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Prevalence and Pattern of Hearing Loss among Head and Neck Cancer Patients Receiving Chemotherapy with or without Radiation Therapy at Ocean Road Cancer Institute, Tanzania

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Abstract

Background
Head and neck cancers are primarily treated by three main modalities; surgery, radiotherapy and chemotherapy administered alone or in combination. Radiotherapy and chemotherapy may cause complications to patients including hearing loss with various outcomes on types and severity.

Broad objective
To determine the prevalence and pattern of hearing loss among head and neck cancer patients receiving chemotherapy with or without radiation therapy at Ocean Road Cancer Institute, Tanzania.

Methodology
This was a hospital based descriptive cross sectional study which included 138 histopathological confirmed head and neck cancer patients from June to December 2017. Data collected using structured questionnaires included demographic characteristics, site of the tumor, treatment modality, type of chemotherapy groups used, dosage and duration. Pure tone audiometry at a frequency range of 250HZ to 8000HZ using Amplivox 270 audiometer was performed to all patients after otoscopy. Data was analyzed using Statistical Package for Social Science version 20 and a p value of <0.05 was considered to be statistically significant.

Results
Out of 138 patients who were involved in the study, 98(71%) had hearing loss. Among 98 patients who had hearing loss, 53(54.1%) received chemotherapy alone and all had sensorineural hearing loss, the remaining 45(45.9%) patients received concurrent chemoradiation and 40(88.9%) had sensorineural hearing loss. Conductive and mixed hearing loss were observed in 3 (6.7%) and 2 (4.4%) patients who received chemoradiation, respectively (p value = 0.045). The severity of sensorineural hearing loss was higher among patients who received chemoradiation than those who received chemotherapy alone (p value =0.682). Use of a single drug group or combined drug groups had no significant difference in terms of outcomes on severity of hearing loss (p value =0.603) but high cumulative doses of platinum and taxane compounds had significant increase in terms of outcomes on severity of hearing loss. (p value =0.003, 0.021 respectively).

Conclusion and recommendation
Hearing loss following chemotherapy alone or with concurrent chemoradiation therapy is quite prevalent in our settings thus hearing evaluation pre, during and post chemotherapy/radiotherapy is encouraged for earlier detection of hearing loss and establishing prompt intervention.

Key words: *Prevalence, Hearing loss, Chemotherapy, Chemoradiation, Head and neck cancer.*

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Introduction

Hearing loss which is defined as a partial or total loss of ability to hear is a public health problem affecting quality of life, social and economic aspects of the affected individuals thus creating a need for more attention and efforts to address it. There are several causes of hearing loss such as high frequency noise, congenital causes, trauma, ear infections and ototoxic agents (1–3).

Head and neck cancers, a heterogeneous group of primary cancers involving the upper aerodigestive tract, are on the increase worldwide including Tanzania (4). Head and neck cancers are primarily treated by three main modalities; surgery, radiotherapy and chemotherapy administered alone or in combination. Radiotherapy alone is the most common modality of treatment for certain types of head and neck cancers such as nasopharyngeal carcinoma (5). For local regional advanced cancers, concurrent chemoradiation is mainly used (5,6).

Treatment modalities in head and neck cancers can have various outcomes on types and severity of hearing loss. This depends on site of the tumor in proximity to the ear, stage and chemotherapy/radiation dose given and duration of exposure (7). Chemotherapy poses systemic effects and has cumulative effects on the cochlear hair cells.(8,9)On the other hand, radiation therapy causes local effects including physical and cellular changes on the external, middle, and inner ear structures thus patients receiving combination therapy (concurrent chemoradiation) on the head and neck areas may suffer from mixed type of hearing loss(7,10) Some of the chemotherapeutic drugs such as cisplatin, carboplatin and vincristine are ototoxic and patients receiving these drugs may end up with hearing loss that further reduces their quality of life.(9)) 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, medication (s) used, cumulative dose, and administration techniques.(11–14) Radiation therapy in tumors of the nasopharynx, sinonasal area, salivary glands especially the parotid gland and base of the skull have high risk of hearing loss occurrence since the likelihood of involving the temporal bone during irradiation is high (2,7).

It is very important to understand the magnitude of otological complications especially hearing loss in patients with head and neck cancers who are treated with chemotherapy with or without concurrent radiotherapy so that immediate measures to detect the complications can be taken and such patients can be helped on immediate basis so as to reduce the socio-economic burden and improve the quality of life. Such information is lacking in our country

and the aim of this study was to address this existing gap by determining the prevalence and pattern of hearing loss among head and neck cancer patients receiving chemotherapy with or without radiotherapy at Ocean Road Cancer Institute (ORCI).

Methodology

Study design, setting, sampling technique, and participants

This was a hospital based descriptive cross sectional study which included 138 patients with histopathological confirmed head and neck cancers and no pre-existing hearing loss due to other causes as ascertained from history and tuning fork test during clinical examination. Being exposed to other ototoxic drugs during study period was also ascertained through thorough history taking and commonly available ototoxic drugs in our setting such as amikacin, gentamycin, streptomycin and loop diuretics were inquired. Those who were found to use any of them during the study period were excluded. These patients were receiving chemotherapy with or without radiation therapy for a period of not less than six weeks at ORCI. Concurrent recruitment sampling technique was used to obtain the desired sample size for a period of six months, June to December 2017. ORCI is the National Cancer Centre located in Dar es Salaam. It provides treatments in terms of chemotherapy, radiotherapy or concurrent chemoradiation to cancer patients countrywide. About 259 new patients with head and neck cancers are seen per year at ORCI (ORCI cancer data 2006-2014). Over 70% of these patients are treated with chemotherapy or concurrent chemoradiation.

Data collection

Data was collected using pre–tested questionnaire with structured questions designed by authors. History of hearing loss before the patient started chemotherapy was inquired and those with positive history of hearing loss were excluded. The information collected included demographic characteristics, site of the tumor and treatment modalities. The type/group of chemotherapy used, dosage and duration were inquired from patients and confirmed from the patient's medical record file.

Clean gloves, cotton wool, cotton wool applicator, portable otoscope with various sizes of aural specula, spirit and boric acid ear drop, cerumen hook, hydrogen peroxide ear drop (3%), tuning fork (512 HZ) and pure tone audiometer (Amplivox 270) were used for otoscopy and audiometry. Otoscopy was done prior to tuning fork test and pure tone audiometry at the outpatient clinics or in the ward for admitted patients. Impacted wax or foreign bodies

were removed when found during otoscopy. Ear mopping was done when pus was found and appropriate ototopical medications were prescribed for 7 days prior to tuning fork test and pure tone audiometry (PTA). Similarly, other otological conditions encountered were addressed accordingly.

PTA was performed by an audiologist in a clean and dry ear in a quiet room, using an audiometer {Amplivox 270}. Both air and bone conductions were performed. Hearing was tested at a frequency range from 250HZ to 8000HZ. Hearing was graded as per World Health Organization (WHO) grades of hearing impairment as follows: Normal: 0-25 dB, mild: 26-40dB, moderate: 41-60dB, severe: 61-80dB and >80dB profound hearing loss. The type and severity of hearing loss was assessed in each ear and stipulated on the audiogram. Patients found to have hearing loss were counseled and referred for appropriate management according to the type and severity of hearing loss.

Data analysis

Data were analyzed by using Statistical Package for the Social Sciences (SPSS) version 20 as per specific research questions and results were presented in cross tabulations and figures. Relationship between independent and dependent variable was established using Chi-square test. A variable with p value less than 0.05 was considered to be statistically significant.

Ethical considerations

Ethical clearance was obtained from the Senate Research and Publications Committee of the Muhimbili University of Health and Allied Sciences. Permission to conduct the study was sought from ORCI administration. A written informed consent was obtained from all patients and the interview was conducted in a private room. The information obtained was kept confidential. Patients found to have hearing loss were counseled and referred for appropriate management according to the type and severity of hearing loss.

Results

Among 138 patients involved in the study, 68(49.3%) were males and 70 (50.7%) were females. Their age ranged from 16- 89 years with a mean age of 50.78 ± 14.958 years. Most patients were in the age group of 36-55years, 66(47.8%) and few 5(3.6%) were above 75years. In this study 79(57.2%) patients received chemotherapy alone while 59(42.8%) received concurrent chemoradiation.

The prevalence of hearing loss was found to be 98(71%) and was bilateral in most of the patients. The age groups of 56-75 years and >75years had higher proportions of hearing loss, 36(80%) and 4(80%), respectively (p value =0.029) compared to other age groups. Males had higher prevalence of hearing loss 52(76.5%) compared to females 36(65.7%) (p value =0.164) (Table 1).

Table 1: Prevalence of hearing loss among patients receiving chemotherapy with or without radiation therapy by age and sex (N=138)

Age (in years)	Hearing loss		Total	P value
	Present N (%)	Absent N (%)	N (%)	
16 – 35	10 (45.5)	12 (54.5)	22 (16.0)	0.029
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)**	
Sex				
Male	52 (76.5)	16 (23.5)	68 (49.3)	0.164
Female	46 (65.7)	24 (34.3)	70 (50.7)	
Total	**98 (71.0)**	**40 (29.0)**	**138 (100.0)**	

In this study the pattern of hearing loss studied included type according to tumor site and treatment modality, severity of hearing loss according to treatment modality, type and cumulative dosage of the chemotherapeutic drug used. All patients 62 (100%) with cancer of the oral cavity, oropharynx, hypopharynx, larynx and salivary glands had sensorineural hearing loss among patients with nasopharyngeal cancer 17(81.0%) had sensory neural hearing loss and 3(14.0%) had conductive hearing loss (p value=0.23).

Out of 98 patients who had hearing loss, 53(54.1%) received chemotherapy alone and 45(45.9%) received concurrent chemoradiation. Of the 53 patients who received chemotherapy alone all had sensorineural hearing loss while 40(88.9%) out of the 45

patients who received chemoradiation had sensorineural hearing loss, 3 (6.7%) had conductive and 2 (4.4%) had mixed hearing loss (p value =0.045) (Table 2).

Table 2: Types of hearing loss among patients receiving chemotherapy with or without radiation therapy by treatment modality (N=98)

Treatment Modality	Type of Hearing Loss			Total N%	P Value
	CHL N (%)	SNHL N (%)	MHL N (%)		
Chemotherapy	0(0.0)	53(100)	0(0.0)	53(54.1)	0.045
Chemoradiation	3(6.7)	40(88.9)	2(4.4)	45(45.9)	
Total	**3(3.1)**	**93(94.9)**	**2(2.0)**	**98(100)**	

Regarding the severity of sensorineural hearing loss with respect to treatment modality, moderate hearing loss was higher among patients who received chemoradiation than those who received chemotherapy alone (p value =0.682) (Table 3).

Table 3: Severity of sensorineural hearing loss among patients receiving chemotherapy with or without radiation therapy by treatment modality (N=93)

Treatment modality	Severity of sensorineural hearing loss				Total N (%)	P value
	Mild N (%)	Moderate N (%)	Severe N (%)	Profound N (%)		
Chemotherapy	25(47.2)	16(30.2)	7(13.2)	5(9.4)	53(57.0)	0.682
Chemoradiation	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)**	

Platinum compounds such as cisplatin and taxane compounds such as docetaxel are the commonly used drugs in our setting. Profound hearing loss was higher in patients who received combined platinum + taxanes 4 (15.0%) than in those who received platinum compounds alone 1(4.3%) though these findings were not statistically significant (p value =0.603) (Table 4).

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Table 4: Severity of sensorineural hearing loss among patients who received chemotherapy alone by chemotherapy group (N=53)

Drug groups	Severity of sensorineural hearing loss				Total N (%)	P value
	Mild N (%)	Moderate N (%)	Severe N (%)	Profound N (%)		
Platinum alone	12(52.2)	6 (26.1)	4(17.4)	1(4.3)	23 (43.4)	0.603
Taxanes alone	1(100.0)	0 (0.0)	0(0.0)	0 (0.0)	1 (1.9)	
Platinum+taxane	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)**	

At cumulative cisplatin dosage of (439-519) mg/m^2, 3(100.0 %) patients had profound hearing loss while none had profound hearing loss at cumulative dosage of (115-195) mg/m^2. These findings were statistically significant (p value =0.003) (Table 5).

Table 5: Severity of sensorineural hearing loss among patients who received chemotherapy alone by cumulative dosage of the platinum compounds (cisplatin) (N=40)

Cumulative Cisplatin Dosage(mg/m^2)	Severity of sensorineural hearing loss				Total N (%)	P value
	Mild N (%)	Moderate N (%)	Severe N (%)	Profound N (%)		
(115_195)mg/m^2	5 (55.6)	3 (33.3)	1 (11.1)	0 (0.0)	9(34.0)	0.003
(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)**	

All three patients who received docetaxel at cumulative dosage of (191-270) mg/m^2 had mild hearing loss while all two patients, who received docetaxel at cumulative dosage of (351-430) mg/m^2 had profound hearing loss. These findings were statistically significant (p value=0.021) (Table 6).

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Table 6. Severity of sensorineural hearing loss among patients who received chemotherapy alone by cumulative dosage of taxanes (docetaxel) (N=20)

Cumulative docetaxel dosage (Mg/m^2)	Severity of sensorineural hearing loss				Total N (%)	P value
	Mild N (%)	Moderate N (%)	Severe N (%)	Profound N (%)		
(191-270)mg/m^2	3(100.0)	0(0.0)	0 (0.0)	0(0.0)	3(15.0)	0.002
(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)**	

Discussion

The prevalence of hearing loss following chemotherapy alone or with concurrent chemoradiation among patients with head and neck cancer in our setting was high (71%) with majority having bilateral hearing loss observed at both speech and high frequencies. There was a statistically significant increase in the risk of developing hearing loss with age but not sex. The high frequency observed in this study appears to be similar to what has been found elsewhere (15,16) but different from findings from the study which was done in Brazil which was 42.5% (13). This could be due to differences in the study population as our study had a range of young to old age patients while the study in Brazil had children and adolescents only. Variations in methods and classification system used could also account for the dissimilarity. However the high frequency of hearing loss observed in our study is in accordance to what was observed in America (14,17)

In this study, patients with nasopharyngeal and sinonasal malignancies had conductive and mixed hearing loss. Since these patients had no hearing loss before treatment initiation and owing to the close proximity of the nasopharynx and sinonasal areas to the ear, these findings could have been attributed to the physical effect of radiation to the external and middle ear leading to conductive hearing loss and chemotherapy effect to the inner ear leading to sensorineural hearing loss concurrently. However, tumor site did not have any statistically significant relationship to the type of hearing loss. This finding was different with Wang et al study which reported increased incidence of sensorineural hearing loss among

patients with advanced nasopharyngeal carcinoma who received cisplatin followed by radiation therapy (18).

Similar to other studies in literature, sensorineural hearing loss was observed in all patients who received chemotherapy alone (7,19) while all three types of hearing loss were observed in patients who received concurrent chemoradiation and these findings were statistically significant. Conductive and mixed hearing loss were observed in patients with nasopharyngeal and sinonasal malignancies thus their relationship to the tumor site, type of treatment modality received and their absence in patients who received chemotherapy alone explain their relationship to the effects of radiation to the ear. Regarding severity of sensorineural hearing loss with respect to treatment modality, majority of patients who received chemoradiation had moderate hearing loss as compared to those who received chemotherapy alone and vice versa in the profound hearing loss though these findings were not statistically significant. This can be explained by the fact that edema to the neural system caused by irradiation may subside after sometime.

Use of combined drug groups seemed to be associated with increased severity of hearing loss than when a single drug group was used. For example, patients who used platinum compounds alone had lower frequency of profound hearing loss as compared to those who had combined Platinum +Taxane compounds. However, this difference was there was not statistically significant but it is similar to study done in Michigan which found that the ototoxicity of cisplatin was increased in combined drug regimen and proposed the presence of synergistic effects (15).

In this study an increase in cumulative total drug dosage had statistically significant influence in the severity of hearing loss as reported in other studies(17,20) Among patients who received cisplatin none had profound hearing loss at cumulative dosage of (115-195) mg/m2 while at cumulative total dosage of (439-519) mg/m2 (high dose), all had profound hearing loss. This was similarly observed in the Taxanes group whereby all patients who received cumulative dosage of (191-270) mg/m^2 and (351-430) mg/m^2 had mild and profound hearing loss, respectively. 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.

Conclusion and recommendations

Chemotherapy with or without radiotherapy remains to be the main stay in treatment of head and neck cancers. Hearing low was found to be quite prevalent in our setting and therefore

there is urgent need to screen patients for hearing loss pre, intra and post chemoradiation or chemotherapy. Strategies directed at ensuring otological safety in patients with head and neck cancers will have positive impact in improving the quality of life of such patients.

Study limitation

Preexisting hearing loss was ruled out clinically from patients' history, therefore some forms of preexisting hearing loss might have been missed and this could affect the prevalence of hearing loss that has been observed in this study.

Competing interests

The authors declare no competing interests.

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Authors' contributions

AAK contributed to study design, analysis and prepared this manuscript, PCM designed the study, collected data and performed data analysis and comments to the manuscript draft, ZSA contributed to study design, analysis and comments to the manuscript drafts. JCK and ER supervised and contributed to study design, data analysis and reviewed this manuscript. All authors have read and approved the final manuscript.

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Abbreviations

CRT/XRT	Chemo Radiation therapy
CHL	Conductive hearing loss
dB	Decibels
SNHL	Sensorineural Hearing Loss

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SPSS	Statistical Package for Social Sciences
MHL	Mixed Hearing Loss
MNH	Muhimbili National Hospital
MoHCDGEC	Ministry of Health Community Development, Gender, Elderly and Children
MUHAS	Muhimbili University of Health and allied sciences
ORCI	Ocean Road Cancer Institute
ORL	Otorhinolaryngology
PTA	Pure Tone Audiometry

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