The Efficacy of Strategies Used to Minimize and Prevent Cisplatin Ototoxicity in Patients

By

Student: Zenzo Stanford Chakara

Student Number: CHKZEN001

SUBMITTED TO THE UNIVERSITY OF CAPE TOWN

In fulfilment of the requirements for the degree

MSc in Audiology

Faculty of Health Sciences

UNIVERSITY OF CAPE TOWN

Date of Submission: 19 February 2018

Supervisor: A/Professor Lebogang Ramma: Division of Communication Sciences & Disorders, Department of Health and Rehabilitation Sciences, UCT

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Abstract

Aims and objectives.

This study aimed to evaluate the efficacy of different treatment modifications used to prevent or minimise hearing loss during Cisplatin-based chemotherapy as part of patient management at Groote Schuur Hospital. The study also sought to compare different ototoxicity grading criteria; namely the National Cancer Institute Common Terminology Criteria for Adverse Events Version 4 (CTCAE v4) and TUNE criteria, with respect to early identification of changes in the patient's hearing thresholds following treatment with ototoxic drugs as well as ability to guide recommendations for aural rehabilitation including hearing amplification.

Background

Non-communicable diseases (NCD) (including cancer, diabetes, cardiovascular and chronic respiratory diseases) are responsible for an estimated 36 million deaths annually across the world. Approximately 80 % of these deaths occur in developing countries. Cancer, the NCD of interest in this study, causes an estimated 8.2 million deaths per year, globally and about 70 % of these occur in developing countries. In South Africa, cancer is estimated to cause approximately 40 000 deaths per annum, which is more than the number of deaths caused by a combination of HIV/AIDS, TB and malaria every year. Cisplatin is the most common and effective anti-cancer drug for most types of cancers. However, it is also associated with severe adverse effects, including hearing loss. Cisplatin-induced hearing loss is usually bilateral, high-frequency sensorineural hearing loss and is permanent.

Cisplatin-induced hearing loss can lead to communication difficulties, lack of participation, loss of employment and social isolation. This decreases patients' quality of life. Prevention of ototoxicity relies on serial audiologic monitoring to detect any significant change in patients' hearing thresholds that may be resulting from chemotherapy treatment. When a deterioration in the patient's hearing thresholds is detected, treating physician(s) can decide on whether to modify the patient's treatment to prevent further deterioration of hearing or not. Some of the common treatment modifications used by physicians include; reducing the drug dose administered to the patient, changing from Cisplatin to a less ototoxic drug such as Carboplatin or keeping a patient on Cisplatin only regimen (no treatment modification). However, there is

currently lack of research evidence that document the effectiveness of these treatment modifications with respect to preservation of the patient's hearing thresholds. Also, given that there are several ototoxicity grading scales available that can be used to grade severity of ototoxicity-induced hearing loss, there is currently a lack of uniformity regarding communication of the severity of hearing loss across different professionals. There is a need to identify or develop an ototoxicity grading criterion which can be adopted by different professionals to communicate results during ototoxicity monitoring of patients.

Research design

This study employed a descriptive, quantitative retrospective cohort design. Medical folders of patients who underwent cisplatin chemotherapy treatment and had their hearing thresholds monitored at Groote Schuur Hospital during from 2011 up to 2016 were reviewed.

Methods

A non-probability, convenience sampling method was used to select medical folders that underwent review. Data which were extracted from the patients' medical folders includes demographic information (for example age and sex,), chemotherapy treatment information including type and dose of treatment; and audiological information including baseline, check-up and exit audiogram thresholds. Data obtained from the folders were analysed using *R,* a software environment for statistical computing and graphics. Descriptive statistics and the following inferential statistical tests, Chi-squared, Fisher's exact tests and the Wilcoxon signed-rank test for paired samples, were used to determine significant associations between hearing loss and several factors revealed in the data. The American Speech-Language and Hearing (ASHA, 1994) criteria were used to determined incidence of significant threshold shift whilst the CTCAE v4 was used to determine both incidence of hearing loss and severity of the loss. The CTCAE v4 and TUNE criteria were compared based on incidence of hearing and ability to predict need for hearing amplification

Results

A total of 128 medical folders met inclusion criteria for this study and the following were the patient characteristics; median age = 43 years (range: 18 – 75 years); 92 males, 36 females; average length on treatment: 13.45 weeks). Out of these, 64 had information on the type and dose information of chemotherapy drug used during the period when monitoring of ototoxicity was conducted. The American Speech-Language and Hearing (ASHA) criteria revealed

ototoxicity in 74.2 % (95/128) of the sample. The Wilcoxon signed-rank test for paired samples showed a significant difference ($p = 0.0000000039$, $p < 0.05$) between follow-up and exit monitoring thresholds which indicated a significant decline of patients' hearing thresholds throughout the treatment duration. There were no statistically significant associations between age, duration of treatment and treatment modification. The study showed three treatment modifications which included dose adjustment (reduction), switching drug and continuing with the same drug. There was no significant association between treatment modifications and hearing loss. The CTCAEv4 criteria identified more people (53.9 %) who experienced a deterioration in their hearing thresholds than TUNE criteria (41.7%). However, TUNE performed better with respect to identifying patients who are likely to be candidates for further audiological rehabilitation including hearing amplification.

Conclusion

This study found a high incidence of cisplatin-induced hearing loss despite the possible modification of treatment. This shows that current strategies that are used by physicians at GSH Radiation Oncology department to prevent or minimize further deterioration of the patient's hearing thresholds during cisplatin chemotherapy can arguably be rendered ineffective. This is owing to the inability of conventional audiometry to detect hearing loss before it affects the speech frequencies. There was no significant association between hearing loss and age, dose, duration of treatment and treatment modification. The study also showed that CTCAE v4 grading criteria detected a higher incidence of ototoxicity than the TUNE criteria. However, the TUNE criteria were better at detecting the number of patients who need further audiological rehabilitation than the CTCAE v4. Therefore, both scales have their strengths and weaknesses.

Implications of the study include the incorporation of Extended High Frequency Audiometry (EHF) and Distortion Product Otoacoustic Emission (DPOAE) testing into the monitoring protocol where possible to allow for early detection and intervention of ototoxicity. Incorporation of otoprotectors into the prevention protocol is suggested as they have recently shown otoprotective efficacy in animal models without interrupting Cisplatin's therapeutic agency. Finally, more studies are required to validate the TUNE grading criteria to explore its utility as an ototoxicity grading criterion that can be universally used to communicate ototoxicity outcomes during Cisplatin chemotherapy.

Keywords

Cisplatin, Cancer, Ototoxicity, Hearing loss, Chemotherapy

Key Abbreviations

ASHA: American Speech-Language-Hearing Association

dB HL: decibel Hearing Level

DPOAE: Distortion Product Otoacoustic Emission

EHF: Extend High Frequency audiometry

GSH: Groote Schuur Hospital

Hz: Hertz

KHz: Kilo Hertz

CTCAE v4: National Cancer Institute Common Terminology Criteria for Adverse Events version 4

WHO: World Health Organisation

Acknowledgements

Praise God from whom all blessings flow. I did not deserve it, but You did it anyway. Thank you.

A/Professor Lebogang Ramma for the guidance and support throughout this significant part of my academic journey. Ke a leboga.

To the staff at Groote Schuur Hospital, I say thank you for allowing me to conduct my data collection and helping me during that process.

Heartfelt gratitude goes to the Mandela-Rhodes Foundation who provided me with the financial freedom to pursue my postgraduate studies and an unforgettable leadership training. I will continue to "aspire to be…" Many thanks to A/Professor Singh who recommended this opportunity and lead the team that helped me create a competent application.

Kago, the statistician who worked tirelessly to ensure that the data's findings were accurately captured and interpreted.

To friends and family who provided support in many forms. Your generosity will always be remembered.

Finally, to my dearest Mother. Words can never be enough to express my gratitude towards your unfailing love and support. This one is also equally yours!

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*The American Psychological Association (APA) referencing style was used throughout this thesis

Chapter 1: Introduction

Introduction: This chapter sets the scene for the study by contextualizing the global burden of disease due to Non-communicable diseases (NCDs) with a specific focus on cancer which is the non-communicable disease of interest in this study. The chapter also presents negative consequences of hearing loss that may result chemotherapy treatment for cancer.

Global Burden of Non-Communicable Diseases

Non-communicable diseases (NCD), predominated by diabetes, cancer, cardiovascular diseases and chronic respiratory diseases, are an international epidemic causing an estimated 63 % of global mortality annually (Hunter & Reddy, 2013). That is, 36 million out of 57 million deaths globally are attributed to NCDs (Hunter & Reddy, 2013; Wagner & Brath, 2012). According to the World Health Organization (2013), eighty percent of these deaths occur in low and middle-income countries, such as South Africa. NCDs are preventable and reduction of their contribution to the global burden on disease could be significantly reduced if major risk factors behind their prevalence are eliminated. However, with increases in world population size and age respectively, NCDs are expected to cause 70 % of global deaths by 2030 (Hunter & Reddy, 2013).

In South Africa, NCDs contribute approximately 28 % to the overall burden of disease and this proportion is expected to increase substantially if measures are not enacted to counteract the current trends (Mayosi et al., 2009). This warrants the urgent need to upscale primary healthcare services to accommodate the high demand in chronic care needs resulting from NCDs (Mayosi et al., 2009). There is also a need for the generation of knowledge on distribution, impact and risk factors of NCDs; which is important for advocacy and planning purposes (Stefan, 2015). Unfortunately, prevention and treatment of NCDs still remains under-prioritized at the expense of communicable diseases who's comparably overwhelming prevalence tends to be prioritized (Hunter & Reddy et al., 2013; Mayosi et al., 2009).

Cancer, which is the NCD of interest in this study, is one of the leading causes of death globally. It now claims more lives than the combination of HIV/AIDS, malaria and tuberculosis worldwide (Stephan, 2015, Mayosi et al., 2009). According to WHO (2014), 8.2 million deaths due to cancer were recorded in 2012 worldwide, with projections showing that this number is expected to reach 17.5 million by 2050 (Stefan, 2015). Approximately 70 % of total annual global mortality due to cancer occurs in Africa, Asia, Central and South America combined (WHO, 2014). In terms of incidence, WHO estimates that at least 14 million new cases of cancer were diagnoses globally in 2012. Furthermore, this figure is expected to rise by 70 % in the next two decades (WHO, 2014). Global trends showed that incidence of cancer is higher in men than women; at 201 per 100 000 and 165 per 100 000 in men and women respectively (WHO, 2014). Overall, there is a higher burden of diseases due to cancer in underdeveloped countries and it is estimated that at least 60 % of the annual new cases of cancer diagnosed come from these countries (Stefan, 2015).

Specific to South Africa, approximately 100 000 people are diagnosed with cancer annually, and like many developing countries, numbers are expected to rise by 46% by the year 2030 (Cancer Association of South Africa, 2015; Paken, Govender, Pillay, & Sewram, 2016). The lifetime risk of cancer is currently estimated to be 1 in 8 males and about 1 in 9 females (National Cancer Registry, 2010). In 2013, cancer was the second-leading cause of death in South Africa after Tuberculosis, causing 8% of the total annual deaths (Stefan, 2015). Prostate, colorectal, idiopathic and lung plus Kaposi's sarcoma cancer are the top five most prevalent types in men, whilst breast, cervical, colorectal, idiopathic and uterine cancers respectively affect women the most (Mayosi et al., 2009). Also, considering that approximately 12% of the South African population is infected by HIV/AIDS and the majority of those individuals are also exposed to antiretroviral treatment, the risk of developing HIV related cancers, such as Kaposi's sarcoma, is likely to create a great burden on the already strained health system (Mayosi et al., 2009; Paken et al, 2016). Anticipated reductions in HIV and TB related deaths owing to the roll out of active antiretroviral therapy may usher a rise in life expectancy in SA; and health experts anticipate a rise in the burden of disease attributable to cancer which may see the disease becoming the leading cause of death (Mayosi et al., 2009).

In the Western Cape province of South Africa, where the current study was conducted, the burden of cancer mimics national trends; ranking as the second leading cause of mortality with 16 % of total deaths recorded being attributed to the disease (Bradshaw et al., 2000). However, in the Western Cape province lung cancer was shown to cause most of the cancer-related death amongst both men (3.7 %) and women (3.2 %); and overall causing 2.7 % of total deaths in the Western Cape province (Bradshaw et al., 2000).

The complexity: Cancer and co-morbidities in South Africa

Survival rates for cancer are on the rise due to development of more effective chemotherapeutic regimens (Waissbluth, Peleva, & Daniel, 2016; Langer, am Zehnhoff-Dinnesen, Radtke, Meitert & Zolk, 2013). A systematic review by Waissbluth et al. (2016) showed that global five-year survival rates for all cancer types combined are estimated to have risen to 68 % and 81 % in adults and children, respectively. Similar trends have been reported in South Africa where survival rate has been reported to be six out of ten people (CANSA, 2015, National Cancer Registry, 2010).

The paradoxical 'concern' emerging from the increase in the survival rates of cancer patients in developing countries is that affected individuals often must live with permanent side effects resulting from chemotherapy. For example, treatment with some of the anti-cancer drugs like Cisplatin causes permanent side effects including neural damage and hearing loss (Rybak, 2007). Cisplatin, although effective in the treatment of neoplasms, often causes a poor quality of life as survivors end up developing severe and lifelong hearing disability (Rybak & Ramkumar, 2009; Rybak, 2007). Reviews have reported that incidence of chemotherapy induced hearing loss was found to vary such that it was as low as 0% and as high as 100 % of patients in different studies (Paken et al., 2016; Rybak & Ramkumar, 2009). In one South African study, incidence of Cisplatin-induced ototoxicity was reported to be 55.1 % (Whitehorn et al., 2014). Therefore, given the high burden of cancer, access to Cisplatin, and possible increase in the number of cancer survival rates in developing countries, there is a likelihood of an increase in number of people who will live with negative consequences of chemotherapeutic cancer treatment, particularly hearing impairment. This may lead to a growing burden of health care due to the increase in the number of individuals living with hearing impairment who will require chronic care (Mayosi et al., 2009).

Impact of Hearing loss

The effects of hearing loss resulting from chemotherapy treatment for cancer result in negative consequences on individuals affected. These include; difficulties in perceiving sound (including speech sounds), psychological problems, negative impact on personal relationships, cognitive decline, economic hardships as well as negatively impacting on an individual's overall quality of life (Arlinger, 2003; Clark, 2008; Hallam, Ashton, Sherbourne, & Gailey, 2008; Langer et al, 2013; Lin et al. 2013; Wilson, Tucci, Merson, & O'Donoghue, 2017).

Langer et al. (2013) reported that individuals with hearing loss experience difficulties with perception of consonants, sibilant sounds, speech comprehension and speech recognition especially in the presence of competing sound signals. Hearing impairments also cause challenges with music perception and listening to ambient noises like bird sounds (Langer et al., 2013). Even seemingly negligible mild losses can cause poor word analysis and poor phonological discrimination (Gelfand, 2009). In children, this evokes delayed spoken language acquisition (Wilson et al., 2017).

Hearing loss has been found to expose impaired individuals to risks of mental, emotional and physical abuse, with extreme cases that have resulted in murder (Olusanya, Neuman, & Saunders, 2014). It exposes them to environmental dangers which are usually signalled by certain sounds such as sirens and doorbells (Paken et al., 2016). This risk can induce fear and further hamper an individual's ability to fully interact with his or her environment (Ciorba, Bianchini, Peluchhi, & Pastore, 2012). To maximize interaction with acoustic signals from their environment, hearing-impaired individuals need more concentration than their normal hearing peers. This induces fatigue and frustration from requesting repetition often or being unsure if a message was understood correctly (Arlinger, 2003). This resultantly causes withdrawal from participation in activities such as parties, theatre visits and cinemas; leading to reduced cultural as well as intellectual invigoration and further evoking passivity and social isolation (Paken et al., 2016; Arlinger, 2003). Hallberg (1999) investigated the impact of hearing loss in people with acquired hearing loss. He found that they used either avoidance or taking control of the conversational environment as a coping mechanism.

Personal relationships of hearing impaired individuals and their frequent communication partners such as family members, friends, work colleagues and spouses, are also affected in their respective settings (Ciorba et al., 2012). These different stakeholders often

must put effort into accommodating the hearing-impaired person through slowing down their speech, articulating better, facing them so they can lip-read and moving closer to them. This might cause avoidance behaviour as people make less contact with hearing impaired individuals so as to avoid the pressure of having to put in more effort (Wilson et al., 2017). In the Hallberg (1999) study, spouses of the participants reported that they would either mediate for or distance themselves from their partners in situations where communication repair was needed. Thomas (1984) found rates of separation and divorce of up to fifteen percent in a group of couples in which one had a severe hearing loss or greater. Fifty three percent of participants reported that hearing loss had impacted their marriage (Thomas, 1984).

Over the past decade, there has been an increase in the amount of research literature that suggests an independent association between hearing impairment and an accelerated cognitive decline and increased risk of incident all-cause dementia (Lin & Albert, 2014; Lin et al. 2013; Lin et al, 2011). A study by Lin and colleagues (2011) revealed that increased hearing impairment severity resulted in increased risk of incident all-cause dementia over a ten-year follow up period; with risk increasing five-fold for severe-impairment on the WHO grading scale. Decreased brain structure together with the effects of hearing loss on cognitive load are attributed as being the mechanistic pathways underlying the contribution of hearing loss to poor cognitive performance (Lin and Albert, 2014). Lin and Albert (2014) also found accelerated rates of whole brain atrophy and specific volume declines have been shown in the right temporal gyri over an average 6.4 years follow-up. Resultant effects from this decline impact functions like spoken communication and sensory integration which are associated with early stages of Alzheimer diseases (Chetelat et al., 2005).

Research has revealed socio-economic repercussions of hearing loss in the adult population (Clark, 2008). Limited career pathways, employment acquisition, employment strains and low earnings are among the many noted effects of hearing impairment in adulthood (Olusanya et al., 2014; WHO, 2016). In a world driven by an educated and healthy workforce, people with hearing impairment have significantly restricted opportunities (Wilson et al., 2017). This is because jobs that are heavily reliant on spoken communication and high literacy are on the rise and in demand. In high-income countries, hearing impaired people have been found to have unemployment levels and income levels that are half those of their hearing peers (Wilson et al., 2017). This directly impacts on one's ability to escape or avoid the cycle of poverty once they are out a job. Negative consequences resulting from hearing loss tend to be

more calamitous in developing countries due to lack of rehabilitation and social services in those regions (Harris, Peer & Fagan, 2012).

Given the negative impact that a hearing loss due to cancer treatment can have on an individual, there has been a lot of interest on how side effects of cancer treatment can be ameliorated (Paken et al., 2016). Specific to prevention of chemotherapy-induced hearing loss because of cancer treatment, it is recommended that patients who are undergoing cisplatin-chemotherapy have their hearing thresholds closely monitored during their treatment (i.e. ototoxicity monitoring) (Harris et al., 2012; Van As et al., 2016). This enables early detection of treatment-induced hearing loss to prevent further deterioration of hearing thresholds (Langer et al. 2013). Most recently, there has been an increase in exploring agents that can prevent treatment-induced hearing loss during therapy (i.e. otoprotectors) (Callejo, Sedo-Cabezon, Juan, & Llorens, 2015; Sheth et al., 2017).

Chapter 2: Literature Review

Introduction This chapter will present literature on incidence of cisplatin-induced hearing loss as well as characteristics of hearing loss resulting from cisplatin chemotherapy. Literature on interventions that are used to minimize and prevent cisplatin-induced hearing loss also will be presented. The chapter will conclude with a discussion of grading scales used to indicate severity of cisplatin-induced hearing loss.

The global increase in the number of people affected by cancer has become a major concern to hearing-related professionals because of the continued use of chemotherapeutic drugs such as Cisplatin (Bisht, & Bist, 2011). Cisplatin or Cis-diamminedichloroplatinum (II), was the first platinum compound to be approved for treating cancer by the Federal Drug Agency of the United States in 1978 (Dasari, & Tchounwou, 2014). To date, it is the most reputable antineoplastic chemotherapeutic agent used in the treatment of various cancers of the ovary, testis, head, neck, cervix, oesophagus, lungs, medulloblastomas, osteogenic sarcomas carcinomas and lymphomas amongst many (Callejo et al., 2015; Rybak, Mukherjea, Jajoo, & Ramkumar, 2009; Rybak & Ramkumar, 2007). However, besides causing side effects of neurotoxicity and nephrotoxicity, Cisplatin causes the cochlear-confined and dose-limiting effect of hearing loss, also known as ototoxicity. Cisplatin causes an irreversible, bilateral, high-frequency, symmetric and progressive sensorineural hearing loss. Temporary or permanent tinnitus also occurs with or without the presence of hearing loss (Callejo et al., 2015; Paken et al., 2016; Rybak, et al., 2009; Rybak & Ramkumar, 2007). Cisplatin also results in vascular toxicity and endothelial dysfunction which has associations with idiopathic sudden sensorineural hearing loss (Waissbluth, Peleva, & Daniel, 2017).

There are currently nine analogues in clinical trials globally to enhance Cisplatin's therapeutic index, amongst them are enloplatin, oxaliplatin, and ormaplatin (Dasari, & Tchounwou, 2014). The only analogue that has shown comparable efficacy is Carboplatin, which is currently used globally to treat cancers of lungs, ovaries, head and neck (Waissbluth et al., 2017). However, Carboplatin exhibits slower reactivity and binding kinetics than Cisplatin; and has one out of forty-five chances of being as effective as Cisplatin (Dasari & Tchounwou, 2014). For one single dose of cisplatin required for chemotherapy, four doses of

Carboplatin will be required to produce comparable outcomes. This makes Cisplatin the most potent drug that is currently available for clinical use (Dasari, & Tchounwou, 2014; Paken et al., 2016). Overall, the data indicates that Cisplatin carries a higher risk of hearing impairment than Carboplatin. Nevertheless, treatment with high dose Carboplatin, such as during autologous stem cell rescue, has been indicated as a significant risk of nephritis, tubular injury and ototoxicity especially in paediatrics (Bertolini et al., 2014; Knight, Kramer, Winter, & Neuwelt, 2007; Langer et al., 2013).

Incidence of Cisplatin induced ototoxicity

There is variation in the reported incidence of ototoxicity in patients who undergo cisplatin-based chemotherapy (Paken et al., 2016). Eimprapai et al. (2012), using Distortion Product Otoacoustic Emission (DPOAE) measures to investigate cisplatin-induced hearing loss in patients with cancer of the head and neck, reported an incidence of 77%. Some studies have even reported incidence rates as high as 100 % (Whitehorn et al., 2014). A prospective randomized observational study by Arora et al (2009) investigated the effects of Cisplatin dose in 104 patients. Tumours included carcinoma of the larynx, lungs, cervix, head and neck cancers; using high frequency audiometry (0.25 – 16 Kilo Hertz) for ototoxicity monitoring. Incidence of hearing loss was 100% in the high (n=12; receiving a total dose of ≥ 81 mg/m² in three weeks) and middle (n=35; receiving a total dose of 61-80 mg/m² in three weeks) dose groups; and 60 % (n=6; receiving a total dose of ≤ 60 mg/m² in three weeks) in the low dose group. Six patients developed tinnitus during chemotherapy (Arora et al, 2009). Conversely, Dutta et al. (2015) found an incidence of 12 % and 33 % in groups of low and high dose Cisplatin chemotherapy respectively.

Strumberg et al (2002) conducted a retrospective study in which 32 testicular cancer patients received Cisplatin-based chemotherapy and were monitored using transient evoked otoacoustic emissions in addition to high frequency audiometry of up to 12 KHz. Seventy percent (70 %) of these patients developed ototoxicity by the end of treatment. A study by Bokemeyer et al (1998) in Germany found almost comparable results in terms of proportions developing ototoxicity. The study included 86 patients who also received chemotherapy. Patients had a mean age of 31 and average follow-up time of 58 months. Case history included

evaluations of patients' audiological risk factors to ototoxicity and circumstances of symptoms. Ototoxicity prevalence was 66 % in this study with statistically significant risk factors for ototoxicity found in this study to include high cumulative dose and previous noise exposure (Bokemeyer et al., 1998).

It is clear from the above cited literature that most of the studies investigating Cisplatin-induced ototoxicity were conducted in developed countries. There are currently very few studies from Africa (Whitehorn et al., 2014). In one of the few published studies which included a sample of 107 adult South Africans, Whitehorn et al. (2014) used conventional air (250-8000 Hz) and bone (250-4000 Hz) conduction testing to monitor patient thresholds. Incidence of ototoxicity was reported in 55.1 % of this cohort.

There are several factors that may assist in explaining differences in reported incidence of ototoxicity as noted in the studies reviewed above. Some of those factors include difference in testing procedures used to monitor the patients (Yasui et al., 2014; Whitehorn et al., 2014). Whilst some studies used pure tone audiometry at conventional (Whitehorn et al, 2014) at conventional (Whitehorn et al., 2014) or high (Arora et al., 2009; Strumberg, 2002) frequencies to determine the incidence, others resorted to objective measures like DPOAE (Eimprapai et al. 2012) and these different tests have varying sensitivity and specificity which means that they will not give comparable proportions of people affected by ototoxicity at any given time. (Dell'Aringa et al 2009). Age differences of participants play a significant role in determining differences in reported effects as susceptibility to ototoxicity is higher in children and geriatrics than it is in young and middle-aged adults (Eimprapai et al., 2012). DPOAEs assess only the function of the outer hair cells whilst pure tone (conventional and high frequency) assess the function of the entire auditory system (Gelfand, 2009). As ototoxic damage has been noted to begin in the high frequencies, this implies that DPOAEs and high frequency pure tone would be better suited to detect ototoxic hearing loss than conventional pure tone testing

Differences also emerge due to differences in the treatment schedules, dose and frequency of administration. High cumulative dose has been cited as a high risk for developing ototoxicity (Langer et al., 2013; Rybak, 2007). Another factor concerns differences in definitions used for cisplatin-induced ototoxicity as well as the grading criteria used to identify

the presence of hearing loss during chemotherapy. Differences in grading criteria lead to differences in reported incidence of ototoxicity and without a common criterion it is difficult to compare results across studies (Chang & Chinosornvatana, 2010; Langer et al., 2013).

Characteristics of Cisplatin induced ototoxicity

Cisplatin-induced ototoxicity is characterized by a bilateral, irreversible, high frequency sensorineural hearing loss. The hearing loss is irreversible because once destroyed by Cisplatin chemotherapy, mammalian hair cells cannot regenerate (Sheth et al., 2017). A study by Bertolini et al (2014) reported that hearing loss tends to progress over time even after the end of chemotherapy treatment. In this study a statistically significant decline in patients' hearing thresholds was found between two assessments in a two-year post treatment period (Fisher exact test, $p < 0.00001$). However, Neuwelt, Gilmer-Knight and Kramer (2005) reported that Cisplatin-induced hearing loss tends to plateau between 40-60 dB HL in the high frequencies and thereby suggesting limits to the progression of loss. This plateau in the degree of hearing loss was attributed to total damage of outer hair cells (Neuwelt et al 2005).

While Cisplatin-induced hearing loss is typically bilateral, some studies have reported cases of asymmetry in hearing loss (Paken et al., 2017). Schmidt et al (2008) conducted a study with 55 paediatric patients and found high frequency thresholds to be worse in the left than right ear, and males had more elevated thresholds than females. Jenkins and Mitra (2009) also found asymmetry of at least 10 dB between ears post treatment in 75 % of women who underwent breast cancer chemotherapy. Unilateral hearing loss can also result from tumour location and surgical or therapeutic treatment on the affected ear (Schmidt et al., 2008).

Finally, tinnitus is one of the primary warning signs of Cisplatin ototoxicity (Crundwell et al., 2015) but it can also occur in the absence of hearing loss. It usually precedes measurable hearing loss changes (Bisht & Bist, 2011). Tinnitus refers to the ringing or buzzing sound in the ear. It can be transient or permanent, and disappears after hours post treatment or can persist for weeks (Arora et al., 2009; Frisina et al., 2016; Paken et al., 2016). There is variability in incidence of tinnitus and studies have revealed tinnitus in up to 40 % of participants (Frisina et al., 2016). Glucocorticoids have been suggested as treatment for tinnitus (Callejo et al., 2015).

Risk factors associated with Cisplatin induced ototoxicity

Several factors have been shown to contribute towards predisposing patients to adverse auditory outcomes following treatment with Cisplatin. These include cumulative dose, patients' age, genetic predisposition, renal insufficiency, pre-existing hearing loss, radiation therapy and drug administration among many. These risk factors are discussed below.

Cumulative Dosage. There is variability in literature about the amount of Cisplatin it takes for ototoxicity to appear. An increase in Cisplatin dosage increases the drugs' efficacy (Rybak, 2007). However, high single doses (defined as 70—85 mg/m^2) and cumulative dosages 400 mg/m^2 or more respectively have been associated with significant increase in ototoxicity (Rybak et al., 2009). For example, Yancey et al (2012) found a significant correlation between ototoxicity and cumulative dose in patients receiving doses above a median of 429 mg/m^2 ($P = 0.034$, $P<0.05$), below which no ototoxicity occurred. However, in the same study, patients who received a combined regimen of Cisplatin and Carboplatin developed significantly more hearing loss than those who received cisplatin only ($P = 0.02$, $P<0.05$), raising the question of whether it is the cumulative or synergistic effect responsible for observed results.

Bokemeyer et al (1998) also found a significant association between ototoxicity and the cumulative dose of cisplatin for patients with doses above 600 mg / m² as all patients above this dosage developed ototoxicity ($P < 0.0001$). This study highlighted the long-term effects of high cumulative dose of Cisplatin and need for long term follow up in patients to check for ototoxicity. Schellak and Naude (2013) found a cumulative dose of 200mg for Cisplatin to be a risk factor for the development of ototoxicity. Frisina et al (2016) found significant associations between hearing loss and cumulative Cisplatin doses of 300 mg/m^2 (odds ratio, 1.59; $P = .0066$).

A study by Dutta, Venkatesh and Kashyap (2005) revealed significant association between a median cumulative dose of 300 mg/ m² and incidence of hearing loss above 4 KHz. Conversely, no significant correlation was found with ototoxicity in the Dell'Aringa et al

(2009) study for the same cumulative dose (300 mg/m²). Yasui et al (2014) found 56 % incidence with a cumulative dose of less than 360 mg/ m² and even greater incidence with a dose above 360 mg/ m². According to Langer et al (2013) the incidence of cisplatin-induced ototoxicity tends to increase by 5–7% per additional 100 mg/m² cumulative dosage. Whilst this clinical risk factor has become an important predictor, dosage does not comprehensively account for interindividual variations in susceptibility to Cisplatin-induced hearing loss. For example, whilst ototoxicity was visible after only 120md/m² doses of cisplatin, some children were tolerant of cumulative doses as high as 480 mg/m² (Lanvers-Kaminsky, C. et al., 2006). Arora and colleagues (2009) found 100 % incidence of ototoxicity above 8 KHz with single doses of 80 mg/ m². 90-100 mg/m² single doses were associated with an increase in severity of hearing loss by more than 60 dB (Arora et al., 2009).

Renal insufficiency. Although renal damage has been found to be manageable through long-term electrolyte supplementation and hyperhydration, it remains a dose limiting factor for the administration of cisplatin and a predisposing factor for the resultant ototoxicity. Dutta et al (2005) found significant associations between increase in serum creatinine and high incidence of ototoxicity. Bokemeyer and colleagues (1998) also observed a correlation between prechemotherapeutic kidney function with incidence of ototoxicity.

Age. Children are more susceptible to cisplatin induced ototoxicity than adults (Neuwelt et al 2005). Young age at the time of treatment has been found to increase a child's risk for ototoxicity. In a study by Li et al (2003), children who received treatment at the age of 5 had 21 times more likelihood of acquiring moderately severe high-frequency hearing loss than patients aged 15 to 20 years. Children younger than 15 years took shorter times to ototoxicity than older ones. Because of alterations in metabolism and organ function, young children and the elderly are most vulnerable to Cisplatin (Laurell and Jungnelius, 1990, Li et al., 2004). Risk at a young age could be attributed to immaturity of the cochlea (Yasui et al., 2014). Dell'Aringa and colleagues (2009) found age above 60 years to be significantly associated with increase in incidence of hearing loss and a four times higher chance of developing hearing loss after treatment ($p= 0.046$; $p<0.05$). Rademaker-Lakhai et al (2006) also found hearing loss to be more significantly severe in older adult patients versus paediatric patients ($P = .013$).

Genetics. There is also some research evidence that seems to suggest that mutation of mitochondria is the reason behind certain patients' genetic predisposition to cisplatin induced ototoxicity (Whitehorn et al., 2014). Cisplatin-induced hearing loss has a strong correlation to genetic variation in genes Catechol-O-Methyltransferase (COMT) and Thiopurine S-Methyltransferase (TPMT) (Yasui et al., 2014). Ross et al. (2009) reported a significantly increased risk for ototoxicity with variant alleles of TPMT and COMT in children. Conversely, the GSTM3*B allele was found to have a protective effect on cisplatin induced hearing loss in a study by Peters et al (2000).

Pre-existing hearing loss. Bokemeyer et al (1998) found pre-existing hearing loss due to a history of noise exposure being correlated to a threefold increased risk for ototoxicity ($p = 0.04$) and persistent subjective symptoms ($p = 0.006$). The presence of a hearing loss makes the ear structures, especially the cochlea, more vulnerable to damage resulting from ototoxicity (Neuwelt et al., 2005).

Radiation therapy: RT prior to or concomitant with cisplatin is administered to reduce failure of local treatments and has been shown to result in organ preservation and thus improved survival rates (Malgonde et al., 2015). However, combination therapy chemotherapy has been found to be a risk for ototoxicity. Neuwelt et al (2005) found incidence of ototoxicity in 70 % of (16/23) of patients who had prior radiotherapy. Malgonde and colleagues (2015) found a significant difference in ototoxicity between patients who were treated with RT only and those treated with cisplatin-radiotherapy regime one-month post treatment ($P < 0.05$).

Other risk factors in literature include intravenous bolus administration (Bernhard et al (2001), gender (Yancey et al (2012), low hemoglobin, red blood cell count and serum albumin at the time of chemotherapy as well as co-administration with aminoglycoside antibiotics or loop-diuretics and furosemide (Langer et al., 2013; Yancey et al., 2012; Neuwelt et al., 2005). Lautermann, Song, McLaren and Schacht (1995) suggested diet as a risk factor in ototoxicity. They found a correlation between cisplatin ototoxicity and decreased levels of cochlear glutathione and serum albumin in a group of guinea pigs. After 12 days of injection, the group which was put on a high protein diet exhibited low hearing loss whilst the low-protein diet group showed significant loss (Lautermann et al., 1995). Bokemeyer et al., (1998) found a

strong correlation between the presence of other toxicities, like symptomatic neurotoxicity, to ototoxicity. Recently, ethnic differences have been suggested as a factor underlying observations of how Japanese patients seem to be more susceptible to cisplatin ototoxicity but this needs further research (Yasui et al., 2014). This study is supported by reports from Neuwelt et al (2005) who found that Asians had significantly earlier time (86 days) to ototoxicity than Whites (139 days). This study should however be cautiously interpreted as only 3 Asian participants were assessed.

Ototoxicity prevention and treatment: Ototoxicity monitoring and use of otoprotectors

It is not yet possible to determine individual susceptibility or risk of developing ototoxicity following treatment with cisplatin-based chemotherapy (Yasui et al., 2014). Thus, early identification of hearing loss using the current best practice strategies should be prioritized for all patients undergoing cisplatin-based chemotherapy. These strategies include ototoxicity monitoring and use of otoprotective agents respectively, the latter strategy whose efficacy is yet to be fully validated. The most common strategy currently used to prevent cisplatin-induced hearing loss is to prospectively monitor patient's hearing thresholds throughout their chemotherapy treatment i.e. ototoxicity monitoring (Arora et al., 2009).

Ototoxicity monitoring. Reavis and colleagues (2008) recommend that monitoring patients' hearing thresholds should always be considered as part of the therapy battery where a risk of ototoxicity exists. Ototoxicity monitoring enables early identification of hearing loss which allows for treatment modification by physicians when possible. Treatment modification used by physicians are aimed at either slowing down or stopping the progression of hearing loss (Sheth et al, 2017). Monitoring also allows for prompt prescription and provision of hearing aids or other forms of assistive listening devices where speech frequencies have been impacted (Crundwell, Gomersall, & Baguley, 2016). Ototoxicity monitoring is also a useful tool during counselling to inform patients about hearing loss, setting realistic expectations of treatment outcomes, discussing available adaptive communication strategies, tinnitus and the debilitating effect of exposing oneself to high intensity noise levels which could worsen the hearing loss by up to three times (Knight et al., 2007).

The American Speech-Language and Hearing Association (ASHA) guidelines from observation of large clinical trials summarise the ideal components of a standard ototoxicity monitoring program (Knight et al., 2007). In these guidelines, ASHA (1994) specifies the following components as basic elements of an ototoxicity monitoring program: Timely identification of patient at risk of developing ototoxicity, pre-treatment counselling regarding risk of ototoxic effects from the treatment, baseline (audiometric) assessments prior to initiation of cisplatin chemotherapy, monitoring evaluations before each cycle of chemotherapy treatment and a pre-selected criterion for determining the presence of an ototoxic shift and grading adverse effects on hearing due to ototoxicity.

According to Durrant et al (2009) a baseline evaluation taken before initial ototoxicity treatment enables associations to be made between cisplatin and hearing loss. Follow up testing should be done twenty-four hours after cisplatin treatment is provided to give time for recovery of any temporary threshold shifts which might have occurred (Durrant et al., 2009). To check for long term impact of ototoxic drugs, it is generally agreed that follow up should be done every six months for the first two years after treatment then subsequently done annually for another three years (Durant et al., 2009).

Treatment modifications

During the ototoxicity monitoring period, a physician has several options to choose from, in terms of medical intervention, once a decline in a patient's hearing sensitivity is noted, to prevent further progression in hearing loss (Fausti et al., 2005; Schultz et al., 2009). Among these medical interventions are; discontinuing the administered medication, adjusting the dosage of medication, changing the frequency of the drug administration, switching to a less ototoxic drug, or the option to continue with the medication for which they would have to prepare the patient and family on coping strategies to adjust to the hearing loss (Fausti et al., 2005; Yasui et al., 2014).

Dose reduction: Dose reduction is thought to stave the ototoxic effects of cisplatin for a temporary period (Yasui et al. 2014). In a study by Peleva et al (2014), 25 patients had dose reduction to prevent further progression of hearing loss. 56 % of this group already had

developed hearing loss following cisplatin-chemotherapy and despite this dose modification, incidence rose to 83% at follow-up, bringing into question the effectiveness of reduction or cessation. This study emphasized the need for extend high frequency audiometry in early (HFA) detection of loss and thereby allowing intervention like dose adjustment before hearing loss had occurred in speech frequencies. Further research is necessary to assess the efficacy of dose reductions based on HFA monitoring protocols in the effective reduction of the incidence of ototoxicity.

In a study by Lafay-Cousin et al. (2013), 35 paediatric patients undergoing cisplatin chemotherapy for medulloblastoma were reviewed. Guidelines were established to reduce or discontinue cisplatin treatment in average risk (AR) and high risk (HR) medulloblastoma respectively, with reductions of up to 50 % when hearing loss with a significant shift of between 20-30 % was noted. 63 % (22) of the cohort required dose adjustment whilst 27.1 % had to discontinue treatment due to ototoxicity respectively. The median cumulative dose of cisplatin administered in AR patients was 412.5 mg/m² (150–600) and 270 mg/m² (225–270) for the HR group; corresponding to 68 % and 100 % of intended doses in the two groups respectively. Eighteen (81.3%) in the AR patients and 3 (23%) in the HR group required dose reduction. In the AR group, dose modifications were indicated after median of four cycles (cumulative dose of 300 mg/m²). Treatment was discontinued in 6 AR patients and none in the HR group. Interestingly, despite strict protocols which resulted in dose adjustment than any of the other studies reviewed here, 25 % of the population still developed ototoxicity.

Knight et al (2007) assessed 32 children for ototoxicity using conventional audiometry, high frequency audiometry and DPOAE measures. Bilateral ototoxicity was observed in 62.5 % of patients with unilateral ototoxicity observed in four additional patients. Loss was found in ten cisplatin only patients, 9 cisplatin-carboplatin patients and only one carboplatin high-dose patient. 10 children had dose reduction due to ototoxicity and all of them had ototoxicity in at least one ear with conventional audiometry with a grade 2 and above loss for all patients on the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4 (CTCAE v4) scale. Therefore, a trend of ototoxicity is being noted despite reduction in dose.

Changing drug (Cisplatin to Carboplatin): Changing the drug regimen to Carboplatin as an ototoxicity preventive strategy has been shown to also eventually lead to ototoxicity. This could be explained by the fact that Carboplatin needs to be administered in high dose to serve its life-preservation purpose; and high dose Carboplatin has been found to lead to incidence of ototoxicity (Peloquin et al 2004). Nitz and colleagues (2013) found ototoxicity in 46.2 % in a sub-group of participants after treatment had been changed from Cisplatin (median dose: 240 mg/m²) to Carboplatin (median dose: 1200 mg/m²). Bertolini and colleagues (2004) conducted a study to evaluate the effect of cisplatin and/or carboplatin on hearing thresholds in a group of one hundred and twenty children (aged between 0 - 17 years) being treated for neuroblastomas, osteosarcomas, germ cell tumours and hepatoblastomas respectively. Cisplatin was administered at a median cumulative dose of 400 mg/m² and Carboplatin at 1600 mg/m². Results revealed hearing loss of grade 2 and above on the Brock's ototoxicity grading scale in 37% of the patients who received only Cisplatin and 43 % of patients who received a combination of Cisplatin and carboplatin. High frequency ototoxicity resulted after a cumulative dose of 400 mg/m² and progressed to the low frequencies when follow-up audiometry was conducted. Whilst only 5 % of audiograms indicated loss of at least grade 2 before the conclusion of therapy, this percentage increased to 11 % during early post-therapy and further increased to 44 % at 2-year follow-up (Bertolini et al., 2004). Results did not change when the sequence of administration was changed between Cisplatin and Carboplatin. Kushner et al 2006 evaluated ototoxicity using the Brock method in neuroblastoma paediatric patients. Two groups received Cisplatin treatment at 400 mg/m² and 600mg/m² cumulative dose respectively and one of the groups contained two Cisplatin cycles which were followed by a Carboplatin-containing myeloablative therapy. Severe hearing loss was found in 50 % (29) of patients in the Carboplatin-containing treatment group. Results showed no significant change at two-year follow-up.

In the Neuwelt et al (2005) study, hearing loss occurred in 55% of children who were treated with Cisplatin (22/40), 38 % treated with carboplatin (3/8) and 84 % (16/19) who were treated using both chemotherapy drugs. Like results from the study by Yancey and colleagues (2012), results from this study suggest that combination therapy had the greatest risk for developing loss, followed by Cisplatin only and then Carboplatin only. 8 of the 17 children treated with both Cisplatin and Carboplatin, and 9 treated with Cisplatin only needed hearing aids respectively and although the different groups showed no statistical difference between each other. High incidence after change of medication to a seemingly less ototoxic one should

be a cause for concern as it is meant to have a protective as opposed to a damaging effect. However, change to carboplatin here was used during bone marrow transplantation post Cisplatin chemotherapy; with both Carboplatin conditioning and transplantation being risk factors for development of loss. Therefore, it can be argued that the multi-modal nature of the treatment regimen as opposed to mere change in type of drug, was responsible for observed ototoxicity (Kushner et al., 2006).

Overall, there is currently limited evidence on the effectiveness of other forms of treatment modification strategies implemented post detection of deterioration in hearing, especially in the adult population (Yasui et al., 2014). Use of lower cumulative cisplatin doses or less ototoxicity medications such as carboplatin has not been implemented as a standard preventative strategy for cisplatin-induced ototoxicity in clinical practice, because it is unclear whether these modifications would fully keep the antitumor efficacy and thus survival rates of standard cisplatin regimens. Nevertheless, modification strategies are being implemented as part of treatment protocols for specific cancerous tumours (Langer et al., 2013). According to Van As, van den Berg, & van Dalen (2016), there is currently no literature which assesses the effectiveness of having different durations of medication in preventing ototoxicity. It is therefore a fundamental aim of the current study to bridge the gap in the literature by trying to establishing how efficacious the currently used treatment modification strategies are. It is not yet fully established through clinical practice whether these treatment modification strategies would not impact Cisplatin anti-tumour efficacy and resultantly hinder survival rates (Lange et al., 2013). However, change of doses and type of drugs have been recommended for tumours such as medulloblastoma (Lafay-Cousin et al. 2013). This warrants the need for further studies to standardize treatment modification strategies in the clinical setting

Ototoxicity grading scales/criteria

Defining and grading the severity of hearing loss following the platinum-based chemotherapy is essential for assessing the impact of treatment, and for determining appropriate clinical interventions for the different attending members of the multi-disciplinary team, especially the audiologist who is the primary caregiver where hearing is concerned (Schultz et al., 2009). Grading criteria/scales are important for grading medication's side effects and provide a guideline for subsequent medication and therapy (Waissbluth et al., 2016). However, there is currently no gold standard procedure for ototoxicity classification that is universally adopted or accepted (Rybak, 2007). This means that clinicians use their preferred

classification procedures which in turn means that outcomes from grading scales cannot be compared to establish which is most effective and can be universally adopted (Chang, 2011).

Furthermore, the definition of ototoxicity can affect the prevalence reported (Waissbluth et al., 2016). Results showed variation on the different grading scales in a prospective study by Schultz and colleagues who investigated ototoxicity in 31 Brazilian patients with different tumor types (Schultz et al, 2009). Using air and bone conduction audiometry, the CTCAEv4 criteria showed ototoxicity in 38 % of the population, 29 % on the ASHA criteria, 54 % on the Brock criteria and 29 % using the David and Silverman's criteria (Schultz et al., 2009).

When it comes to specifying a criterion for a significant change in patient's hearing thresholds due to cisplatin chemotherapy, the American Speech-language Hearing Association (ASHA, 1994) criterion consists of: a significant change in hearing thresholds of >20 dB at one frequency or >10 dB worsening at two consecutive frequencies; and also a loss of thresholds at three consecutive frequencies (Crundwell et al., 2016). The disadvantage of this criterion is that it does not convey any information about the severity of the ototoxic hearing loss as well as how the loss clinically impacts a patient (Chang, 2011).

The most widely accepted grading scale in oncology clinical trials is the National Cancer Institute Common Terminology Criteria for Adverse Events version4 (CTCAE v4) (Chang & Chinosornvatana, 2010). This grading scales overcomes the disadvantage of ASHA (1994) because it specifies the severity of hearing loss. It uses four categories of hearing loss and combines objective and subjective hearing assessments in rating hearing impairment (Chang & Chinosornvatana, 2010). Despite its wide spread use, its limitations include a lack of instruction where there are missing frequencies, downplaying the impact of low frequencies in impacting hearing loss and failing to accommodate clinically significant hearing loss in its sub-categories (Theunissen et al., 2014; Gurney & Bass, 2012).

Table 1: National Cancer Institute Common Terminology Criteria for Adverse Events Version 4 (CTCAE v4)

Grades	**Criteria**

Grade 1	**No hearing loss**
Grade 2	Threshold shift of 15 to 25 dB averaged at 2 contiguous test frequencies in at least 1 ear or subjective change in absence of a Grade 1 threshold shift
Grade 3	Threshold shift of > 25 dB averaged at 2 contiguous test frequencies in at least 1 ear
Grade 4	Profound bilateral hearing loss (> 80 dB at 2 kHz and above)

One of the most recently developed grading scale is the TUNE grading scale (Theunissen et al., 2014). The TUNE is a refined version of the CTCAE v4 (Figure 1) and ASHA scales combined (Crundwell et al., 2016). It documents how ultra-high-frequency hearing losses impact daily listening function through utilization of frequency regions critical for sound quality and speech intelligibility (Crundwell et al., 2016). Thus, it can be used for grading ototoxicity where Word Recognition scores are missing. The criteria consider a hearing loss >/= 35 dB HL (PTA at 1,2,4 KHz) to represent a 50 % loss of speech intelligibility, whilst a loss >/= 70 dB HL without amplification to be equal to profound loss (Theunissen et al., 2014). The TUNE scale is expressed in air conduction thresholds to represent the entire auditory system and not just bone conduction which solely representative of the inner ear (Gelfand, 2009). Theunissen et al (2014) showed an incidence of 80 % using the TUNE scale, which was more than that shown by the CTCAE v4 criteria of 78 %.

Table 2: The TUNE grading criteria

Grades	**Criteria**

Grade 0	**No hearing loss**
Grade 1a	**Threshold shift ≥ 10 dB pure tone average at 8-10-12.5 kHz**
Grade 1b	**Threshold shift ≥ 10 dB pure tone average at 1-2-4 kHz**
Grade 2a	**Threshold shift ≥ 20 dB pure tone average at 8-10-12.5 kHz**
Grade 2b	**Threshold shift ≥ 20 dB pure tone average at 1-2-4 kHz**
Grade 3	**Hearing level ≥ 35 dB pure tone average at 1-2-4 kHz de novo**
Grade 4	**Hearing level ≥ 70 dB pure tone average at 1-2-4 kHz de novo**

Therefore, given the above review regarding variation in grading scales used to classify ototoxicity-induced hearing loss, there is a need for a common scale for grading ototoxicity which will allow for comparison of changes in hearing thresholds and the resultant impact on quality of life across different settings. The current study will utilize the above-mentioned scales to determine their usefulness in detecting the presence of hearing loss in cancer patients. A major drawback with the different criteria is that none of them elaborately evaluate and consider the patients' complaints (Schultz et al., 2009). This information is often asked from the attending physicians to get a clear picture of the implication which hearing loss has on the patients' quality of life (Schultz et al., 2009).

Study Rationale

Use of Cisplatin as a therapeutic agent has been found to successfully lead to remission in various cancerous tumors. Thus, therapeutic agency often takes precedence over subsequent risk of developing ototoxicity when using this drug during chemotherapy (Whitehorn et al., 2014). However, Cisplatin's adverse effect on the auditory system frequently leads to

permanent hearing loss. With high success rates of treatment, many cancer survivors have to live with the ototoxic side effect from mainline drugs like Cisplatin. It is therefore imperative now more than ever that attention is paid to measures which can be taken to ensure good quality of life post treatment.

One such measure is monitoring of patients' hearing at regular intervals during the course of their treatment. The reason for monitoring patients during treatment is to ensure early detection of changes in patient's hearing thresholds due to Cisplatin chemotherapy in order to give treating doctors an opportunity to modify treatment and prevent further deterioration of patients' hearing thresholds. However, there is currently limited amount of empirical research evidence on the effectiveness of the different preventive medical measures (i.e. treatment modifications) currently being used to prevent or minimize the occurrence of hearing loss during this monitoring period once ototoxicity is indicated (Harris et al., 2012). Limited research available seems to suggest that some of the modifications, such a switching from Cisplatin to the less ototoxic Carboplatin, causes a worsening of the hearing loss and increases the incidence of hearing loss.

Ototoxic monitoring of patients on Cisplatin chemotherapy requires a close cooperation between audiologists and oncologists. However, often time these professionals use different systems that could potentially make communication between them challenging. For instance, in Groote Schuur Hospital, audiologists use the ASHA (1994) criteria to communicate outcome of audiological assessment during ototoxicity monitoring whereas oncologists within the same institution use the CTCAEv4 grading scale to communicate the same information. Thus, there generally exists a lack of consensus regarding the best grading scale that could be adopted across different contexts to classify or grade hearing loss following cisplatin-based chemotherapy treatment (Crundwell et al, 2016).

The current study will help to bridge the gap in literature by providing data that evaluates, in a descriptive and comparative manner, the different preventative strategies used when Cisplatin-based ototoxicity has been detected, to determine which of them are highly effective in preserving patients' hearing during chemotherapeutic treatment in the adult population; and thus, result in low incidence of hearing loss. This study will also compare different grading scales and recommend the most effective scale that could be used to classify ototoxic hearing loss. Therefore, this study aims to answer the following research questions:

a). What is the efficacy of strategies that are currently used at Groote Schuur Hospital (GSH) Radiation Oncology department in preventing cisplatin induced ototoxicity in patients?

b). What is the most effective grading scale with respect to early detection of ototoxicity and guiding further clinical management of patients that could be used across different contexts?

Chapter 3: Methodology

Introduction: This chapter will present the study design and data collection procedures used in this study. Issues relating to reliability and validity of the study procedures, and ethical considerations will also be presented.

Aims and Objectives

Aim:

To determine the efficacy of strategies used to prevent or minimize cisplatin-induced hearing loss in chemotherapy patients seen jointly by the departments Radiation Oncology and Audiology Outpatients at GSH; as well as to determine the most effective grading scale to communicate the negative impact of treatment across these two departments.

Objectives:

- Determine incidence of cisplatin induced hearing loss in the GSH Oncology patients
    - Characterize HL in terms of type, severity and symmetry
- To determine common treatment modification strategies used to prevent cisplatin-induced ototoxicity in these patients at GSH.
- To compare the different treatment modification strategies with respect to efficacy in the minimization or prevention of cisplatin-based ototoxicity.
- To compare 2 ototoxicity grading scales for adults; namely the CTCAE v4 and TUNE scales, regarding early detection of deterioration in patients' hearing thresholds and ability to make predictions for further audiological management.

Study Design

An observational retrospective cohort study of the patients' medical folders was used in this study. Retrospective cohort studies use already collected and stored information from health records to explore associations between named risk factors and a health condition (Cozby & Bates, 2011). Events that have already occurred are reconstructed like they are being followed prospectively (Hess, 2000; Sedgwick, 2014). In this study, medical records of all patients who went under Cisplatin-based chemotherapy in the GSH Radiation Oncology department whilst receiving periodic ototoxicity monitoring services at the GSH Audiology Outpatients department between years 2011 and 2016 were reviewed. Advantages of a retrospective study design include the fact that there is already existing clinical records from which data is derived and analyzed (Hess, 2004) and that exposure to risk factors is noted first before the outcome occurs which allows for the analysis of risk factors and outcomes to happen in a sequential and temporal manner (Sedgwick, 2014).

In the current study, selection bias was minimized by having all patients who received CBC whilst being monitored for ototoxicity in GSH Outpatients department between 2011 and 2016. The health records in GSH were not established to study any associations between chemotherapy and ototoxicity therefore no systematic differences could have existed between groups in the current cohort specificity of the information reported. A checklist and data collection form were used to ensure collection of all pertinent information required for the current study. The study also included an inclusion and exclusion criteria that specified the type of information needed or unnecessary for the study respectively.

Participants and Sampling

Participants

This study did not involve direct interaction with patients. Therefore, medical folders of Cisplatin-based chemotherapy patients who were treated at the Radiation Oncology department whilst being monitored for ototoxicity at GSH Outpatients and completed treatment between the years 2011 and 2016 were retrieved to be reviewed. A total of 680 patients'

medical folders were accessed to be reviewed. One hundred and twenty-eight (128) of these met the inclusion criteria for the study (see figure 1).

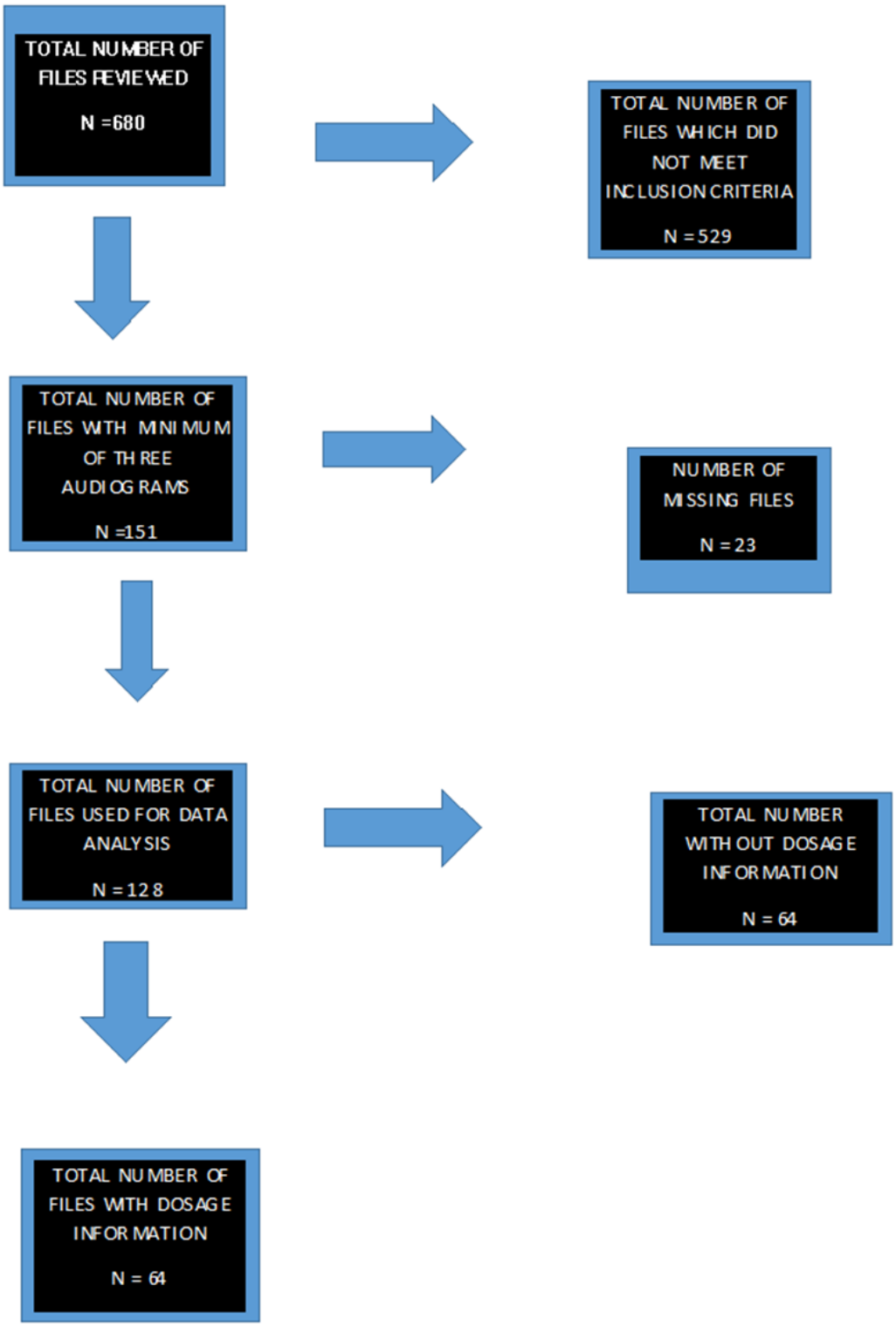

Figure 1: Flow chart depicting the sampling method

Sampling Strategy

A convenience sampling strategy was used to select the participants for this study. In this non-probability sampling strategy, units or participants are selected and included in a sample based on their easy accessibility and proximity to the researcher (Cozby & Bates, 2011). Folders of participant in the current study were easily accessible because the patients had received both chemotherapy and audiological treatment at the same facility, GSH. The advantages of convenience sampling are that it is easy to execute with limited regulation on how the sample can be collected. It requires much less time and costs to be carried when compared to other strategies such as probability (Cozy & Bates, 2011; Terre-Blanche et al., 2012). The disadvantages are that because the strategy relies solely on the available information, collected data might under-represent or over-represent certain groups of participants in the sample, and thus sampling bias occurs. The sampling frame is unknown and there is no randomization during convenience sampling (Cozby & Bates, 2011). This means that the selected sample will not be representative of the entire population from which it was drawn (Cozby & Bates, 2011).

Participant Recruitment Strategy

This study did not involve direct contact with patients. Instead, medical folders of Cisplatin-based chemotherapy patients who had been jointly seen in GSH Oncology and Audiology departments between 2011 - 2016 were identified to be reviewed. Approval to access the folders was first sought from relevant authorities; Hospital Chief Executive Officer (see Appendix B); and Heads of the Oncology and Audiology departments prior to commencement of the study. The inclusion and exclusion criteria respectively are described below.

Inclusion Criteria

- Hospital files of patients who underwent cisplatin-based chemotherapy whilst concurrently receiving audiological ototoxicity monitoring services at GSH Outpatients between the years 2011 and 2016.

- Patients' medical folders which includes a minimum of three audiograms; first audiogram obtained at the start of cisplatin-based chemotherapy(baseline), final audiogram

taken at the end of cisplatin-based chemotherapy (exit audiograms) and at least one audiogram (check-up audiogram) between the baseline and exit audiograms.

- Patients must be ≥ 18 years at the start of chemotherapy

Exclusion Criteria

- Audiograms indicating a pre-existing hearing loss prior baseline audiogram
- Patients with a conductive component in hearing loss
- Patients who are currently undergoing treatment with ototoxic medications (e.g. aminoglycosides, and loop diuretics)
- Patients on radiation therapy treatment for head and neck cancers

Medical records of patients with the above-mentioned points were excluded from the study to minimize the number of confounding variables in this study (Hess, 2004).

Sample Size

The Groote Schuur Hospital Department of Radiation Oncology in collaboration with the Audiology department jointly attend to an approximated 100 cisplatin-based chemotherapy patients annually. Therefore at least 500 medical folders were expected to be available for review. CliniCal, an online calculator, was used to estimate the required sample size and the following parameters were used; Alpha =0.05, Beta =0.2 and Power = 80% and a known incidence of 55% in this population (Whitehorn et al ,2014). The calculations revealed that a minimum of 82 participants would be required for the study.

Data Collection Tools

Data collection form

An adapted collection form was used in the current study (See Appendix A). This form contained three sections: (i) Patient's personal details (ii) patient's audiometric data and (iii) Oncology Management information (i.e. duration of chemotherapy and type of modification of the cisplatin based chemotherapy). The information was obtained from the patient's folder.

Characterization of Hearing Impairment

Criteria for a significant hearing thresholds shift

The American Speech-Language-Hearing Association (1994) criteria was used to define a significant threshold shift in frequencies between 0.25 and 8 KHz. Significant shift occurs when there is either a change of 20 dB HL at one frequency, an absence of response at three frequencies where they previously were present, or a 10 dB HL shift at two consecutive frequencies (ASHA, 1994).

Degree of hearing loss

The ASHA (1994) criteria only gives information about the presence and/or absence of a significant hearing threshold shift but provides no information about the severity of the resulting hearing loss. To provide additional information on the degree of the hearing loss and to facilitate ease of communication between audiologists and oncologists, the CTCAEv4 grading scale was used. As discussed in the literature review, CTCAEv4 is commonly used hearing loss grading scales in oncology literature (Crundwell et al., 2016).

Type of hearing loss

The Margolis and Saly criteria was used to describe and classify the type of hearing loss. A conductive hearing loss was defined as a 10 dB air-bone gap at 3 or more frequencies or 15 dB at any one frequency (Margolis & Saly, 2007). A sensorineural hearing loss was defined as an air-bone gap equal or less than 10 dB whilst mixed hearing loss was described as an air-bone gap of greater than 20 dB (Margolis & Saly, 2007).

Research Staff

The researcher served as the primary data collection person for this study. For data quality assurance purposes and to check reliability of data collected, a fellow Audiology Masters level student examined at least 10% of randomly selected forms that had been completed by the researcher to double check the accuracy, thoroughness and completeness are maintained when capturing the data.

Data collection

Before commencement of the current study, ethical approval was sought from the University of Cape Town, Faculty of Health Sciences Human Research Ethics Committee (HREC REF: 023/2017) (see Appendix D). Institutional approval to conduct the study was granted by the GSH Chief Executive Officer (see Appendix E) and relevant Heads of Departments (see Appendix F). A pilot study was conducted soon after ethical approval and permission from relevant authorities had been granted.

Pilot Study

A pilot study refers to a small preliminary study used to test the sampling strategies, research protocols and data collection tools, before the main study is conducted (Hassan, Schattner, &, Mazza, 2006). It serves to refine a research's aims and objectives; as well as to estimate the amount of resources needed for the main project (Hassan et al., 2006). The pilot study was used to help the researcher to familiarize themselves with the way information was recorded in the patient folders and the contact people to approach in the Audiology and Oncology departments respectively. It was also conducted to identify measurement error sources that could potentially be detrimental to test score interpretations, allow the errors to occur to measure the extent of their effect on the tool, and refine the tool to minimize measurement error (Kimberlin & Winterstein, 2008). The pilot study also assessed the plausibility of the data collection methodology and to ensure the standardization of data

collection procedures by the primary researcher (Cozby & Bates, 2011). It was used to determine the pace which the researcher would take in reviewing the folders and this facilitated the determination of the timeline needed to review all eligible folders for the main study.

For the pilot study, 10 medical folders (i.e. 10% of the annual number of people seen at GSH oncology) were extracted by the medical records personnel and handed over to the researcher who used them to extract data needed for the study and determine how long it would take per patient folder. It was noted that it would take shorter time to extract data directly onto the Excel spreadsheet using the headings from the data extraction sheet. This would help to avoid duplication of effort. It was also noted that, due understaffing in the central medical records department, alternative ways of retrieving data would be required as it took long waiting periods to access files from the department.

The researcher contacted the departments of Radiation Oncology and Audiology respectively to seek permission to directly retrieve information from their records as opposed to the medical records department. Thus, information obtained was as follows:

1. Audiometric information was retrieved from the Audiology department's white cards

2. Chemotherapy information (including the type and dose of drug used) was obtained from the Radiation Oncology department's folders.

Data Collection

In terms of hospital protocol, patients who undergo Cisplatin-based chemotherapy at GSH are referred to the Audiology Clinic for ototoxicity monitoring as the standard of care. Hearing assessments are conducted by a team of qualified audiologists. The hospital protocol requires that patients have baseline audiograms prior to the start of chemotherapy treatment, followed by regular monitoring during the treatment. Patients' hearing thresholds were typically assessed prior to their next chemotherapy cycle on the same day. At the end of chemotherapy treatment, an exit audiogram was determined.

Data collection for the main study commenced soon after the pilot study had been implemented and relevant modifications mentioned above were made to the study protocol. A

list of all patients who underwent chemotherapy treatment and had their hearing status monitored at GSH during 2011-2016 was requested from GSH Audiology department. Audiometric information was retrieved from the Audiology white cards while Chemotherapy information (including the type of drug and dose used) was obtained from the Radiation Oncology department's folders. Each patient's record accessed was assigned a study number and this was kept separate from the list used to request the patients' records. All the patients' records accessed were reviewed and data relevant to the study was copied onto to the data collection form which was in an electronic format (Excel Spreadsheet with headings as those found on Appendix A). Data collection was conducted between March and July 2017.

Data Management

To maintain anonymity and confidentiality, no patient identifying information such as names or identity (ID) numbers were recorded in the data abstraction form. Instead, a unique study number was assigned to each folder that underwent review. The recorded data was secured in a password protected spreadsheet that was only accessible to the researcher and supervisor.

Reliability

Reliability is exhibited when there is consistency and stability in outcomes each time a named methodology is used (Golafshani, 2003). Several forms of reliability were assessed in the current study as described below.

In terms of reliability of audiometric records used in this study, all tests were conducted by a qualified audiologist with at least two years' experience. Furthermore, all assessments were conducted in a sound treated audiometric booth meeting South African National Standards (SANS10083:2004) for audiometric booths (South African National Standards, 2004) and all equipment used to assess the patients was calibrated according to SANS standard (SANS, 2004). Behavioural audiometry is a subjective test that depends on the health status of the patient and the motives behind why they are coming for testing (Gelfand, 2009). To ensure obtained thresholds were reliable, the assessing Audiologist noted the patient's condition

during testing and made a record how reliable the patient was during the assessment. This was recorded in the audiograms that were reviewed. The adapted data collection tool used in this study was successfully used in a previous and comparable study; its validity and reliability were thoroughly assessed in the previous study (Whitehorn et al., 2014).

Inter-rater reliability refers to the consistency of results on a construct when measured by two different assessors (Cozby & Bates, 2011). To assess for inter-rater reliability, the researcher gave the ten randomly selected patient folders to a fellow Masters student who cross checked whether the information in the folders was similar to the information entered onto the Excel spreadsheet. This ensured the maintenance of accuracy and consistency in data capturing. Accuracy has been shown to improve once team members realize that they are under observation, thus reliability increases (Babbie & Mouton, 2007). The fellow student also cross-checked results graded using the grading scales in order to determine if they were accurately and consistently used. To ensure intra-rater reliability, the researcher used 10% of randomly selected forms to compare their data against their respective hospital folders from which data was extracted. A Cohen's score of 0.7 or more denotes acceptable (Cohen, 1960) and therefore the current study's inter-rater reliability was confirmed because it yielded a score of 0.85.

Validity

Validity refers to the integrity of research in measuring what it is intended to measure together with the degree of accuracy when doing so. (Johnson & Danhauer, 2002). Face validity refers to how representative a research project is 'at face value,' and whether it appears to be a good project; whilst content validity refers to an estimate of how much a measure represents every single element of a construct (Cozby & Bates, 2011). The adapted data collection instrument's content and face validity was established in a previous study by having it reviewed by two independent Audiologists with research experience in ototoxicity monitoring (Sibanda & Ramma, 2013) to ensure that it contains all the relevant fields that would enable the researcher to obtain the information needed for analysis and discussion (Kimberlin and Winterstein 2008). The techniques and protocol used for ototoxicity monitoring at GSH, involving conventional audiometry (250 Hz – 8000 Hz) testing, are highly validated and they are currently best practice standards (Vasquez & Mattuci, 2003).

Ethical considerations

Ethical clearance for the current study was sought and granted by the University of Cape Town, Faculty of Health Sciences Human Research Ethics Committee (HREC REF: 023/2017) (see Appendix D). The study was conducted in accordance to the Declaration of Helsinki (World Medical Association, 2013). The declaration's principles assist to maintain the conduct of research with transparency, the respectful and dignified treatment of participants' overall health for the duration of the study; and safe-keeping of participants' data in an integral manner. The study also adhered to the following ethical principles; Autonomy, beneficence, non-maleficence and justice to preserve the integrity of human research (Irving, 2013).

Autonomy

Autonomy is the principle referring to the ability by an individual or institution to deliberately decide about if they would like to become a subject in research (Cozby & Bates, 2011). Since the current study did not involve any direct interaction with the participants, permission to access the cisplatin-based chemotherapy patients' hospital files was requested from and granted by the Hospital CEO and department heads. These personnel granting permissions for the study were therefore regarded as the consenting parties who allowed this study to be conducted and who had the right to withdraw consent of the study.

Beneficence

Beneficence describes how researchers should ensure that the study is conducted in the participants' best interests whilst maintaining maximising on ensuring their well-being (Terre-Blanche et al., 2012; Brink, 1996). There was no direct benefit to patients whose medical records will be reviewed as part of this study. However, the findings of this study will be shared with all the relevant stakeholders at GSH in the form of a presentation. The results will be used by them in improving services for future management of patients during chemotherapy should significant findings be revealed.

Non-maleficence

Non-maleficence is the principle of doing no harm and minimizing risk for harm to persons who participate in research (Jonsen, Siegler and Winslade, 2006; Terre-Blanche, Durrheim, & Painter, 2012). There are no significant risks or harm associated with the current study. Due to the study's descriptive nature, little known, if any, harm that will be caused to the participants. The risk of losing patient folders was minimized by extracting the needed information from them whist within the hospital departments (i.e. Radiation Oncology and Audiology respectively) without removing them.

Confidentiality

Confidentiality refers to the safekeeping of all data gathered during the study and protected from being accessible to any other individual outside of the study (Cozby & Gates, 2011). Confidentiality was highly regarded by the researcher and was strictly guarded. The confidentiality of the medical records of the patients in this study was ensured by making sure that only the researcher had access to the study data, which was kept in a password-secured electronic spreadsheet.

Anonymity

A new study number, consisting of a combination of three letters and three numbers, was allocated. The hospital folder numbers were linked to an allocated study number. Therefore, it is these study numbers that were used from the onset of the study and no recording of the patients' name was done. This ensured privacy of the participant's medical records for the participants to whom the records belonged. The names of the patients to whom the hospital files to be used in this study remained anonymous to everyone else who would handle the data except for the primary researcher. This helped to maintain the greatest degree of privacy possible in this context. No names would be revealed in the instance where data would be used for publication purposes.

Justice

Justice is the act of distributing the burdens or benefits of a society fairly amongst the people involved (Irwin et al, 2007). Distributive justice will ensure that all patient files which meet the eligibility criteria are used in the study. The results for this study would be presented to the Radiation Oncology and Audiology departments respectively so that key outcomes are used to directly benefit patients at GSH which is the institution from which data was collected.

Statistical Data Analysis

R, a statistical environment used for statistical analysis and graphic was used (Team R, 2016) to analyse the data. This program enabled importing data from Microsoft Excel spreadsheet into a database and derive means, averages and frequency statistics Descriptive statistics and inferential statistics were calculated as described below.

Figures graphs and tables were used to summarize, describe and arrange the data into organized visual presentations (Terre-Blanche et al., 2012). The Chi-square test was used to assess for significant associations between two categorical variables (Cozby & Bates, 2011). The Fisher's exact test was also used together with the Chi-square test to fulfil the same objectives because it accurately assesses associations where the sample is small (Cozby & Bates, 2011). A Wilcoxon signed-rank test for paired samples used to determine if two data samples that are matched arise from identical distribution without assuming a normal distribution for the samples. Thus, the test was used to test the null hypothesis that the median of the paired samples is equal. It is usually used for ordered categorical variables where a numerical scale is inappropriate but it is possible to scale the observations (Cozby & Bates, 2011).

Chapter 4: Results

Introduction: This chapter will present the study findings according to its aims and objectives. Findings regarding incidence of Cisplatin-induced ototoxicity, types and effectiveness of different treatment modifications to minimize cisplatin-induced hearing loss will be presented. Finally, the outcome of a comparison of different grading scales will also be presented.

Out of a total of 680 patients' medical folders that were accessed for review, only 128 of those folders met the inclusion criteria for this study. Table 3 below presents a description of patients whose folders were included in this study.

Table 3: Participants' Description (n=128).

Patient characteristics	**n**	**%**
Age (median, range)	43 (18 - 75)	
Sex • Males • Females	92 36	71.9 % 32.1 %
Tumor Type • Squamous cell carcinoma (SCC) • Other tumor types	27 101	21.1 % 78.9 %

History of noise exposure	7	5.5 %
Tinnitus	11	8.6 %
Renal pathology	2	1.56 %
Treatment duration [weeks] median (range)	13.45 (2 – 85)	
Chemotherapy Drug		
Baseline*:		
• Cisplatin	58	90.6 %
• Carboplatin	4	6.25 %
• Unknown	2	3.15 %

*Chemotherapy drug at time after the first (baseline) audiogram was recorded.

Sixty-four (64) out of the 128 eligible participant files had information on the type and dose of chemotherapy drug used. Majority (91%) underwent Cisplatin-based chemotherapy at baseline. At the time of the exit audiogram, the proportion of patients who were on cisplatin chemotherapy was slightly lower (69%) (Table 4).

Table 4: Chemotherapy drug during treatment (n=64).

Chemotherapy Drug	Baseline	Check-up	Exit	Median Cumulative Dose (mg/m²)
Cisplatin	58	59	44	465 mg/m²
Carboplatin	4	5	20	1290 mg/m²
Others (e.g. 5FU)	2	-	-	-

The median single dose for cisplatin remained unchanged while that of carboplatin increased throughout treatment (see figure 2).

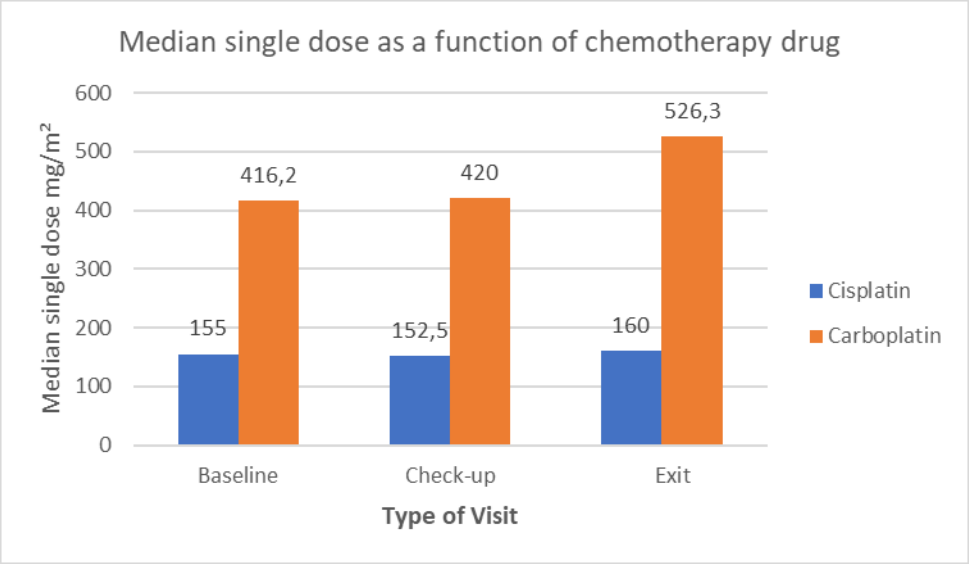

Figure 2: Median Single dose as function of drug throughout treatment: (n =64).

Incidence of significant threshold shift following treatment

Out of 128 folders reviewed, 95 (74.2 %) had a significant hearing threshold shift based on the ASHA (1994) criteria. Table 5 below provides a summary of the patient audiological characteristics.

Table 5: Audiological characteristics of the patients (*n* =128)

Group		Hearing Loss							
		Left ear only		Right ear only		Bilateral		Disabling[3]	
	N	Yes	No	Yes	No	Yes	No	Yes	No
Unknown treatment[1]	64	44	20	38	26	35	29	5	115
Known treatment[2]	64	40	24	41	23	33	31	8	
Total	128	84	44	79	49	68	60	13	115

[1]Unknown treatment = folders with no information on chemotherapy drug, dose and treatment modification
[2]Known treatment = folders with chemotherapy drug, dose and treatment modification information
[3]Disabling hearing loss = a hearing threshold with a pure tone average of 41 – 80dB HL in the better hearing ear for adults, and a pure tone average of 31 – 80dB HL in the better ear for children (WHO, 2014).

The CTCAE v4 also recorded incidence of hearing loss and severity of loss. According to the CTCAE v4 criteria, incidence of hearing loss was 53.9% and the distribution of severity is shown in figure 3 below. Hearing loss grade 3 & 4 typically requires further audiological intervention or rehabilitation (Crundwell et al., 2016).

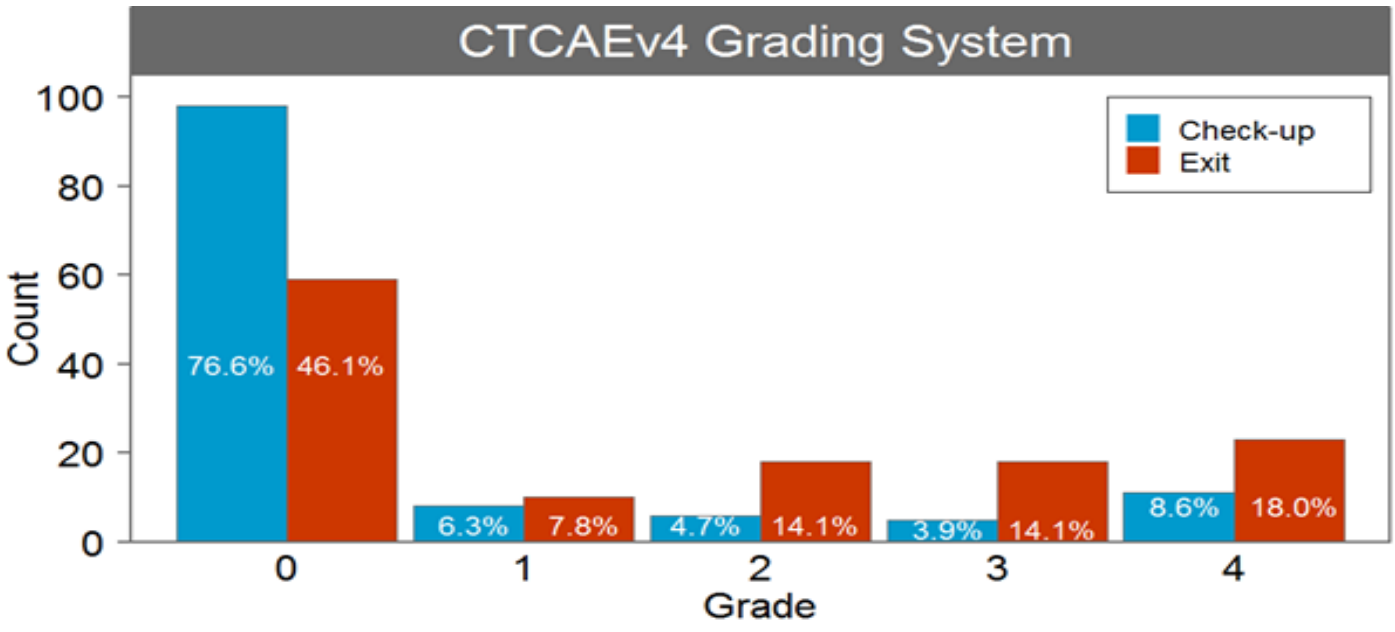

Figure 3: Incidence and severity of hearing loss (n=128) based on the CTCAE v4 criteria

The Wilcoxon signed-rank test for paired samples was used to determine whether there was a statistically significant difference in distribution of severity of hearing loss at check-up

and exist stages respectively. The analysis showed that the distribution of the hearing loss severity during the check-up and exit stages were different ($p = 0.00000000039$, $p<0.05$).

To determine the association between cumulative dose and hearing loss, data from 32 patients who were on Cisplatin-only chemotherapy were used. The median cumulative dose in this group of patients was 465 mg/m². Cumulative dose refers to the total quantity of medication given over a given period; which is over three cycles in the current study. Cumulative dose data was split into three categorical ranges according to statistical distribution; <400 mg/m^2, 400-500 mg/m^2 and >500 mg/m^2. Due to small numbers, the Fisher exact test was used for analysis. The Fisher exact test reveal no statistically significant association between cumulative dose and hearing thresholds ($p=0.186$, $p<0.05$)

The Chi-square test for independence and Fisher exact test were used to determine whether there was association between the age of patients and hearing loss. Patient's ages were divided into three categories; 18-35 years old, 36-60 years old and over 60 years old. The results revealed no association between the two (Chi-square: $X^2= 1.87$; df = 3; $p=0.599$ ($p<0.05$); Fisher exact: $p = 0.602$ ($p<0.05$). Both the Chi-square and Fisher exact tests were also used to determine whether there was an association between duration of treatment and hearing loss. The duration of the treatment was grouped to 0 – 3 months and over 3 months. The analysis showed that there were no association between the two (Chi-square: X2=; df; $p= 0.299$ ($p<0.05$); Fisher exact: $p = 0.292$ ($p<0.05$)

Treatment modification strategies at GSH

Out of the 128 folders reviewed, only 64 had information of treatment dose and modification strategies respectively. Figure 4 below provides a summary of proportions of patients under each modification category.

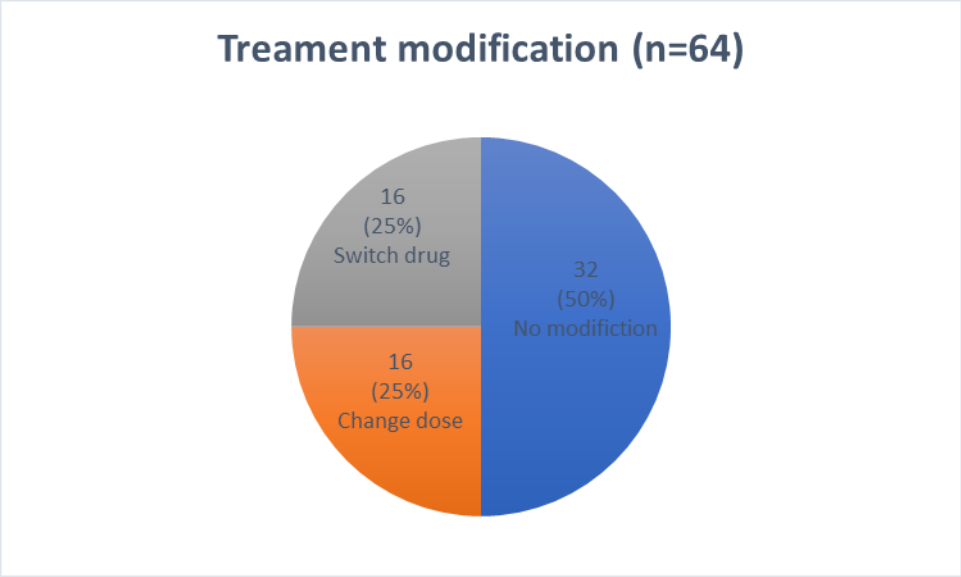

Figure 4: Distribution of patients according to chemotherapy treatment modification (n = 64).

Comparison of efficacy of common treatment modification strategies

The distributions of ototoxicity incidence and severity according to the different treatment modifications at the end of treatment are presented on Table 6. The CTCAEv4 criteria was used to grade presence and severity of hearing loss. The Chi-square test showed that there is no significant association between treatment modifications and incidence of hearing loss as classified by the CTCAEv4 grading criteria (see Table 6)

Table 6: Distribution of ototoxicity severity by treatment modification as assessed by the CTCAE grading criteria at the end of treatment.

Grading System	Treatment Modification	n	Grade 0 (%)	Grade 1 (%)	Grade 2 (%)	Grade 3 (%)	Grade 4 (%)
CTCAEv4	No change	32	43.8	9.38	9.38	18.8	18.8

Adjusted dose	16	50.0	6.25	6.25	12.5	25.0
Switched drug	16	25.0	-	18.8	31.3	25.0

Chi-Square test ($X^2 = 2.33$, df = 2, p = 0.31, p <0.05).

Comparison between CTCAE v4 and TUNE grading criteria.

Two scales used for grading the severity of cisplatin-induced hearing loss in adults; CTCAEv4 and TUNE criteria were compared with respect to their ability to identify patients who developed hearing loss following cisplatin chemotherapy (i.e. incidence of hearing loss). Comparisons were also made with respect to the ability of each scale to identify individuals who are candidates for further audiological rehabilitation. Incidence of hearing loss was higher when using CTCAEv4 (53.9%, see figure 3 above) when compared to the TUNE (41.7%, see figure5 below)

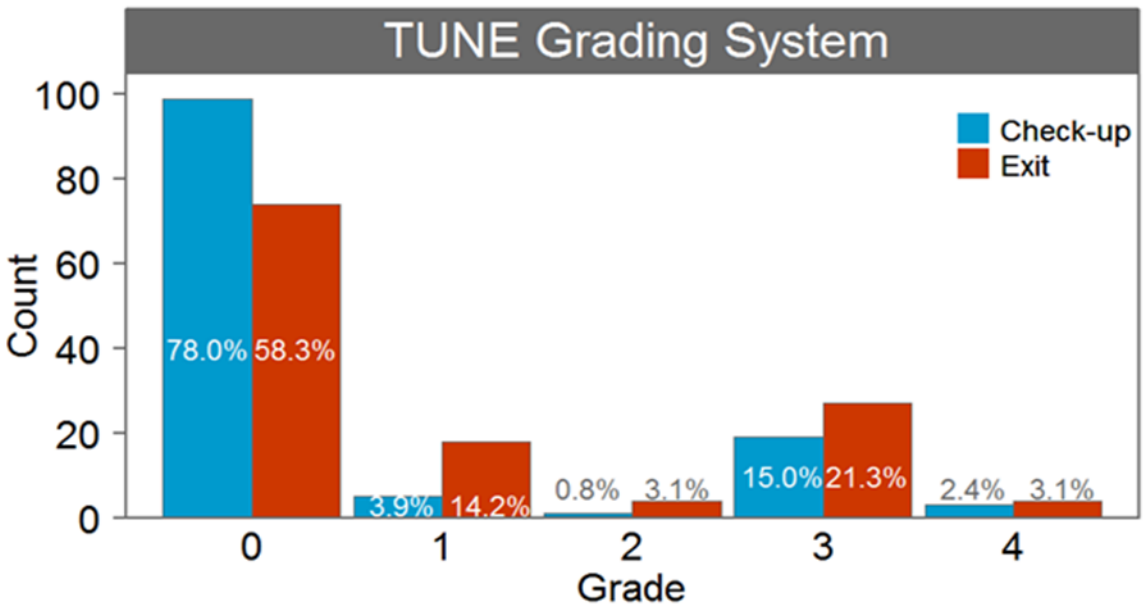

Figure 5: Incidence of hearing loss according to the TUNE criteria

The CTCAEv4 also showed more (41) patients who developed grade 3 or worse hearing loss following treatment when compared to the TUNE criteria (32). In both grading systems, hearing loss grade 3 and 4 typically require further audiological rehabilitation.

Chapter 5: Discussion and Conclusion

***I**ntroduction:* This chapter will present a discussion of the findings of the current study relative to existing research literature on the topic. The chapter will also consider the strengths and limitations of this study, implications of its findings as well as recommendations for future research. Finally, a conclusion emanating from the study findings will be presented.

This study set out to determine the efficacy of strategies used to prevent or minimize Cisplatin-induced hearing loss in chemotherapy patients seen jointly by the departments of Oncology and Audiology Outpatients at GSH between years 2011 and 2016. Overall, the findings of the study indicated that despite a variety of treatment modifications being implemented when a change in patient's hearing threshold is detected, many patients continue to experience a significant deterioration in their hearing thresholds following treatment with Cisplatin. This has led to a high incidence of hearing loss (74.2 %) in this cohort of patients. Overall, severity of hearing loss was significantly worse at the exit stage than the follow-up stage (Wilcoxon signed-rank test for paired samples, $p = 0.00000000039$, $p<0.05$) thus indicating that patients' hearing thresholds continue to deteriorate despite the treatment modifications. Several studies have reported that progression of hearing loss is part of the pattern that is commonly observed and reported for Cisplatin ototoxicity (Paken et al, 2016; Rybak et al., 2009; Rybak et al., 2007).

There were three common strategies that were implemented by the Radiation Oncology department and Groote Schuur Hospital when a patient's hearing thresholds showed signs of deterioration; change (adjust) the drug dosage, switch the patient to a less ototoxic drug and no modification (i.e. continue with the original treatment plan). These strategies have been cited in previous studies (Chauhan et al., 2011). The Chi-square test showed that there was no statistically significant association between treatment modifications and incidence of hearing loss ($p = 0.31$, $p <0.05$). This was an unexpected finding in this study because one of the premises upon which audiological monitoring of ototoxicity in patients who are treated with ototoxic medications is the assumption that further deterioration of patient's thresholds can be

minimized or prevented if an appropriate intervention is implemented (Chauhan et al., 2011; ASHA, 1994).

The findings of this study showed that there was a high incidence of hearing loss in patients whose Cisplatin dose was adjusted (reduced). Similar findings were reported by Peleva et. al (2014) who also reported that incidence of hearing loss increased from 76% to 83 % at post follow up monitoring despite dose reductions in a sub-group of 63 out of a total 306 cancer patients who were treated with Cisplatin or Carboplatin chemotherapy. Lafay-Cousin et al (2013) also reported 25% incidence of ototoxicity even after dose reduction was implemented. Knight et al. (2007) reported occurrence of ototoxicity in all 10 Cisplatin-chemotherapy patients in their study despite dose reductions being implemented as a strategy to prevent further deterioration of hearing loss. While it seems intuitive that a reduction in drug dose must lead to less incidence of Cisplatin-induced hearing loss, none of the studies reviewed thus far (; Knight et al., 2007; Lafay-Cousin et al., 2013; Peleva et al., 2014) seem to support that. However, a possible explanation for the lack of effectiveness of this intervention strategy could be due to lack of early warning signs in deterioration of patient's hearing thresholds. For example, in this study and all other studies reviewed which reported implementing dose reduction to prevent further deterioration of hearing loss (Knight et al., 2007; Lafay-Cousin et al., 2013; Neuwelt et al., 2005; Peleva et al. 2014) used conventional audiometry (250-8000 Hz) as the primary method to monitor patients' hearing status. This test protocol is only sensitive to ototoxic changes below or equal to 8 KHz (Chauhan et al. 2011), which means that changes in patients' hearing thresholds were only detected after it has started affecting frequencies that are useful for speech perception. It is highly likely that all the studies that reported that this strategy was not effective was mainly because changes in patients' hearing thresholds were detected too late and therefore any intervention that was implemented at that stage was less likely to succeed. It should also be noted that all the studies reviewed that reported the ineffectiveness of this (dose reduction) intervention were conducted on paediatric population and could therefore be reflecting a ceiling effect (Cozby & Bates, 2011) due to the reflected homogeneity in age group. Studies showing dose reductions in adult populations could not be found and therefore further research is needed which looks at this type of treatment modification in adults

Another strategy that was implemented to minimize further deterioration of patient's hearing thresholds during Cisplatin-based chemotherapy at GSH oncology department was to switch the patient from cisplatin to carboplatin. Carboplatin is known to be less ototoxic than Cisplatin (Langer et al., 2013). However, just like the preceding intervention (i.e. dose reduction) switching the patient from Cisplatin to Carboplatin did not lead to prevention of further deterioration of patient's hearing threshold. Patients who were managed using this strategy showed the highest incidence of ototoxicity when compared to patients who were managed using the other two treatment modifications. Comparable results have been reported in previous studies in which using a combination of Cisplatin and Carboplatin was shown to lead to greater incidence of ototoxicity than using Cisplatin only. For instance, in a study by Knight et al, (2007) the number of patients who developed ototoxicity was almost similar for those in the Cisplatin and Cisplatin-Carboplatin groups respectively. In a study by Neuwelt et al. (2005), 84 % (16/19) of patients who switched from Cisplatin to Carboplatin developed ototoxicity. Furthermore, of the 17 patients requiring hearing aids, 8 of them received a combined Cisplatin-Carboplatin regimen. However, it should be noted that Carboplatin was used as myeloablative therapy during bone marrow transplant procedures post chemotherapy in this study. A study by Bertolini et al (2014) also reported that Cisplatin-Carboplatin group had more patients (43 %) developing ototoxicity than Cisplatin only (37%) group; and more combination (Cisplatin-Carboplatin) chemotherapy patients developed more severe degrees of than the Cisplatin only group. Therefore; based on the studies reviewed thus far and the findings of this study, there appear to be a synergistic effect between cisplatin and carboplatin therapy which increases the risk of hearing loss during chemotherapy as evidenced by the high incidence of hearing loss in that group; and causes more severe hearing loss when compared to other treatment modification groups.

There are several reasons that can potentially be used to explain the high incidence of hearing loss in this group of patients. Patients who are switched from Cisplatin to Carboplatin are likely to be patients who are already showing susceptibility to ototoxicity which means that they are the likely to be the type of patients who will lose their hearing regardless of the ototoxic drug used. Therefore, switching them from Cisplatin to Carboplatin which is also ototoxic is less likely to be effective. Furthermore, it has also been established by several studies that simultaneous use of ototoxic medication is a risk factor on its own (Paken et al., 2016; Langer et al., 2013). Therefore, introducing Carboplatin to a patient who has just been treated with

cisplatin is less likely going to reduce risk to ototoxicity, but conversely further increase their risk of developing hearing loss.

The last strategy implemented was to continue with the original treatment plan (i.e. no treatment modification. For patients whom this strategy was implemented, the trend was of an increase in proportions of patients with ototoxicity from follow-up to exit which is like results from previous studies that had cisplatin only as seen in studies reviewed in the literature review with Cisplatin-only regimens (Whitehorn et al., 2014; Arora et al., 2009; Strumberg et al., 2002; Bokemeyer et al., 1998). However, an unexpected finding from this study was that incidence of ototoxicity in patients who were managed using this strategy was very similar to incidence of ototoxicity from patients who were managed using the other two strategies. One would have expected that more patients who were managed using this strategy will experience a significant deterioration in hearing thresholds when compared to patients in the other two strategies. However, that was not the case. A possible explanation for this finding could be that patients who were managed using this strategy were those who showed better tolerance to Cisplatin chemotherapy (i.e. initially showed less deterioration in hearing thresholds) and therefore were not prioritized for other strategies. This could probably mean that these patients could potentially have biological factors (e.g. genetic markers) that mitigate against the effects of Cisplatin. Some gene alleles, like GSTM3*B have been found to protect against on Cisplatin ototoxicity (Peters et al., 2000).

Nearly three quarters of patients whose records were reviewed for this study developed hearing loss despite various interventions used to prevent further deterioration of hearing loss. Results from the previous and current study respectively suggest that conventional audiometry the primary methods that was used for ototoxicity monitoring of these patients) is not sensitive to cisplatin-induced hearing loss and is thus ineffective in early identification ototoxicity (Chauhan et al., 2011). This could potentially be the reasons why all the treatment modification strategies that were implemented at Groote Schuur radiation oncology department were not effective because they likely to have been implemented only after treatment has caused significant damage to the cochlear. Therefore, protocols that include tests that are sensitive to early changes in hearing sensitivity are required DPOAEs, and extended high frequency (EHF)

pure tone audiometry up to 20 kHz have both been shown to be the most sensitive audiological tests for early detection of hearing loss. DPOAEs would be useful in the chemotherapy population where patients are often sick during treatment and where subjective results will mostly be flawed especially for subjective assessments (Chauhan et al., 2011). Both tests take a short time of up to ten minutes to administer, provide frequency specific information and they are non-invasive (Knight et al., 2007). Chauhan et al (2011) found that EHF can detect ototoxicity before it has become bilateral, which would be an ideal time to introduce effective treatment modifications.

Incidence of ototoxicity in this study was found to be 74.2 % (95/128). This is slightly higher than the incidence reported by a similar study (Whitehorn et al, 2014) which was conducted in patients with relatively the same demographic profile. This was not unexpected because incidence of cisplatin-induced ototoxicity tends to vary extensively across different studies (Dutta et al., 2015; Nitz et al., 2013; Strumberg et al., 2002). In these studies, incidence of HL reported ranged from 12% (Dutta et al., 2015) to 100% (Arora et al., 2009). There are various reasons which can be used to explain variation in reported incidence across the different studies. One of the factors could be sample size; Studies with smaller sample sizes generally reported higher incidences of ototoxicity ((Dell'Aringa et al., 2009; Strumberg et al (2002). Another significant factor that can influence the magnitude of the incidence reported is the dosage that patients were administered. For instance, most of the participants in the current study received a higher cumulative Cisplatin dose (427.7mg/m^2) and therefore a resultant higher incidence of ototoxicity than the Whitehorn study (236.8mg/ m^2). Cumulative dose of greater than 400 mg/ m^2 has been shown to have statistically significant associations with increased risk and resultant high incidence of ototoxicity (Sheth et al., 2017). However, high incidence of ototoxicity has also been found with lower doses (Dell'Aringa et al., 2009) which means that cumulative dose alone cannot explain the observed variation.

Homogeneity versus heterogeneity of the cancer types in studies is another possible explanation for the observed variation (Paken et al., 2016). In the Whitehorn et al (2014) study, patients had various cancer types including reproductive, head and neck cancer and lymphoma. Patients for head and neck cancer developed ototoxicity faster than patients with other cancer types. However, this could have also been because the head and neck patients also received

cranial irradiation as part of their treatment regimen; and were thus at a higher risk than patients without cranial irradiation. Cranial irradiation increases patients' risk of developing ototoxicity (Malgonde et al., 2015) and thus patients receiving radiation were excluded from this study as they would have compounded results. Peleva and colleagues (2014) showed that medulloblastoma and Wilms tumour patients produced significantly different risk for ototoxicity than any other tumour types ($p=001$, $p<0.05$ for both tumour types). However, risk could have been because the sample consisted of paediatric patients although age was not significantly correlated to risk for ototoxicity (Peleva et al., 2014). Different tumours sometimes have different dosing schedules (Rybak et al., 2009) and a study by Yancey et al, 2012 reported that patients treated for germ cell tumours, associated with 5 daily infusions of 20 mg/m^2, were found to have significantly less ototoxicity than neuroblastoma patients who received 100-120 mg/m^2 daily doses.

It was also found in this study that there were no significant associations between hearing loss and several factors which were investigated. Age (Paken et al., 2016; Yasui et al.,2014 Rademaker-Lakhai et al. 2006), and cumulative dose (Frisina et al, 2016; Yancey et al., 2012; Schellak & Naude, 2013) have previously been reported to be risk factors for developing ototoxicity and thus were anticipated to be statistically associated with hearing loss. This study also found no association between duration of treatment which has previously been found in previous studies (Kushner et al., 2006; Neuwelt et al., 2005). These reported findings can be explained by the sample size of this study. Whilst 128 participants met the inclusion criteria of having three monitoring audiograms and satisfied the criteria needed to ensure that the study had enough power of inferential statistics to yield significant results; only 64 of them had information on the type of treatment received. This made this group with treatment information underpowered to yield any statistically significant results because for power of 80 % to be achieved, 82 participants with dose information would have been required for associations to be statistically significant. Larger samples increase the chance of finding a significant difference because they have greater power to do so (Cozby and Bates, 2011).

The final objective of this study was to compare two adult ototoxicity grading criteria; CTCAE v4 and TUNE in terms of early detection of deterioration in hearing thresholds during cisplatin-chemotherapy treatment and their ability to guide recommendations regarding hearing amplification. Results from this study showed that the CTCAE v4 criteria (53.9 %)

detected more people with deterioration in hearing thresholds when compared to the TUNE criteria (41.7 %). This was an unexpected result considering that the TUNE scale is an improvement of the CTCAEv4 and ASHA criteria combined (Theunissen eta al, 2014). A possible explanation for observed results is that TUNE criteria was created to incorporate the effects of both ultra-high-frequency hearing loss on daily listening situations in addition to the frequency regions involved in speech intelligibility and sound quality; and it also considers subjective patient symptoms in grading ototoxicity which the CTCAEv4 criteria does not (Crundwell et al., 2016). Thus, in the absence of high frequency information and subjective symptoms, grade 1a and 2a of the TUNE scale could not be determined. This means that the number of patients who were identified with deterioration in their hearing thresholds using the TUNE criteria was possible an underestimation of the number that could have been obtained had the ultra-high frequency information been available. However, the absence of ultrahigh frequency information did not impact negatively on higher grades of hearing loss when using the TUNE grade.

Finally, a good ototoxicity grading system or criteria should accurately identify and quantify disabling hearing loss for which audiological rehabilitation, including hearing amplification, is recommended. Therefore, the two grading criteria were also compared on their ability to guide decision making regarding recommendation for amplification. According to the World Health Organisation (WHO), a disabling hearing loss is defined as a hearing threshold with a pure tone average of 41 – 80dB HL in the better hearing ear for adults, and a pure tone average of 31 – 80dB HL in the better ear for children (WHO, 2001). This criterion is like the one used clinically by audiologists (Gelfand, 2009), which recommends that patients with disabling hearing loss be fitted with hearing amplification. In comparison, both CTCAE and TUNE criteria recommends that all people with grade 3 and 4 hearing loss be recommended for hearing amplification. Therefore, according to the WHO criteria, 13 patients in this study would have been identified to have disabling impairment and recommended for amplification. However, in comparison, the CTCAEv4 found 41 people with disabling impairment whilst TUNE scale identified 32 people. This suggests that both scales reviewed here tend to overestimate the number of people in need of hearing amplification, but the TUNE was closer the correct number in need of amplification than the CTCAEv4 criteria. The TUNE scale incorporates an appraisal of patients' speech intelligibility post treatment in daily-life situations (Crundwelll et al., 2016) Therefore, because of this qualitative component in addition

to severity of loss, the TUNE criteria is better suited to predict which patients with a severity of loss need hearing amplification. It is also important to bear in mind that candidacy for hearing amplification is hardly ever made solely based on pure tone averages information alone (Gelfand, 2009). However, pure tone average is usually a starting point in determining who specifically requires amplification and who does not; and who needs other forms of aural rehabilitation such as assertive training or speechreading.

Study Limitations

The findings of the current study should be interpreted considering its methodological limitations; study design (i.e. this was a retrospective record review, no ultra-high frequency audiometry data and no audiological follow-up of patients post chemotherapy. This study was retrospective in nature. The drawbacks to this study design include; its inability to establish cause and effect, reliance on how accurate the written records are and the difficulty in controlling for bias because there is no implementation of blinding and randomization (Hess, 2004). Also, the study might be rendered ineffective if pertinent information is missing in the files and if institutional regulations control the amount of information which the researcher can get access to (Hess, 2004). Only 128 of 680 files reviewed in this study met the inclusion criteria. This impacted on the sample size and resultantly the power of the study which enabled significant associations to be made. Majority of patients were excluded due to incomplete data and this affected the conduction of sub-analysis such as establishing associations of previous noise exposure or renal failure to the incidence of ototoxicity; risk factors that have been illustrated in many papers (Whitehorn et al., 2014).

Collection of data by one person could bring about various individual biases such as recall bias (Yancey et al., 2012). However, this was addressed in the current study by having a fellow student to randomly select any ten files and check for test-retest reliability.

Conventional audiometry was used to monitor patients. This is known to be ineffective and this could have led to modification strategies being implemented only after treatment has caused significant damage to audition. Use of conventional audiometry also limited the extent to which the TUNE criteria could be used to determine incidence of ototoxicity in this study. The TUNE criteria is able to determine the presence hearing loss in the extended high frequency range because its grades 1a and 2a include detection of hearing loss in this range (Crundwell et al, 2016).

Lack of long-term and follow-up audiologic data meant that the current study could not assess for changes in incidence and progression of ototoxicity post treatment. Arora et al (2009) reported that majority of their patients developed ototoxicity one-month post treatment, Bertolini et al (2014) showed progression of up to 136 months post treatment and Fausti et al (2005) found that progression and increase in incidence of loss increased with increasing follow-up time from 25 % of patients with dose reduction up to 76%. This highlighted the importance of long term follow-up with suggestions for long term follow periods of up to ten years (Yasui et al., 2014).

Despite its limitations, this is one of the studies in South Africa that sought out to investigates the effectiveness of current measures being used to ensure that patients' hearing is minimally affected when they go through chemotherapy with Cisplatin. Namely it has revealed that conventional audiometric monitoring for ototoxicity, although widely and commonly implemented, causes delays in identification of patients who are at risk of developing significant hearing loss; and this makes the resultant treatment modifications ineffective. Furthermore, it showed that the CTCAEv4 criteria gave higher incidence of ototoxicity than the TUNE criteria; but the TUNE criteria gave better therapy predictions for ototoxicity. This finding added to the current body of knowledge regarding the need for consensus on a common ototoxicity grading criterion that will be used by different health professionals and thus ensure multi-disciplinary collaboration should a patient be identified as being at risk of hearing loss.

Chapter 6: Conclusions, Implications and Recommendations for future research

The findings of this study revealed that none of the current strategies implemented at GSH Radiation Oncology department were effective in preventing or minimizing further deterioration of patients' hearing thresholds during cisplatin chemotherapy. This finding could potentially be since the tests conventional audiometry (250 – 8000 Hz) used for monitoring the hearing thresholds of these patients was not sensitive to early deterioration of hearing loss. This may have impacted negatively on the treatment modifications which were therefore rendered ineffective once hearing loss has progressed to the conventional frequencies. As a result, almost three quarters (74.2%) of patients whose medical folders were reviewed for this study developed hearing loss following cisplatin chemotherapy.

The incidence of cisplatin-induced hearing loss reported in this study was higher than that has been previously reported in most of the reviewed studies. The following patient and treatment factors; age, gender, cumulative dose and treatment duration, which have been reported as risk factors for ototoxicity in previous studies, were not found to be associated with hearing loss in this study. Cumulative dose is a risk factor for developing cisplatin-induced hearing loss therefore it was expected that similar findings will be found in this study. However, this finding may be due to small sample size of this study.

The CTCAE v4 criteria identified more patients with a significant deterioration in hearing thresholds when compared to the TUNE criteria. The CTCAE v4 criteria revealed higher proportions of patients with need for further audiological intervention (i.e. grade 3 or worse hearing loss) than the TUNE scale. However, these results indicate that the TUNE criteria is better suited for making recommendations of the proportion of people who are eligible for hearing amplification. It can therefore be concluded that both grading criteria/scale have their own merits and demerits. The discrepancies between different scales emphasises the need for a common scale between different health professionals which will not only quantify hearing loss in terms of type and grade, but also include patient complaints highlighting how loss functionally impacts patients (Schultz et al., 2009).

Implications and Recommendations for Future Research

The current study highlighted the high incidence of hearing loss in patients who undergo cisplatin-based chemotherapy. It has also revealed the lack of evidence that underlie the rationale behind implementing treatment modifications that are currently being implemented at GSH when patient's hearing thresholds decline during treatment. This is one of the few studies in South Africa which has overtly documented and assessed the efficacy of preventive strategies for ototoxicity conducted in during chemotherapy, revealing that current strategies are proving unsuccessful. Further research is therefore recommended to investigate the rationale behind the treatment modifications chosen in the clinical settings when ototoxicity develops as well as to try to document the effectiveness of different treatment modifications and or intervention strategies. More research should also be conducted to further investigate on the diverse risk factors associated with the incidence of ototoxicity within the South African context.

Results from the current study could be used to advocate for more effective and sensitive ototoxicity monitoring protocols for early detection of hearing loss in patients during cisplatin chemotherapy treatment. There is a need to, make use more sensitive test protocols such as extended high frequency (EHF) audiometry (9-16 kHz) and DPOAE measure to monitor patient's hearing thresholds (Ress et al., 1999). EHF should be incorporated into the monitoring protocol because it is the most highly efficacious early identification audiometric test (Paken et al., 2016). Both these tests have been documented to be sufficiently sensitive to early changes in patients' hearing thresholds before speech frequencies are affected (Ress et al., 1999).

Furthermore, considering that treatment modifications used in this study were not effective with regards to protecting patients from developing hearing loss, there is need for a multi-modal approach to providing effective protection from hearing loss during cisplatin chemotherapy. Recently, there has been an increase in the number of clinical trial studies investigating the efficacy of otoprotectors to reduce ototoxicity in patients (Schultz et al., 2009). Oto-protectors are chemical agents that have been discovered and continue to be developed in clinical trials to effectively combat the toxic effects of Cisplatin and therefore minimise as well as prevent ototoxicity, without depleting the anti-tumour agent's efficacy

(Rybak, 2007). There are two main types of otoprotectors namely endogenous mechanisms and exogenous molecules respectively. Endogenous mechanisms work by eliminating cisplatin-induced oxidative stress whilst exogenous compounds ensure the prevention of hair cell death (Berg et al., 2006; and both also maintain glutathione levels and thereby reduce free radicals from forming (Paken et al., 2016). They include anti-oxidants which prevent cell death initiation through upstream protection of the cochlea (Rybak, 2006). Sodium thiosulfate, N-acetylcysteine and Amifostine are amongst these antioxidants and they act as scavengers for free radicals because they are highly electrophilic (Rybak & Whitworth, 2005). More research studies are needed to document the effectiveness of these agents with respect to protecting patients from the hearing loss resulting from cisplatin chemotherapy.

More studies are also required to validate the TUNE grading criteria for ototoxicity. The TUNE criteria are a fine-tuned version of the ASHA and CTCAEv4 combined (Crundwell et al., 2016). The criteria include information on EHF when determining the incidence of ototoxicity and it has a potential to make accurate predictions of the need for amplifications (Theunissen et al., 2014). This will facilitate better communication regarding ototoxicity management across health professionals.

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Appendix A: Data collection sheet

Study Number:
Folder Number:
Sex (M/F):
Date of Birth:
Previous History of Noise Exposure
History of Renal Function (Y/N)
Other Ototoxic drug exposure and period (Y/N):
Tinnitus
Vestibular Pathologies
Treatment Modification
Dates of Follow-up Appointments:

		FREQUENCY (Hz)															
Date	**Audiogram Number**	**500Hz**		**1000**		**2000**		**3000**		**4000**		**6000**		**8000**		**16000**	
		L	**R**	**L**	**R**	**L**	**R**	**L**	**R**	**L**	**R**	**L**	**R**	**L**	**R**	**L**	**R**

	1																
	2																
	3																

Appendix B: Letter for Permission to Conduct Research

Division of Communication Science and Disorders

School of Health and Rehabilitation Sciences

Faculty of Health Sciences

F45 Old Main Building

Groote Schuur Hospital

Telephone: (021) 406 – 6401

Fax: (021) 406 – 6323

Email: Lebogang.Ramma@uct.ac.za

Dear _____

Good day.

My name is Zenzo Chakara and I am a researcher from the University of Cape Town. I am currently conducting a research study as part of my MSc in Audiology project, investigating the effect of cancer treatment on hearing as well as establishing what preventative methods are being utilised to minimise this effect amongst patients. I therefore request permission to conduct this research at your hospital.

The first part of this study is aimed at determining the proportion of cisplatin-based chemotherapy patients seen at the audiology department who developed hearing loss. Another part of the research is the determination of the efficacy of preventative measures used to prevent and minimise cisplatin induced ototoxicity in patients. This will help close the current knowledge gap on the subject and will help in improving the quality of life for the population under investigation.

I therefore plan to review medical folders of patients who underwent cisplatin based chemotherapy. The folders which will be reviewed will be of those patients who had their hearing tested at the Audiology department in your hospital during the time period of 2011 through to 2016 whilst receiving chemotherapy in the Radiation Oncology Department.

An appropriate level of ethical conduct will be upheld in the current study as guided by the World Medical Association Declaration of Helsinki, 2013. Autonomy, beneficence, non-maleficence and justice are chief amongst the ethical principles and will therefore be observed accordingly in this study. Only the researcher will know of the personal details of involved participant and all efforts will be made to keep their information as confidential as possible. The UCT FHS Human Research Ethics Committee can be contacted on 021 406 6338 in case participants have any questions regarding their rights and welfare as research subjects on the study A summary of findings, implications and recommendations will be presented to you as feedback upon completion of the study.

If you have any queries or concerns regarding this study, please feel free to contact myself or my supervisors at the numbers provided below:

Yours faithfully

1. Zenzo Chakara -Student (081 476 7533)
2. A/Prof Lebogang Ramma - Supervisor (021) 406-6954 and 073 153 3803

Appendix C: Informed Consent Sheet

Informed Consent Sheet

Department of Communication Sciences and Disorders: Health and Rehabilitation at the University of Cape Town

The Efficacy of Strategies Used to Minimise and Prevent Cisplatin Ototoxicity in Patients

I agree to participate in this study. I understand that the information I will provide will remain anonymous and that Groote Schuur patients' identities will not be disclosed. I understand that participation is voluntary and that I may withdraw from the study at any time without any penalties. I am over the age of 18 years old and am legally able to provide consent.

HREC reference number

_____ _____

Signature of participant Date

Appendix D: Faculty of Health Sciences Ethics Approval Letter

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room E3-46 Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6492
Email: sumayah.ariefdien@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

16 January 2017

HREC REF: 023/2017

A/Prof L Ramma
Division of Audiology
Health & Rehab Sciences
F-45-OMB

Dear A/Prof Ramma

PROJECT TITLE: THE EFFICACY OF STRATEGIES USED TO MINIMISE AND PREVENT CISPLATIN OTOTOXICITY IN PATIENTS (MSc candidate- Zenzo Chakara)

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee for review.

Before formal approval, please address or respond to the following issues:

1. Please fully ethically and scientifically justify the inclusion of race as a variable for this research. Please inform the HREC how race will appropriately be defined in this retrospective folder review.

Please note that no research may occur without formal written HREC approval.

Please quote the HREC reference number in all your correspondence.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE

Appendix E: Groote Schuur Hospital Approval Letter

Western Cape Government
Health

GROOTE SCHUUR HOSPITAL
Enquiries: Dr Bernadette Eick
E-mail : Bernadette.Eick@westerncape.gov.za

Associate Professor L. Ramma
Division of Audiology

E-mail: Lebogang.Ramma@uct.ac.za /CHKZEN001@myuct.as.za

Dear Associate Professor Ramma,

RESEARCH PROJECT: The Efficacy Of Strategies Used To Minimise And Prevent Cisplatin Ototoxicity In Patients (Msc Candidate Zenzo Chakara)

Your recent letter to the hospital refers.

You are hereby granted permission to proceed with your research subject to the approval or Ms Sharon Pithey and Professor Jeannette Parkes, which is valid until **30 January 2018.**

Please note the following:

a) Your research may not interfere with normal patient care.
b) Hospital staff may not be asked to assist with the research.
c) No additional costs to the hospital should be incurred i.e. Lab, consumables or stationary.
d) **No patient folders may be removed from the premises or be inaccessible.**
e) Please provide the research assistant/field worker with a copy of this letter as verification of approval.
f) Confidentiality must be maintained at all times.
g) Should you at any time require photographs of your subjects, please obtain the necessary indemnity forms from our Public Relations Office (E45 OMB or ext. 2187/2188).
h) Should you require additional research time beyond the stipulated expiry date, please apply for an extension.
i) Please discuss the study with the HOD before commencing.
j) Please introduce yourself to the person in charge of an area before commencing.
k) On completion of your research, please forward any recommendations/findings that can be beneficial to use to take further action that may inform redevelopment of future policy / review guidelines.
l) Kindly submit a copy of the publication or report to this office on completion of the research.

I would like to wish you every success with the project.

Yours sincerely

Signed by Mr L. Naidoo

DR BERNADETTE EICK
CHIEF OPERATIONAL OFFICER
Date: 2 March 2017

C.C. Mr L. Naidoo, Ms S. Pithey, Professor J. Parkes

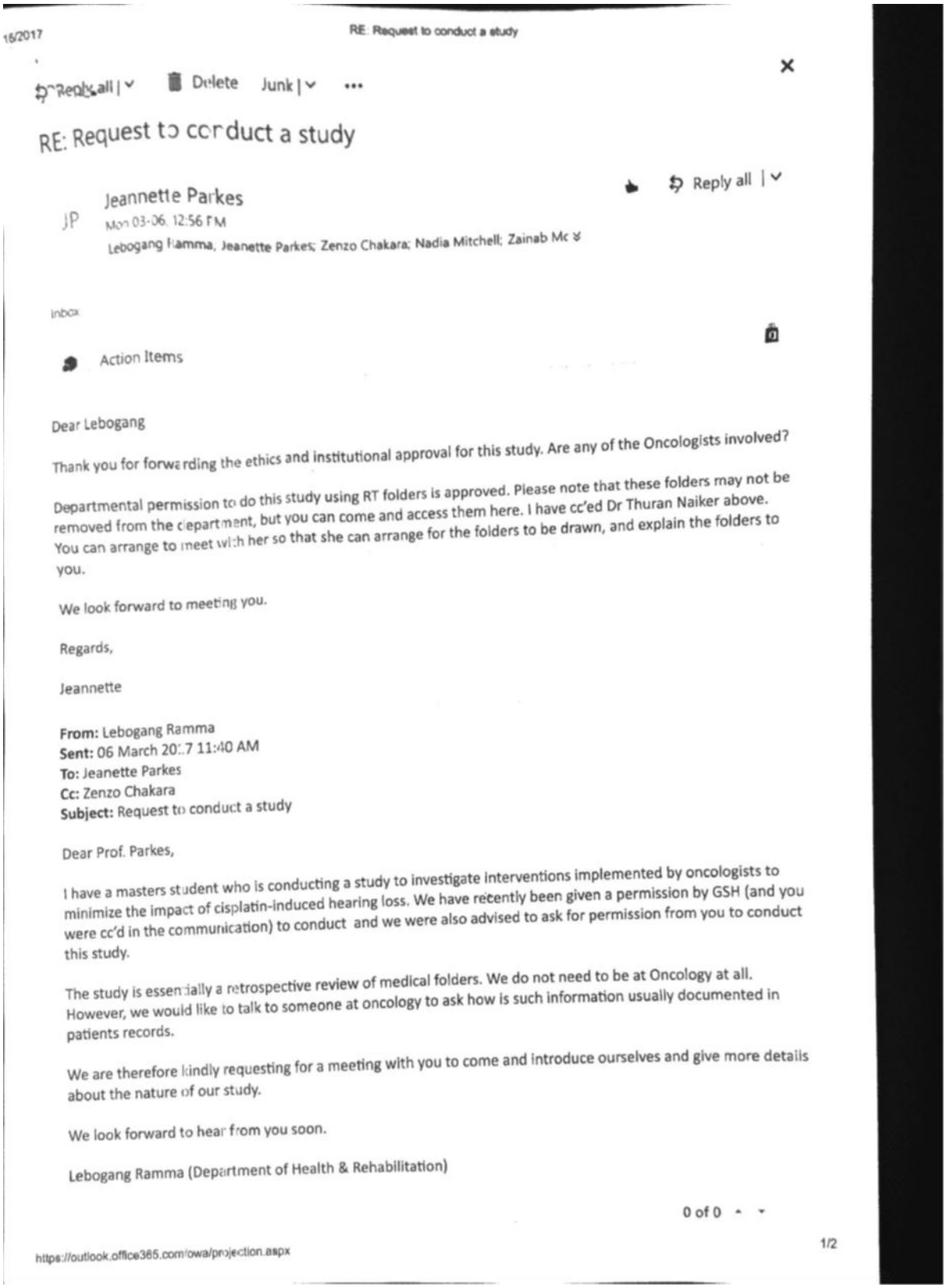
G46 Management Suite, Old Main Building,
Observatory 7925

Tel: +27 21 404 6288 fax: +27 21 404 6125

Private Bag X,
Observatory, 7935

www.capegateway.go.v.za

Appendix F: GSH Departmental Approval



16/2017 RE: Request to conduct a study

Reply all | Delete Junk | ...

RE: Request to conduct a study

JP Jeannette Parkes
Mon 03-06, 12:56 PM
Lebogang Ramma; Jeanette Parkes; Zenzo Chakara; Nadia Mitchell; Zainab Mc

Reply all |

Inbox

Action Items

Dear Lebogang

Thank you for forwarding the ethics and institutional approval for this study. Are any of the Oncologists involved?

Departmental permission to do this study using RT folders is approved. Please note that these folders may not be removed from the department, but you can come and access them here. I have cc'ed Dr Thuran Naiker above. You can arrange to meet with her so that she can arrange for the folders to be drawn, and explain the folders to you.

We look forward to meeting you.

Regards,

Jeannette

From: Lebogang Ramma
Sent: 06 March 2017 11:40 AM
To: Jeanette Parkes
Cc: Zenzo Chakara
Subject: Request to conduct a study

Dear Prof. Parkes,

I have a masters student who is conducting a study to investigate interventions implemented by oncologists to minimize the impact of cisplatin-induced hearing loss. We have recently been given a permission by GSH (and you were cc'd in the communication) to conduct and we were also advised to ask for permission from you to conduct this study.

The study is essentially a retrospective review of medical folders. We do not need to be at Oncology at all. However, we would like to talk to someone at oncology to ask how is such information usually documented in patients records.

We are therefore kindly requesting for a meeting with you to come and introduce ourselves and give more details about the nature of our study.

We look forward to hear from you soon.

Lebogang Ramma (Department of Health & Rehabilitation)

0 of 0

https://outlook.office365.com/owa/projection.aspx 1/2

Appendix G