hearing loss
61-80db……. Severe hearing loss
>81db……. Profound hearing loss



Treatment

Treatment of hearing loss depends on the type of hearing loss can be medical or surgical modality.

Medical modality

In case of conductive hearing loss, treat infections with appropriate antibiotics, remove obstructions eg cerumen, foreign body etc. For sensorineural hearing loss, those children with mild to moderate hearing loss hearing aids can be used and speech therapy is of good help. In adults with moderate to profound hearing loss, hearing rehabilitation services eg hearing aids can be offered where by 40-60Db can be corrected.

Surgical modality

-Myringotomy tube insertion in patients with middle ear effusion.
-Tympanoplasty in patients with tympanic membrane perforation with oscularchain disruption.
In cases of cochlear damage, cochlear implant can be done.(5)

1.3 Literature review

The survival rate and life expectancy of cancer patients who receives chemotherapy with or without radiation therapy has been reported to increase significantly in recent years.(1,2)

According to World Health Organization (2012), about 360 million persons have disabling hearing loss. This represent 5.3% of the world population, almost 183 million adult males greater than 15 years old and 145 million females, which is 7.5% of the adult male population and approximately 6% of the adult female population respectively. With the aging of the world population these numbers are expected to double by 2030-2050. Hearing impairment is considered to be the most prevalent impairment worldwide. However, developing countries have the world's highest prevalence of hearing loss, and hearing screening programmes are limited.(2)

1. **Hearing loss by age and sex.**

A study done by Landier in America, reported that the prevalence of ototoxicity in patients who have received potentially ototoxic therapy ranges from 4% to 90% depending on factors such as age of the patient population, medication (s) used, cumulative dose, and administration techniques.(5,26,27) In 2007 a study done by Alien Medeiros da Silva reported that, the prevalence of hearing loss among children and adolescents in Brazil was found based on classification such that according to ASHA the prevalence was 42.5%, 40.4% using POGT with good concordance between the two methods of classification was almost perfect with K= 0.96.showing that hearing loss was an important side effect in treatment of children with cancer.(6,28)

Rybak, Mukherjea et al, found out that there were significant number of patients developing hearing loss after treatment with chemotherapy, such that among 67 patients aged 8 to 23 years, 61% developed this undesirable side effect, and majority experienced high frequency hearing loss.(3,14) In United State (2003-2004), a study on speech frequency hearing loss was conducted by Orgell et al, the youngest age group (20-29 years) was the most affected with a prevalence of 8.5%, and men were most affected group than females.(29)

This study also discovered that risk factors such as smoking, noise exposures and cardiovascular risk exposures influenced the occurrence of such condition.(7) In the year 2012, Orgel conducted a study on 29 children with brain tumors who were followed up during treatment with Cisplatin dose: 281688mg/m2; and carboplatin dose: 12056277mg/ m2; with no cranial radiation .After treatment, 62% of children had abnormal hearing and 38% required hearing aids.(29) Ibrahim Qaddoumi in the year 2012 found out that among 60 patients with retinoblastoma who received Vincristine and Carboplatin,17% had sustained hearing loss and 9 patients among them were aged < 6months,this study also showed that the incidence of hearing loss was higher in younger age.(30)

Lie et al (2004), reported that young children seem to be more susceptible to side effects of chemotherapy especially hearing loss than adults.(14)

2. Types of hearing loss by tumor site.

In the study by Schultz, M. Vale et.al done in America on Hearing Loss and Complaint in Patients with head and neck cancer treated with radiotherapy, it was observed that hearing loss occurred in 102 (72.3%) of the participants exposed to radiotherapy and 69 (48.9%) of the control group (P.001). Hearing losses were mostly sensorineural and of mild degree, but those exposed to radiotherapy more frequently presented with severe and mixed-type hearing losses (P=0.001), of the participants exposed to radiotherapy, 19.1% had a severe handicap (P0.001). thus concluded that patients undergoing radiotherapy in the head and neck region have a higher incidence of hearing loss and more severe hearing handicap.(24)

Van der Putten retrospectively studied unilateral sensoryneural hearing loss among patients who developed parotid tumors and found that, among 52 patients 32% were found to have hearing loss of > 15 dB in 3 frequencies.(10)

In Taiwan, in the year 2002, Wang, W. Kuo, K. ho et al. found that among 150 patients (261ears) with Nasopharyngeal carcinoma in which those with advanced disease received at least 120mg of Cisplatin and 1000mg 5FU followed by radiotherapy for5-7 weeks, 8.1% ears had severe sensory neural hearing loss at speech frequencies and 16.4% had severe sensory neural hearing loss at high frequencies.(31)

3. Types of hearing loss by treatment modality

Cancer can be treated with either chemotherapy radiotherapy or combined chemoradiation therapy depending on the tumor site, stage and sensitivity of the tumor cells. Each Modality can cause hearing impairment via various mechanisms and lead to various types of hearing loss. Barbara, Jereczek fossa on the study on radiotherapy induced ear toxicity explained that; Damage due to radiation on the ear can affect any organ from the external ear, middle ear, inner ear and auditory path way and cause either conductive, sensorineural or mixed type of hearing loss.(32)

4. Severity of hearing loss by treatment modality

Severe hearing loss among cancer patients using CRT has been reported and it results from chemical and physical damage to the inner ear where cochlear sensory hair cells are most affected.(3,14,33,34) High toxicity of the combined therapy was observed in patient treated with adjuvant chemotherapeutic agent such as Cisplatin and radiation therapy, Van der Putten et al observed that multi-modality of treatment with chemotherapy during chemo radiation therapy increases sensitivity of tumor cells to radiation therapy but is related to undesirable toxic effects, in particular ototoxicity with hearing loss which has negative impact on socio-economic development.(2) The toxicity resulting from synergistic effects of chemotherapy and radiation therapy has been studied and irradiation using threshold dosage of 50 Gy on the cochlea and Eustachian tube.(8,10) Low et al 2006 in Indonesia followed up 105 patients with Nasal pharyngeal Carcinoma, among them 58 received cisplatin 160mg/m2 combined with 70GY radiation. 47 received 70GY alone. One year post treatment those who received chemo radiation had a statistically worse hearing thresholds compared to those who were treated with radiation alone.(33,37) High toxicity of the combined therapy was observed in patient treated with adjuvant chemotherapeutic agent such as Ciplastin and radiation therapy.(10) Various complications, hearing loss being one of them.

Various studies have been done in various parts worldwide and showed that the prevalence of hearing loss in post chemotherapy treatment is high especially in patients who were treated with platinum based drugs like Cisplatin. It is higher in patients who received concurrent CRT

5. Severity of hearing loss based on chemotherapeutic drug groups used.

Ibrahim Qaddoumi in the year 2012 found out that among 60 patients with retinoblastoma who received Vincristine and Carboplatin,17% had sustained hearing loss.(30) Safraz, K. ahmad, 2004-2006 in Iran, evaluated the Para clinical side effects of taxanes on auditory system in 103 patients. 66 patients were treated with Docetaxel, 37 patients were treated with paclitaxel .Out of 66 patients in the docetaxel group 22 patients developed dizziness, four patients developed tinnitus, and two patients developed hearing loss. Out of 37 patients in the Paclitaxel group, 15 patients developed dizziness, most of the patients in this group had nausea and vomiting.(35)

6. Severity of hearing loss among patients receiving chemotherapy by cumulative dosage

The higher dosage of chemotherapeutic drugs and radiation therapy results in increased ototoxicity, which may cause temporary or permanent damage characterized by hearing loss, tinnitus, and loss of balance.(4) M.H. Whitehorn and M. Sibanda in Cape Town South Africa 2014, the study on high prevalence of Cisplatin ototoxicity, out of 377 patients 55.1% developed cisplatin- induced ototoxicity while receiving high-dose (≥60 mg/m2) on Cisplatin treatment. Higher cumulative cisplatin dosages were associated with development of significant hearing loss (p=0.027). The odds of developing cisplatin-induced hearing loss were elevated for patients with head and neck tumours and lymphoma (p=0.0465 and p=0.0563, respectively) and were significantly lower for those with reproductive cancers (p=0.0371).(36)

A study done by Pan et al (2005) with 35 patients , of which 31 of patients were treated by using a median dose of 47.4 Gy (Range, 14.1-68.8) on the ipslateral inner ear and 4.2 Gy (range, 0.5-31.3 Gy) on the contra lateral inner ear, hearing loss was related to the radiation dose received by the inner ear (loss of 21dB was observed in ears receiving >/=45 Gy) and was most appreciable in the higher frequencies (>=2000 Hz) After 58months of follow up ,Bokomeyer et al in1998, found out that among patients treated with Cisplatin 58%had tinitus18%had hearing loss and 23% had both symptoms and 81% had bilateral symptoms.(38) However, higher cumulative doses of cisplatin and carboplatin were associated with increased hearing loss, more over there were no statistical significance difference between carboplatin and cisplatin.(39)

Sarafraz, Ahmad et al did a study on Paraclinical evaluation of side-effects of Taxanes on auditory system and found out that out of 101 cases who used docetaxel and Paclitaxel 9 cases(8.4%) had tympanic membrane perforation (chronic otitis media. ,4patients reported tinnitus at the end of treatment, out of these 4cases 3 cases were treated with docetaxel ,and out of these 3, 2 patients had hearing loss at frequencies of 4KHZ-8KHZ.(35)

1.4 PROBLEM STATEMENT

Patients with cancer receiving chemotherapy with or without radiation therapy develop various complications, hearing loss being one of them. This has detrimental effects on social economic aspects of an individual leading to reduced quality of life in patients who survived cancer by chemotherapy or chemo radiation therapy. Though these patients count themselves lucky to have survived cancer and other complications of treatment in the course, but life cannot be easy and quality of life cannot be improved in the presence of communication barriers. Head and neck malignancies have been increasing currently, and the treatment of choice is chemo radiation therapy with hearing loss being one of its potential side effects.

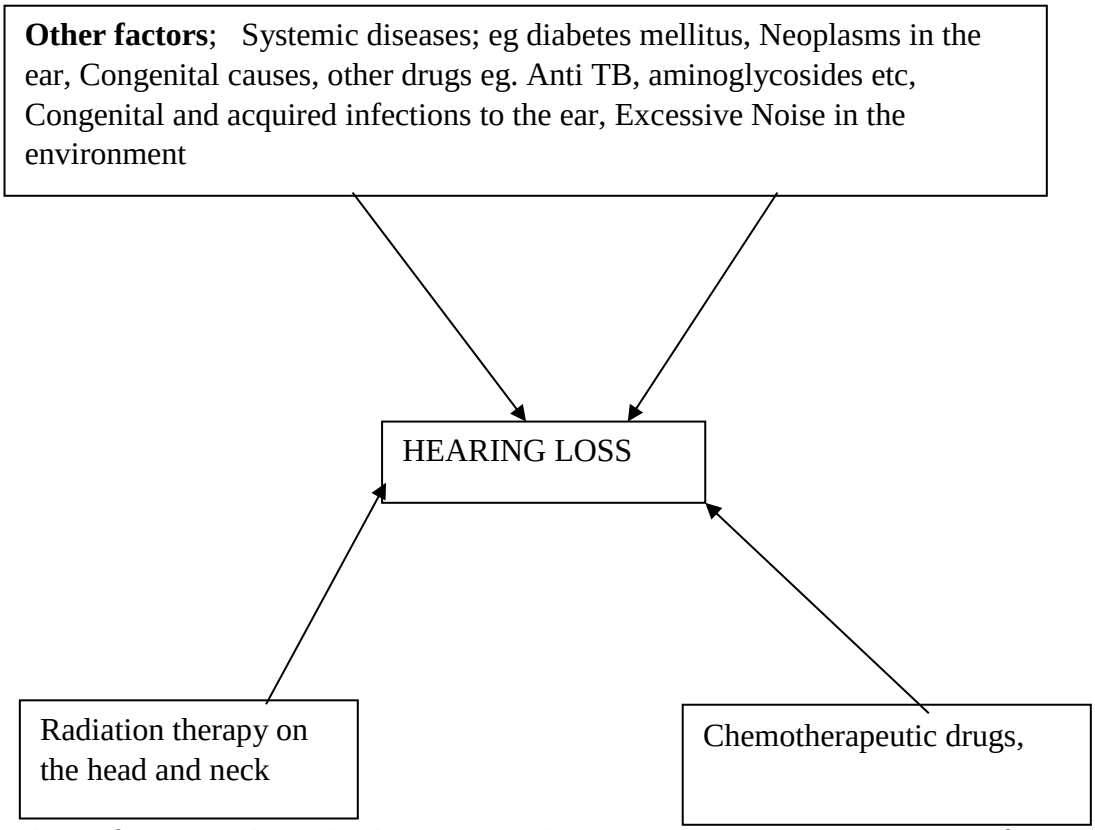
So far, no single study has been published in Tanzania on assessment of the prevalence of hearing loss in patients receiving chemotherapy with or without radiation therapy.

1.5 RATIONALE

It is very important to understand the magnitude of otological complications especially hearing loss in patients with cancer who are treated with chemotherapy with or without concurrent radiotherapy on the head and neck areas so that immediate measures to detect the complications can be taken and the patient to be helped as soon as possible to reduce the burden and improve quality of life.

This study was for partial fulfillment of masters of medicine degree in Otorhinolaryngology at Muhimbili University of Health and Allied Sciences.

1.6 CONCEPTUAL FRAMEWORK



The above factors, independently or in combination can cause hearing loss. If an individual is exposed to one of the factors in the presence of another factor, the effects of that factor on hearing loss can be exacerbated.(5) With other factors ruled out/controlled most studies have shown that chemotherapeutic drugs especially platinum based compounds and radiation therapy to the head and neck areas have a great potential to cause hearing loss.(40,41)

1.7 RESEARCH QUESTION

1. What are the effects of chemotherapy with or without radiation therapy on hearing among head and neck cancer patients?

1.8.0 OBJECTIVES

1.8.1 Broad objective

To determine prevalence and patterns of hearing loss among head and neck cancer patients receiving chemotherapy with or without radiation therapy at ORCI.

1.8.2 Specific objectives

1. To determine the prevalence of hearing loss by age and sex among patients receiving chemotherapy with or without radiotherapy.
2. To determine types of hearing loss by tumor site
3. To determine types of hearing loss in patients receiving chemotherapy with or without radiotherapy by treatment modality
4. To determine severity of hearing loss among patients receiving chemotherapy with or without radiotherapy by treatment modality
5. To determine severity of hearing loss based on type of chemotherapeutic drug groups used.
6. To determine severity of hearing loss among patients receiving chemotherapy by cumulative dosage.

2.0 METHODOLOGY

2.1 Study design

This was a Descriptive, Cross sectional hospital based Study.

2.2 Study Area

The study was conducted at Ocean Road Cancer Institute, Dar es Salaam Tanzania. The center provides cancer treatments in terms of chemotherapy, radiotherapy or concurrent chemo radiation therapy to all cancer patients countrywide. About 259 new cases of head and neck cancer cases are received per year according to ORCI cancer data 2006-2014.Over 70% of these patients are treated with chemotherapy or concurrent chemo radiation therapy.

2.3 Study Duration

The study was conducted for the period of 6months (June to December 2017)

2.4 Study Population

The study included head and neck cancer patients receiving chemotherapy with or without radiation therapy at ORCI who had been on treatment for the period of six weeks.

2.5 Inclusion Criteria

Patients with head and neck cancers with no history of pre existing hearing loss due to other causes and willing to participate.

2.6 Exclusion Criteria

Deaf Patients, Unconscious patients, hand caped patients and those who did not consent.

2.7 Sampling Method

Convenience sampling technique was used, in which selection was based on most available sample.

2.8 Sample Size Calculation

The sample size, n was calculated using Fishers formula for sample size calculation as follows;

$$n = \frac{z^2 p (1-p)}{E^2}$$

z = 95% confidence interval, which is 1.96

E = Margin of error (For this case I considered 5%)

p = Prevalence of hearing loss, In this case I chose (90%). from A study done by Landier, which reported that the prevalence of ototoxicity (hearing loss being one of the ototoxic effect) in patients who have received potentially ototoxic therapy to range from 4% to 90% depending on factors such as age of the patient, medications used, cumulative dose, and administration techniques.(27) Therefore, from the above formula the minimum required sample size was 138 patients.

2.9.0 Data Collection and tools

Patients with head and neck cancer and meeting criteria for the study were seen at ORCI at the chemotherapy unit. Explanation was given about the study, and patients were asked to participate. Those who agreed to participate in the study, were asked to sign the consent form, for those who were not be able consent, consent was sought from their care takers. Very weak patients were stabilized before examination.

Instruments.

Clean gloves
Otoscope with various sizes of aural specula
Cotton wool, spirit and boric acid ear drop
Cerumen hook, hydrogen peroxide ear drop
Cotton wool applicator
Tuning fork (512 HZ)
Pure tone audiometer (Amplivox 270)

2.9.1 Otoscopic examination

This was done prior to tuning fork test and pure tone audiometry test at the units or from the wards for admitted patients. Wax impaction or foreign bodies were removed if found during otoscopic examination, pus if found was cleaned by ear mopping, the patient was treated with appropriate medications and was given seven days to recover before tuning fork and PTA tests. Other otological manifestations were addressed if coincidently found.

2.9.2 Pure tone audiometry test

PTA was done in a clean and dry ear in a quiet room, using an audiometer {Amplivox 270}. Both air conduction and bone conduction were performed. Air conduction was done by placing earphone on each ear, bone conduction was obtained by using bone vibrator placed on the skin over mastoid process of the ear to be tested. Hearing was tested at frequencies range from 250HZ to 8000HZ. PTA was done by audiologist From MNH and the researcher with the help of a trained research assistant. Hearing was graded as per WHO criteria where by 0-25 dB was regarded as normal hearing,26-40dB mild hearing loss,41-60dB moderate hearing loss,61-80dBsevere hearing loss and >80dB profound hearing loss.

Data collection was done by using special and welldesigned data collection form. History of hearing loss before the patient started chemotherapy was asked. The form contained in formations on demographic characteristics, site of the tumor and treatment modality. The type of drugs/drug groups used, dosage and duration were inquired from the patient and confirmed from the patient's medical record file. The type and severity of HL were assessed in each ear and stipulated on the audiogram charts. Patients found with hearing loss were counselled accordingly and referred to MNH ENT department for appropriate management according to the type and severity of HL.

2.10 Data Handling and Analysis

Quality was checked for inconsistence soon after data was collected to ensure that incomplete and missing data were identified and corrected immediately. All information which were collected, including questionnaires were confidentially stored in locked filing cabinets and computer data was stored on secure, password-protected computers.

Data analysis was done using the Statistical Package for Social Sciences (SPSS) version 20 and consultation from biostatics for its analysis and interpretation. A p-value of less than 0.05 was considered as statistically significant.

2.11 Ethical consideration and Ethical Clearance

We introduced ourselves to individual patient**s** and explained about the study then requested the patient to participate in the study. Patients who gave consent were enrolled in the Study, interview was conducted in a private room. For patients younger than 18 years informed consent was obtained from their parents or guardians. The patient's information was confidential.

The proposal was presented to the department of Otorhinolaryngology, Muhimbili University of Health and Allied Sciences. Ethical review and clearance was thereafter obtained from the Research and Publication Committee of the Muhimbili University of Health and Allied Sciences. Permission to conduct the study was sought from ORCI Administration.

2.12 Study Limitations and Mitigation

In this study, I assessed Hearing loss in patients using chemotherapy with or without radiation therapy, These Patients needed to be followed up for the whole periods of treatment and at least 2years post treatment so that cumulative effects of chemotherapeutic drugs after treatment can be assessed. But it was not possible due to time limitations on my study.

Due to time factor, Preexisting hearing loss was ruled out clinically (ie from patient's history) therefore some forms of preexisting hearing loss might have been missed.

3.0 RESULTS

3.1 Table 1. Demographic characteristics of the study population

Sex	Age in years				Total
	16-35	36-55	55-75	>75	
Male	8(11.8%)	30(44.1%)	26(38.2%)	4(5.9%)	68(49.3%)
Female	14(20.0%)	36(51.4%)	19(27.1%)	1(1.4%)	70(50.7%)
Total	22(16.0%)	66(47.8%)	45(32.6%)	5(3.6%)	138(100%)

Out of 138 patients in the study population70(50.7%) were females and 68(49.3%) were males. Majority of cases were in the age group of 36yrs-55years (47.8%) while minority were in the age group of >75years (3.6%)

3.2.0 Table 2: Prevalence of hearing loss among patients receiving chemotherapy with or without radiation therapy by age.

Age (in years)	Hearing status		TOTAL
	HLPRESENT	NO HL	
16 – 35	10 (45.5%)	12 (54.5%)	22 (16.0%)
36 – 55	48 (72.7%)	18 (27.3%)	66 (47.8%)
56 -75	36 (80.0%)	9 (20.0%)	45 (32.6%)
>75	4 (80.0%)	1 (20.0%)	5 (3.6%)
TOTAL	98 (71.0%)	40 (29.0%)	138 (100.0%)

Patients in the age groups of 56-75 years and >75years had higher proportions of hearing loss (80%) while the age group of 15years -35 years had lower proportion of patients with hearing loss (45.5%). These findings are statistically significant. (P. value = 0.029)

3.2.1 Table3. Prevalence of hearing loss among patients receiving chemotherapy with or without radiation therapy by sex

SEX	Hearing status		Total
	HL Present	No HL	
Males	52 (76.5%)	16 (23.5%)	68 (49.3%)
Females	46 (65.7%)	24 (34.3%)	70 (50.7%)
Total	98 (71.0%)	40 (29.0%)	138 (100.0%)

Males had higher prevalence of hearing loss (76.5%) compared to females (65.7%) This difference was statistically not significant. (P. value =0.164)

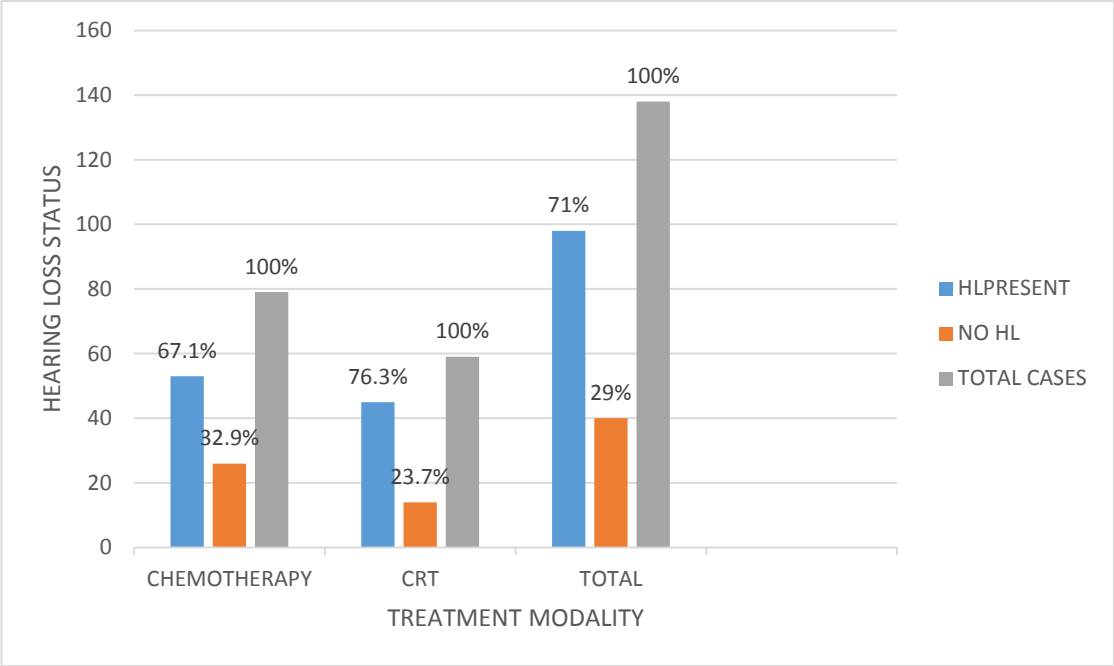
3.3 Table 4. Types of hearing loss among patients receiving chemotherapy with or without radiation therapy by tumor site

Tumor site	Type of hearing loss			Total
	Conductive	Sensorineural	Mixed	
Oral cavity	0(0.0%)	11(100.0%)	0(0.0%)	11(11.2%)
Nasopharynx	3(14.0%)	17(81.0%)	1(5.0%)	21(21.4%)
Oropharynx	0(0.0%)	20(100.0%)	(0.0%)	20(20.4%)
Hypopharynx	0(0.0%)	5(100.0%)	0(0.0%)	5(5.1%)
Larynx	0(0.0%)	15(100.0%)	0(0.0%)	15(15.3%)
Sino nasal	0(0.0%)	14(93.3%)	1(6.7%)	15(15.3%)
Salivary gland	0(0.0%)	11(100.0%)	0(0.0%)	11(11.2%)
Total	3(3.1%)	93(94.9%)	2(2.0%)	98 (100%)

All patients(100%) with tumors of the oral cavity, oralpharynx, hypopharynx, larynx and salivary glands had sensory neural hearing loss, contrary to nasopharyngeal tumor in which 17(81.0%) patients had sensory neural hearing loss and 3(14.0%) had conductive hearing loss These findings are not statistically significant.(P. value=0.23)

3.4. Hearing loss by treatment modality

3.4.1. Figure 1.Hearing loss status among patients receiving chemotherapy with or without radiation therapy by treatment modality



45(76.3%) patients who received chemoradiation therapy had hearing loss compaired to53 (67.1%) patients who received chemotherapy alone.

3.4 Table 5. Types hearing loss among patients receiving chemotherapy with or without radiation therapy by treatment modality

Treatment modality	Types of hearing loss			Total
	CHL	SNHL	MHL	
Chemotherapy	(00.0%)	53(100%)	0(0.0%)	53(54.1%)
Chemoradiation	3(6.7%)	40(88.9%)	2(4.4%)	45(45.9%)
	3(3.1%)	93(94.9%)	2(2.0%)	98(100%)

Sensory neural hearing loss was observed in 53(100%) patients who received chemotherapy alone and 40(88.9%) patients who used chemoradiation therapy. Conductive and mixed HL were observed in patients who received chemoradiation therapy (6.7%, 4.4%) respectively but not in patients who received chemotherapy alone (0.0%) The findings are statistically significant (p.value =0.045)

3.5. Severity of hearing loss among patients receiving chemotherapy with or without radiation therapy by treatment modality.

3.5 .1Table 6. Severity of hearing loss by treatment modality

Treatment modality	Severity of hearing loss				Total
	Mild	moderate	Severe	Profound	
Chemotherapy	25(47.2%)	16(30.2%)	7(13.2%)	5(9.4%)	53(54.1%)
Chemo R.T	15(33.3%)	19(42.2%)	7(15.6%)	4(8.9%)	45(45.9%)
Total	40(40.8%)	35(35.7%)	14(14.3%)	9(9.2%)	98(100%)

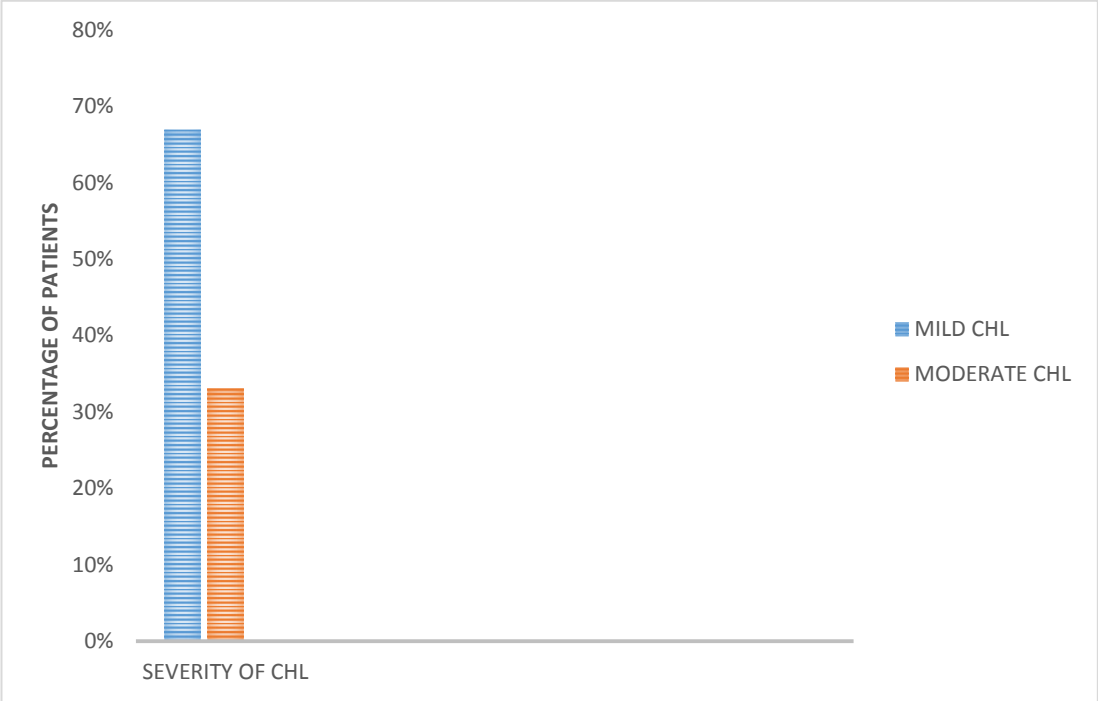
More patients who received chemotherapy alone had mild hearing loss (47.2%) than those who received chemoradiation therapy (33.3%). But patients with moderate hearing loss were seen more with Chemoradiation therapy (42.2%) than chemotherapy alone (30.2%) The difference is not statistically significant (P.value=0.526)

3.5.2 Table 7 Severity of sensory neural hearing loss among patients receiving chemotherapy with or without radiation therapy by treatment modality.

Treatment modality	Severity of hearing loss				Total
	Mild	moderate	Severe	Profound	
Chemotherapy	25(47.2%)	16(30.2%)	7(13.2%)	5(9.4%)	53(57.0%)
Chemo R.T	14(35.0%)	16(40.0%)	6(15.0%)	4(10.0%)	40(43.0%)
Total	39(41.9%)	32(34.4%)	13(14.0%)	9(9.7%)	93(100%)

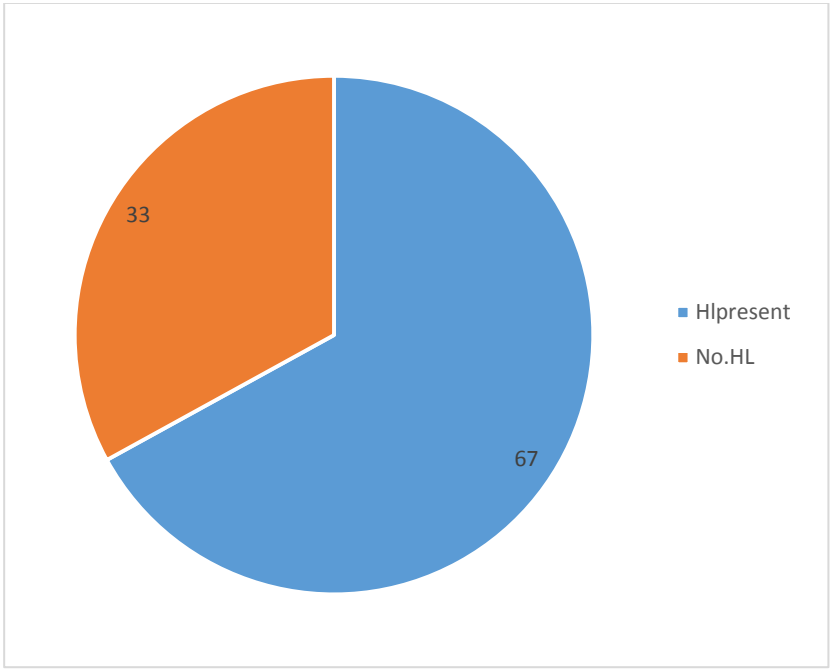
More patients who received chemotherapy alone had mild sensorineural hearing loss (47.2%) than those who received chemoradiation therapy (35.0%). But patients with moderate sensorineural hearing loss were seen more with Chemoradiation therapy (40.0%) than chemotherapy alone (30.2%) The difference is not statistically significant (P.value=0.682)

3.5.3 Figure 2.Severity of Conductive hearing loss in patients who received Chemoradiation therapy



Mild conductive hearing loss was higher in patients who received chemoradiation therapy (67%) than moderate hearing loss (33%).

3.6 Figure 3. Hearing status in patients who received Chemotherapy alone



Out of 79 patients who used chemotherapy alone, 53(67%) patients had hearing loss

3.7 Table 8. Severity of hearing loss among patients who received chemotherapy alone by drug groups

Drug groups	Severity of hearing loss (SNHL)				Total
	Mild	Moderate	Severe	Profound	
Platinum alone	12(52.2%)	6(26.1%)	4(17.4%)	1(4.3%)	23(43.4%)
Taxanes alone	1(100.0%)	0 (0.0%)	0(0.0%)	0 (0.0%)	1 (1.9%)
Platinum+taxenes	11(41.0%)	10 (37.0%)	2(7.0%)	4(15.0%)	27 (50.9%)
Others	1 (50.0%)	0 (0.0%)	1 (50.0%)	0 (0.0%)	2(3.8%)
Total	25(47.2%)	16 (30.2%)	7(13.2%)	5(9.4%)	53(100.0%)

Mild hearing loss was slightly higher (52.2%) in patients who received platinum compounds alone as compared to those who received combined platinum + taxanes (41.0%), while profound hearing loss was higher in patients who received combined platinum + taxanes (15.0%) than in those who received platinum compounds alone (4.3%). These findings were not statistically significant (P. value =0.603)

3.8 Table 9. Severity of hearing loss among patients who received chemotherapy alone by Cumulative Dosage of the platinum compounds (cisplatin)

Cumulative cisplatin dosage(mg/m^2)	Severity of Hearing loss (SNHL)				Total
	Mild HL	Moderate HL	Severe HL	Profound HL	
(115_195)mg/m^2	5 (55.6%)	3 (33.3%)	1 (11.1%)	0 (0.0%)	9(34.0%)
(196-276)mg/m^2	6 (50.0%)	5 (41.7%)	1(8.3%)	0 (0.0%)	12(22.6%)
(277-357)mg/m^2	6(37.5%)	5(31.2%)	3 (18.8%)	2 (12.5%)	16(11.3%)
(439-519)mg/m^2	0 (0.0%)	0 (0.0%)	0(0.0%)	3(100.0%**)**	3 (7.5%)
Total	17 (42.5%)	13(32.5%)	5 (12.5%)	5(12.5%)	40 (100%)

At cumulative Cisplatin dosage of (439-519) mg/m^2 (100.0 %%) of patients had profound hearing loss. None had profound hearing loss at Cumulative dosage of (115-195) mg/m^2. 0(0.0%).These findings were statistically significant. (P. value =0.003)

3.9 Table 10. Severity of hearing loss among patients who received chemotherapy alone by cumulative dosage of taxanes (docetaxel)

Cumulative docetaxel dosage (Mg/m^2)	Severity of hearing loss (SNHL)				Total
	Mild	Moderate	Severe	Profound	
(191-270)mg/m^2	3(100.0%)	0(0.0%)	0 (0.0%)	0(0.0%)	3(15.0%)
(271-350)mg/m^2	4(26.7%)	7(46.7%)	2(13.3%)	2(13.3%)	15(75.0%)
(351-430)mg/m^2	0 (0.0%)	0(0.0%)	0(0.0%)	2(100%)	2(10.0%)
Total	7(35.0%)	7(35.0%)	2(10.0%)	4(20.0%)	20(100.0%)

Mild hearing loss was observed more at cumulative docetaxel dosage of (191-270) mg/m^2 (100.0%) but not at (351-430) mg/m^2 (0.0%) while profound hearing loss was observed at cumulative dosage of (351-430) mg/m^2 (100.0%) but not at (191-270) mg/m^2 (0.0%). These findings were statistically significant. (P. value=0.021)

4.0 DISCUSSION

Hearing loss is a global burden with tremendous effects on quality of life. Having multifactorial causes, its prevalence has been significantly increasing and might increase even more in the future. 5.3% of the global population have hearing loss with 9% residing in Sub sahara Africa (WHO global estimates 2012.(1)

This study aimed at determining the prevalence of hearing loss as a result of treatment with chemotherapy or combined chemo radiation therapy in patients with head and neck cancer. Of 138 patients assessed, 98(71%) had hearing loss which was bilateral (except two patients who had unilateral hearing loss) and was observed at both speech and high frequencies. Gender had no statistical effect on hearing loss but advanced age had statistically significant increase in risk of developing hearing loss. Several studies have been conducted and showed varying results, this could be due to variations in methods and classification systems being used in various studies. Eloenoor et al in America (1999-2004) on long term Hearing Loss after chemo radiation in patients with head and neck cancer, found out that the prevalence of hearing loss was72% at short term follow up and 75% at long term follow up.(42) Contrary to Eloenoor's findings, Elien Medeiros in Brazil assessed hearing loss in children and adolescents who had undergone cancer treatment and found the prevalence to be (42.5%)using ASHA system and (40.4%) using PGOT system, however, there was a good concordance between the two methods of classifications indicating that cancer treatments have effects on hearing.(28) Rybak et al found out that the prevalence of hearing loss in patients aged 8years to 23years after treatment with chemotherapy was(61%) with majority of the patients having hearing loss at high frequencies.(14) These findings were different from my findings where patients had hearing loss at both speech and high frequencies probably due to variations in treatment modalities used, tumor stage and drug dosage. More studies are needed in East, central and Africa at large specifically to assess hearing loss in patients using chemotherapy since they seem to be scarce, with many studies focusing on radiation therapy.

Site of the tumor on the head and neck area can have some influence on the type of hearing loss in cancer patients depending on the tumor proximity to the ear and type of treatment received either chemotherapy alone or chemoradiation therapy, In this

study, among 98 patients with hearing loss, 3 patients had bilateral conductive hearing loss and all of them had nasopharyngeal carcinoma. Two patients among patients with hearing loss in my study had mixed hearing loss among these two patients, one had sinonasal cancer and had unilateral mixed hearing loss, the other one patient had nasopharyngeal carcinoma and had bilateral mixed hearing loss. Since these patients had no hearing loss before starting treatment and owing to the close proximity of the nasopharynx and sinonasal area to the ear these findings could have been attributed by the physical effect of radiation on the external and middle ear producing conductive hearing loss and chemotherapy effect on the inner ear producing sensory neural hearing loss at the same time. However tumor site did not have statistical significant relation to the type of hearing loss(Value =0.23).Wang et al on his study on hearing loss in patients with advanced nasopharyngeal carcinoma who received cisplatin followed by radiation therapy found out that there was increased incident of sensory neural hearing loss, this was different from my findings since the conductive and mixed picture of hearing loss was not seen in that study.(31)

Treatment modality in head and neck cancer can have various outcomes on types and severity of hearing loss. This depends on the site of the tumor, stage and chemotherapy/radiation dose given and duration of exposure. Chemotherapy poses systemic effects having cumulative effects on the cochlear hair cells. on the other hand, radiation therapy causes local effects including physical and cellular changes on the external, middle, and inner ear structures. Radiation therapy in tumors of the nasopharynx, Sino nasal area, salivary glands especially the parotid area, and base of the skull have increased risk of hearing loss since the likely hood of involving the temporal bone during radiation is high. Jereckzeck fos, Barbara A et al, explained the type of damage, etiology and natural history of ototoxicity in the study on Radiotherapy-induced ear toxicity.(32) In this study 98 patients had hearing loss and it was bilateral with equal severity in both sides, among these 53(54.1%) patients were treated with chemotherapy alone and all of them (100%) developed sensory neural hearing loss. 45(45.95%) were treated with combined chemoradiation therapy. Of these patients, 40(88.9%) developed sensory neural hearing loss, 3(6.7%) patients developed conductive hearing loss and 2(4.4%) patients developed mixed hearing loss.

The latter two findings were observed in patients with nasopharyngeal and Sino nasal tumors, thus their relationship to the tumor site and type of treatment modality received and their absence in patients who used chemotherapy alone explains their relationship to the effects of radiation on the ear. The association was statistically significant (P.value=0.045). The difference in severity of hearing loss between patients who received chemotherapy alone and those who used chemoradiation therapy was not statistically significant (p.value =0.526). Hichkok in his study on Relative Contributions of Radiation and Cisplatin-Based Chemotherapy to Sensorineural Hearing Loss in Head-and-Neck Cancer Patient observed that treatment with chemotherapy alone can independently cause sensory neural hearing loss.(43) These findings were similar to my findings since I also observed that all patients who used chemotherapy alone developed sensory neural hearing loss. Chen et al observed that the risk of developing sensory neural hearing loss increased significantly among patients who received $\leq$48 Gy, suggesting that there could be a threshold in cochlear radiation dose–response in the setting of combined modality therapy.(44) These findings are different from my study where sensory neural hearing loss was observed more in patients who received cheomotherapy alone than in the one who received chemoradiation therapy, also my study did not focus on radiation dosage it rather focused on chemotherapy dosage alone.

Use of combined drug groups seemed to be associated with increased severity of hearing loss than when a single drug group was used. Among 53, patients with hearing loss who received chemotherapy alone, 23 used platinum compounds alone and 4.3% of these patients had profound hearing loss, 27 patients used combined Platinum +Taxanes and 15% of these had profound hearing loss. Mild hearing loss was seen more in patients who used a single drug group eg. taxanes, and others (5FU, Vincristine, etc.). However there was no statistical significance in this difference. P. value =0.603. Susan M. Fleming et al in study on Ototoxicity Associated with Cis-Platinum in Three Chemotherapy Multi-Drug Regimens, found out that the ototoxity of cis platinum was increased in combined drug regimen and proposed the presence of synergistic effects. The study also observed that though high frequencies were affected

but 2000Hz was most affected.(45) These findings are not far from my study since the patients had hearing loss at both speech and high frequencies.

Severity of hearing loss in this study was seen to be influenced by increase in cumulative total drug dosage. In the platinum compound group severity of hearing loss in patients who received Cisplatin was assessed, the cumulative total dosage of cisplatin ranged from 115mg/m2 to 500mg/m^2 At cumulative total dosage of (439-519)mg/m2 (high dose),(100%) of patients had profound hearing loss. None had profound hearing loss at cumulative dosage of (115-195) mg/m2. These findings were statistically significant. P. value =0.003. In the Taxane group, severity of hearing loss in patients who received docetaxel was also assessed. The cumulative total dosage of Docetaxel ranged from 190mg/m^2 to 425mg/^{2}m. Mild hearing loss was observed more at cumulative dosage of (191-270)mg/m^2 (100%) but not at (351-430)mg/m^2 (0.0%) while profound hearing loss was observed at cumulative dosage of (351-430)mg/m^2 (100%) but not at (191-270)mg/m^2(0.0). These findings were statistically significant. (P. value=0.021), however further studies are required to assess the effect of each single drug since the two representative drugs were used in combination with other drugs. M.H. White horn and Sibanda et al in Cape Town South Africa 2014, the study on high prevalence of Cisplatin ototoxicity, found the prevalence to be 55.1% in 377 patients who used high-dose (≥60 mg/m2) of Cisplatin, and that higher cumulative cisplatin dosages were associated with development of significant hearing loss (p=0.027).

The odds of developing cisplatin-induced hearing loss were elevated for patients with head and neck tumors and lymphoma (p=0.0465 and p=0.0563, respectively) and were significantly lower for those with reproductive cancers (p=0.0371)(36).In this study however the effect of cisplatin on hearing loss in tumors other than head and neck tumors was not studied. The Study on Para clinical evaluation of side-effects of Taxanes on auditory system by Sarafraz, Ahmad et al found out that out of 101 cases who used docetaxel and Paclitaxel,4patients reported tinnitus at the end of treatment, out of these 4cases 3 cases were treated with docetaxel ,and out of these 3 ,2(66.7%) patients had hearing loss at frequencies of 4KHZ-8KHZ(35). In this study however the

findings were different since hearing loss in patients who received Docetaxel was found at low and high frequencies and the prevalence was higher.

5.0 CONCLUSION

Chemotherapy with or without radiotherapy is the main stay in treatment of most malignancies including head and neck cancers, however its ototoxic effect especially hearing loss needs to be checked in order to prevent permanent disability that can occur post treatment.

Audiological follow up in cancer patients before, during and after treatment is the main stay for earlier detection of hearing loss and can help to guide the dosage to be delivered according to the patient's condition,(where necessary, a more toxic drug can be replaced by an effective less toxic one) and earlier provision of hearing rehabilitation services.

6.0. RECOMMENDATIONS

- Patients should undergo hearing evaluations pre and post chemotherapy/radiotherapy treatments for earlier detection of hearing loss and provision of hearing rehabilitation services
- Patients on chemotherapy/chemoradiation therapy should be provided with prophylaxis eg. Antioxidants to reduce the ototoxic effects especially hearing loss.
- Further studies to be done where patients on chemotherapy will be followed up to determine the time of onset, progression of hearing loss and other cumulative effects of chemotherapy even after treatment

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APPENDICES

APPENDIX I: INFORMED CONSENT FORM

Consent to participate in the study titled patterns and prevalence of hearing loss among patients using chemotherapy with or without radiation therapy at ORCI 2017.

Greetings: I am Dr Proscovia a postgraduate student am doing a research on the above title.

Purpose of the Study: to determine patterns and prevalence of hearing loss among patients using chemotherapy with or without radiation therapy at ORCI 2017.

What participation involves: If you agree to participate in this study, you will be asked questions and examined

Confidentiality: All information collected will be entered into computer with only an identification number; no name included.

Risk: We expect no harm to happen to you during the course of this study.

Rights to withdraw: Taking part in this study is completely voluntary and refusal to participate or withdrawal will not involve penalty or loss of any rights to treatment to which you are entitled. You will be treated and followed up as per the usual treatment protocol at ORCI

Benefits: If you agree to participate in this study, you will be followed-up closely and be assessed on the progress of your hearing status by the investigating doctor. We hope that the obtained information from this study will benefit others.

Who to contact: If you have any other questions regarding this study, feel free to contact me, Dr. Proscovia Mugyabuso. Muhimbili National Hospital, P.O. Box 65000, Tel no.0755303021 Dar es Salaam.

If you have any questions concerning your rights as a participant, you may contact Prof. Said Abood, the Director of Research and Publication MUHAS, P.O. Box 65001, Dar es Salaam. Telephone: 2152489.

Signature

Do you agree to participate? .....
Participant does not agree…….
I, ……..have read the consent form and my questions have been answered and I agree to participate in this study.
Signature of Participant……..
Signature of Investigator…….
Date of signed consent…….

APPENDIX II: INFORMED CONSENT FORM – SWAHILI VERSION

(FOMU YA IDHINI YA KUKUKBALI KUSHIRIKI UTAFITI)

Ruhusa ya Kushiriki Utafiti Kuhusu ushamiri wa upotevu wa usikivu kwa wagonjwa wenye sratani za kichwa au/na shingo wanaotumia dawa za kansa tu au pamoja na mionzi wanaohudhuria ORCI.

Mimi naitwa DrProscovia Mugyabuso, ni mwanafunzi wa shahada ya uzamili kitengo cha pua koo na masikio katika chuo kikuu cha Sayansi na tiba Muhimbili. Ninafanya uchunguzi wa somo tajwa hapo juu.

Dhumuni la utafiti huu: Kuchunguza ushamiri wa usikivu hafifu kwa wagonjwa wanaotumia dawa za kansa tu au pamoja na mionzi wanaohudhuria ORCI.

Ushiriki: Kama unakubali kushiriki kwenye utafiti huu, utaulizwa maswali na utachunguzwa kwa kina katika kliniki yetu.

Usiri: Taarifa zote za uchunguzi zitaingizwa kwenye kompyuta na nambari ya utambulisho; jina halitanukuliwa.

Madhara: Tunategemea kwamba hakuna madhara yoyote yatokanayo na utafiti huu

Haki ya kujitoa kwenye utafiti: Kushiriki kati kutafiti huu ni hiari, na kuto kubali kushiriki au kujitoa hautaadhibiwa au kupoteza haki yako ya matibabu. Utatibiwa na kuendelea kufuatiliwa kama taratibu za hospitali zinavyoelekeza kwa mtu mwenye kansa hapo ORCI.

Faida ya kushiriki kwenye utafiti: Kama utakubali kushiriki kwenye utafiti huu, Faida utakazopata nipamoja na kuonwa na kufuatiliwa kwa ukaribu na daktari anaye fanya utafiti. Tuna tumaini kwamba taarifa zitakazo patikana zitawanufaisha wengine pia.

Kwa mawasiliano zaidi: Kama una maswali au maelezo kuhusu utafiti huu, uwetayari kuwasiliana na mtafiti, Dr. Proscovia Mugyabuso Hospitali yaTaifa Muhimbili, P.O. Box 65000, simu: 0755303021 DSM. Kama una maswali kuhusu haki yako kama mshiriki wasiliana na Prof. Said Abood, Mkurugenzi wa Idara ya utafiti, P.O. Box 65001, DSM. Simu 2152489.

Saini:

Je, umekubali kushiriki? .....
Mshiriki haja kubali kushiriki……
Mimi……. Nimesoma maelezo na kuyaelewa vizuri, na nimekubali kushiriki kwenye utafiti huu.
Sahihi ya Mshiriki……...
Sahihiya
Mtafiti……Tarehe……

APPENDIX III QUESTIONNAIRE-ENGLISH VERSION

PREVALENCE OF HEARING LOSS IN HEAD AND NECK CANCER PATIENTS USING CHEMOTHERAPY WITH OR WITHOUT RADIATION THERAPY AT ORCI

INTERVIEW GUIDE:

Patients Hospital No: …….. Date: ……

Age: …….years Sex: …….

Residence: District ……. Region …….

Telephone no: …….. Body surface area (m^2)

INTRODUCTION

Greetings;

The aim of this interview is to assess hearing loss that might occur in The course of your treatment as one of the side effects of the drugs you are using. The interview will take about 20-25 minutes. I kindly ask for your corporation.

(*screening tool*) Since the beginning of your illness Were you having problems with hearing before starting treatment?.

1. OTOLOGICAL SYMPTOMS, have you suffered from any of this since you started treatment? (Put an x to a positive symptom).

Symptom	Ear	
	Right	Left
Hearing loss		
Ear fullness		
Ear ache		
Ringing		
Others		

2. Site of the tumor? (confirm in Patients file or summary notes)

[a] Oral cavity [e] oropharynx

[b] Hypopharynx [f] Larynx

[c] Nasopharynx [g] Sinonasal

[d] Salivary glands [h]Others

(B) CLINICAL EXAMINATION

OTOSCOPY FINDINGS

External Auditory canal

	Right ear	Left ear
Normal		
Abnormal (mention)		

Tympanic membrane
(Colour)

Color	Right ear	Left ear
Pearl gray		
Red		
White		
Dull		
Bubble sign		
Fluid level		
Others (mention)		

Position

	Right ear	Left ear
Normal		
Bulging		
Retracted		
Perforated		
Others (mention)		

PURE TONE AUDIOMETRY

Type of hearing loss

	Right ear	Left ear
CHL		
SNHL		
MIXED		

Severity of Hearing Loss (WHO 2008)

	Right ear	Left ear
Normal (0-25dB)		
Mild (26-40dB)		
Moderate (41-60dB)		
Severe (61-80dB)		
Profound (>81Db)		

Treatment modality (put an x where appropriate)

Type of treatment	Tick
Chemotherapy	
Combined Chemoradiation therapy	

5. Dosage per each drug (chemotherapy) in mg/m^2

Drug	Total dosage
Cisplatin	
5FU	
Gemcitabine	
Cetuximab	
Capecitabine	
Docetaxel	
Palitaxel	

APPENDIX IV DODOSO … TOLEO LA KISWAHILI

Fomu ya usahili kuhusu ushamiri wa upotevu wa usikivu kwa wagonjwa wenye sratani za kichwa au/na shingo wanaotumia dawa za kansa tu au pamoja na mionzi wanaohudhuria orci

MWONGOZO WA USAHILI:

Numbari ya faili la mgonjwa: …….. Tarehe ……
Umri (miaka) ……. Jinsia: …….
Makazi:(mkoa/wilaya) ……. Dhehebu …….
Nambari ya simu: ……..

UTAMBULISHO

Salaam;

Lengo la usahili huu ni kuangalia upotevu wa usikivu unaoweza kutokea wakati wa matibabu yako kama mojawapo ya madhara ya dawa/mionzi unazotumi. Usahili utachukua takribani dakika 20-25. Ninaomba ushirikiano wako.

1. Tangu uanze kuugua saratani kabla ya kuanza tiba ya saratani umewahi kupata tatizo la kusikia?

2. DALILI KWENYE MASIKIO; Umewahi kuhisi dalili mojawapo kati ya hizi tangu ulipoanza matibabu yako?(weka alama `x' kwa dalili uliyosikia).

Dalili	Sikio	
	Kulia	Kushoto
Kushindwa kusikia		
Uzito sikioni		
Maumivu sikioni		
Kelele sikioni		
Mengine		

3. INDICATION FOR TREATMENT

Semu yenye uvimbe? (Angalia file la mgonjwa au taarifa fupi aliyonayo)

[a] kansa ya kinywa
[b] kansa ya Hypopharynx
[c] kansa ya Nasopharynx
[d] kansa ya tezi mate
[e] Kansa oropharynx
[f] Kansa ya boksi la sauti
[g] kansa ya pua na vishimo vya hewa

4. UCHUNGUZI

MATOKEO YA OTOSCOPY

(a)Mfereji wa nje wasikio

	Right ear	Left ear
Uko kawaida(weka tiki)		
Si kawaida (taja tatizo)		

(b)Ngoma ya sikio
(Ranngi)(weka alama X)

Rngi	Sikio la kulia	Sikio la kushoto
Kawaida		
Nyekundu		
Ina weupe		
Imefifia		
Alam yavipovu		
Alama yaMaji		
Nyingine(mention)		

Nafasi

	s/kulia	S/kushoto
Kawaida		
Imevimba		
Imeingia ndani		

KIPIMO CHAUSIKIVU

Aina ya upotevu wa usikivu (weka alama X)

	S/kulia	S/kushoto
CHL		
SNHL		
MIXED		

Kiwango cha upotevu wa Usikivu (WHO 2008)

	S/kulia	S/kushoto
Kawaida (0-25dB)		
Kidogo (26-40dB)		
Kiasi (41-60dB)		
Kali (61-80dB)		
Umekithiri (>81Db)		

5.Aina ya matibabuy (weka alama X panapohusika)

Matibabu	Tick
Chemotherapy	
Chemotherapy na mionzi	

5. Dozi kwa kaila dawa (chemotherapy)in mg/m^2

Drug	Jumla ya dose
Cisplatin	
5FU	
Gemcitabine	
Cetuximab	
Capecitabine	
Docetaxel	
Palitaxel	