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Chauke, Tlangelani Nyeleti

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HEARING FUNCTION OF PAEDIATRIC PATIENTS WITH CANCER IN JOHANNESBURG, SOUTH AFRICA: RELATIONSHIPS AND INFLUENCES EXPLORED.

DEPARTMENT OF SPEECH PATHOLOGY AND AUDIOLOGY

SCHOOL OF HUMAN AND COMMUNITY DEVELOPMENT



TLANGELANI N. CHAUKE (1374860)

A DISSERTATION SUBMITTED IN FULFILMENT OF THE REQUIREMENTS FOR THE DEGREE OF MASTER IN AUDIOLOGY IN THE FACULTY OF HUMANITIES at THE UNIVERSITY OF THE WITWATERSRAND.

Supervisor: Prof. K. Khoza-Shangase

MARCH 2024

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Name of student	Tlangelani Chauke
Student number	1374860
Title of project	Hearing Function of Paediatric Patients with Cancer in Johannesburg, South Africa: Relationships and Influences Explored.
Supervisor/s	Professor Katijah Khoza-Shangase

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There were no signed informed consent and/or assent sheets as this was a retrospective study.

ABSTRACT

Background: According to the World Health Organization (WHO), there are about 466 million people living with a disabling hearing loss globally, with almost 34 million of them being children, and approximately 7 million of these children are living in Sub-Saharan Africa (SSA). In South Africa, the incidence of childhood cancer represents approximately 1% of all cancers in the population. The standard treatment in South Africa consists of platinum compounds such as cisplatin and carboplatin. Morbidity factors amongst childhood cancer survivors include hearing loss. Between 20% and 70% of patients suffer from cisplatin and carboplatinum-related ototoxicity. In any context including the South African context, for preventive audiology, it is important to describe and characterise the hearing function of paediatric patients with cancer. **Aim:** The main aim of the current study was to investigate the hearing function of paediatric patients with cancer in Johannesburg, South Africa. **Methodology:** A descriptive retrospective record review design was adopted in this study. The patient records were reviewed from Chris Hani Baragwanath Academic Hospital and Charlotte Maxeke Johannesburg Academic Hospital oncology and audiology units. Non-proportional quota sampling was used in this study. Data was reviewed from 47 patient records from the Chris Hani Baragwanath Academic Hospital and Charlotte Maxeke Johannesburg Academic Hospital audiology and oncology units. **Analysis:** In this current study, descriptive and inferential statistics were used in order to indicate any patterns the data may have assumed and to help summarise the collected data. **Findings:** Demographic and diagnostic factors were thought to have an influence on the hearing function of the paediatric population with cancer. When establishing if a relationship existed between age of diagnosis, gender, race, type of cancer, treatment duration, and type of treatment and hearing function, all the objectives were found to be statistically non-significant, except for the type of cancer which was found to have a statistically significant association. The researcher was 95%

confident that the true prevalence of hearing loss in the paediatric population with cancer would fall between 23.5% and 51.2%. The prevalence of hearing loss was found to be 36.2%. **Conclusion:** The participants who were found to have a hearing impairment, had a hearing impairment due to ototoxicity. As evident from all the audiological assessments administered, there was an evident change in the hearing function of participants from session one to two. **Implications:** It was recommended by the researcher that audiological monitoring as well as screening protocols be implemented in the oncology and audiology units. Current findings could contribute towards identifying risk factors that are associated with hearing loss in the paediatric population with cancer. These findings could possibly help guide future researchers, audiologists, pharmacists, oncologists, or policy makers in in developing treatment protocols, policies and interventions that may help minimize the effects and risks of cancer treatment on the hearing function of this population without having to compromise the effectiveness of their treatment. Implications for future research are also raised by current findings.

Keywords: cisplatin; carboplatinum; paediatric cancer; ototoxicity; South Africa; hearing loss; regimens.

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DEDICATION

To my Aunty Nkati, the strongest warrior I know. A woman who fought the strongest fight with this dreaded disease. A woman who won the battle to join God in Heaven, whilst never failing to support me through my dreams and aspirations, including completing this degree. Thank you for showing me what true strength looks like. Thank you for always believing in me. This paper is dedicated to you.

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LIST OF ABBREVIATIONS

AABR	Automated Auditory Brainstem Response
ABR	Auditory Brainstem Response
ALL	Acute Lymphoblastic Leukaemia
ART	Acoustic Reflex Thresholds
APGAR	Appearance, Pulse, Grimace, Activity and Respiration
CHBAH	Chris Hani Baragwanath Academic Hospital
CMJAH	Charlotte Maxeke Johannesburg Academic Hospital
CNS	Central Nervous System
CPA	Conditioned Play Audiometry
DPOAEs	Distortion Product Otoacoustic Emissions
DTM	Dull Tympanic Membrane
ENT	Ear, Nose and Throat (Specialist)
GICC	Global Initiative for Childhood Cancer
Gy	Grays
HFA	High Frequency Audiometry
HIV	Human Immunodeficiency Virus
HPCSA	Health Professions Council of South Africa
INF	Interneural Facilities

LMICs	Low- and middle- income countries
N/A	Not Applicable
NAD	No Abnormalities Detected
NICD	National Institute for Communicable Diseases
OAEs	Otoacoustic Emissions
OW	Occluded Wax
PTA	Pure Tone Average
PTT	Pure Tone Threshold
POW	Partially Occluded Wax
SSA	Sub Saharan Africa
TORCH	Toxoplasmosis, other agents, rubella, cytomegalovirus, herpes Simplex
VRA	Visual Reinforcement Audiometry
WHO	World Health Organization

CHAPTER ONE

INTRODUCTION

1.1. Hearing loss in the paediatric population

A hearing loss or "impairment" indicates a decrease in an individual's hearing abilities, with hearing ranging from barely perceptible to total deafness (Zahnert, 2011). According to the National Institute on Deafness and Other Communication Disorders, approximately 12,000 newborns are diagnosed with hearing loss each year, with an estimated 4,000 to 6,000 additional children between birth and three-years-old who initially passed the newborn hearing screening, acquiring a late-onset hearing loss (Madell & Flexer, 2014). Hearing loss is one of the most common birth defects, with approximately 16,000 to 18,000 new babies and young children diagnosed with hearing loss each year (Madell & Flexer, 2014). Compared to these figures, according to the World Health Organization (WHO), there are about 466 million people (about 5% of the world's population) living with a disabling hearing impairment, and of these 466 million people, almost 34 million are children, 7 million of whom are living in Sub-Saharan Africa (SSA) (WHO, 2021; Pedersen et al., 2022). The number of people living with a disabling hearing loss is expected to reach 900 million by the year 2050 (Pedersen et al., 2022). Low- and middle-income countries (LMICs) account for nearly 80% of people with disabling hearing loss (WHO, 2021). A study by Swanepoel and colleagues (2009) found that at least 25%, roughly 180 thousand, of all infants in SSA are born with permanent bilateral hearing loss each year (Swanepoel et al., 2009); and the WHO estimated that about 2% of children living in SSA have a disabling hearing loss (Pedersen et al., 2022). Furthermore, it was found that in the public healthcare sector, which mainly serves people from low-middle-income communities, there was a prevalence rate of 6 per 1000 live babies born with permanent bilateral hearing loss. In the private healthcare sector, the

prevalence was estimated at 3 per 1000 live babies born annually. It was thus estimated that 6 116 babies were born with permanent bilateral hearing loss or acquired it in the first few weeks of life in South Africa (Swanepoel et al., 2009).

There are several factors that contribute to hearing loss in children, but there is no guarantee that the exact cause is always known with each presenting case. According to Krug et al. (2016), approximately 40% of hearing losses in children are due to genetic factors. According to Fitzpatrick et al. (2023), genetic hearing losses are the most frequent cause of bilateral hearing losses. In a study by Liddle et al. (2022), it was found that 53.4% of the genetic causes of hearing loss were due to non-syndromic genetic aetiologies, and the remaining 46.6% were due to syndromic genetic aetiologies. Trisomy 21 accounts for 12.8% of hearing losses due to syndromic aetiologies (Liddle et al., 2022). Raeisi et al. (2022) reported that risk factors at birth, such as prematurity, perinatal infection, family history of hearing loss, low birth weight, hypoxia, neonatal jaundice, head and facial deformity, and chromosomal abnormality are all associated with the development of a congenital hearing loss. Furthermore, low APGAR (Appearance, Pulse, Grimace, Activity and Respiration) scores, TORCH infections (toxoplasmosis, other agents, rubella, cytomegalovirus, herpes simplex), or Human Immunodeficiency Virus (HIV) can lead to a congenital hearing loss (Zahnert, 2011 ; Raeisi et al., 2022). According to Fitzpatrick et al. (2023) and Liddle et al. (2022), congenital cytomegalovirus is the most common cause of a non-genetic hearing loss, accounting for 15-20% of childhood hearing losses, including unilateral hearing losses. Children can also acquire hearing loss from childhood infections such as meningitis, measles, and mumps (Krug et al., 2016). About 10-30% of children suffer from transient conductive hearing loss due to otitis media with effusion or due to obstructions such as impacted wax (Zahnert, 2011). The most common structural cause to a permanent conductive hearing loss is craniofacial anomalies such aural atresia or microtia, which accounts for 25-39.6% in

children with these anomalies (Fitzpatrick et al., 2023; Liddle et al., 2022). Additional causes of hearing loss include medications such as chemotherapy or ototoxic drugs used in the treatment of neonatal infections, malaria, drug-resistant tuberculosis, and cancers that can cause permanent hearing loss (Krug et al., 2016; Liddle et al., 2022).

1.2. Cancer in the paediatric population

The incidence of childhood cancer varies according to age, sex, race, or ethnicity (Spector et al., 2015). Paediatric cancers develop when embryonal tissue acquire mutations which lead to the uncontrolled division of abnormal cells. Paediatric cancers usually develop between the ages of birth and 19 years old, with approximately 400,000 newly diagnosed cases of cancer in children between these ages worldwide (WHO Global Initiative for Childhood Cancer, 2021). About 80-90% of these cases occur in resource-limited countries or LMICs such as those in sub-Saharan Africa (Otoo et al., 2020; WHO Global Initiative for Childhood Cancer, 2021; Ehrlich et al., 2023). Containing a diverse, multiracial population, South Africa falls within LMICs, with a population of approximately 60 million and is serviced by a dual public-private healthcare system, but this healthcare system is considered to be plagued by immense inequities when it comes to accessing it, which is largely divided by racial lines (Stuart et al., 2022). According to Smith et al. (2017), in South Africa, the incidence of childhood cancer represents approximately 1% of all cancers in the population; with 800-1000 children being diagnosed with cancer in South Africa annually (National Institute for Communicable Diseases “NICD”, 2021). In Africa the overall incidence of cancer is 1.1 million and is set to rise to 2.1 million cases by 2040. Of these 1.1 million cases, an estimated 124 815 cases reside in South Africa (Sharma et al., 2022). Sharma et al. (2022) found that there are an estimated 62,776 cases of cancers, such as leukaemia, Hodgkin’s lymphoma, and kidney cancer, in children and adolescents who are younger than 20 years old in Africa.

There are many types of cancers worldwide and within the African continent, which can be either rare or common types.

The most common childhood cancers reported globally are medulloblastoma, osteosarcoma, lymphoblastic leukaemia, non-Hodgkin lymphoma, nephroblastoma, Burkitt lymphoma, retinoblastoma, hepatoblastoma, neuroblastoma, craniopharyngioma, and germ cell tumours (Brooks & Knight, 2018; WHO Global Initiative for Childhood Cancer, 2021; Amayiri et al., 2023). Cancers such as lymphomas, retinoblastomas and renal tumours have an increased incidence in many African countries (WHO Global Initiative for Childhood Cancer, 2021). In the South African context, leukaemia's are the most common childhood cancers recorded in the Free State, Gauteng, KwaZulu-Natal, and Western Cape (Otoo et al., 2020). In Otoo et al.'s (2020) study, they found that leukaemia, followed by lymphoma, and Central Nervous System (CNS) neoplasms have the highest prevalence among childhood cancers in South Africa. Furthermore, the NICD found that in South Africa, leukaemia, lymphoma, brain and spinal cord tumours, kidney cancer (Wilms tumour) and soft tissue sarcomas are the most common cancers in children (NICD, 2021). Smith et al. (2017) reported that the types of cancers in this population seem to be linked to the age of cancer diagnosis. For example, in children under the age of five, embryonal tumours such as neuroblastoma, retinoblastoma, and acute lymphoblastic leukaemia (ALL) are the most common cancers recorded (Smith et al., 2017). There are varying possible risk factors that can influence the development of childhood cancers.

Although the causes of childhood cancer are largely unknown (Spector et al., 2015), researchers have investigated several risk factors for the development of cancer in children and adolescents (Spector et al., 2015). Genetic factors; patient-specific factors which include sex, race/ethnicity and age at diagnosis; life-style related factors; environmental factors; and controversial factors such as the exposure to electromagnetic fields have all been reported to

be possible risk factors to childhood cancer(American Cancer Society, 2020; Dixon et al., 2018). Furthermore, according to WHO Global Initiative for Childhood Cancer (2021), there is a very small amount of childhood cancer with a known aetiology.

1.3. Treatment for paediatrics with cancer

In South Africa treatment of childhood cancers involves a six or nine-month intensive chemotherapy phase, followed by a two- or three-year maintenance phase (NICD, 2021). Over the last century, much progress has been made in the treatment of childhood cancers (Volberding et al., 2021), with the standard treatment in South Africa being platinum compounds such as cisplatin and carboplatin (Smith et al., 2017). The introduction of chemotherapy in the 1960s, in combination with surgery and radiation, enabled the use of a multimodal approach to the treatment of cancer in this population (Saletta et al., 2014). Used to destroy cancer cells, chemotherapy is one of the treatments used for cancer. Included in these treatments is platinum-based medication, which includes carboplatin, cisplatin, and oxaliplatin; with cisplatin being the most common medication to be used (Zand et al., 2023). Additional treatment options that can be used to treat cancer are Doxorubicin and Vincristine (Johnson-Arbor and Dubey, 2023) Doxorubicin is known to treat leukaemia and Hodgkin lymphoma, as well as soft tissue and bone sarcomas (Johnson-Arbor and Dubey, 2023). Whereas, vincristine is generally used to treat leukaemia, lymphoma, as well as neuroblastoma; and is suspected to be a contributing risk factor to hearing loss in combination with platinum-based chemotherapy such as cisplatin and carboplatinum (Awosika et al., 2023; Strebel et al., 2023). With a 5-year overall survival rate, improved treatment has allowed children with cancer to have an overall survival rate of over 85% today in high income countries (HICs) (Volberding et al., 2021). According to Ehrlich et al. (2023), the 5-year survival rate in LMICs is lower than 20%, with a mortality rate of 45% in children with cancer. It is estimated that the 5-year survival rate can range from less than 10% in

LMICs to 55% in upper-middle-income countries (Ehrlich et al., 2023). The Global Initiative for Childhood Cancer (GICC), which was launched by the WHO in 2018, aims to improve the childhood cancer survival rate in LMICs to 60% by 2030 (Balagadde-Kambugu et al., 2023; Van Heerden et al., 2023).

In most cases, paediatric cancers are not preventable as they are caused by mutations in genes that are not documented, inherited or sporadic, or other unknown factors (Van Heerden et al., 2023). To manage any form of childhood cancer, it is essential to have a core multidisciplinary team, which includes at least, paediatric oncologists, surgeons, radio-oncologists, and nursing staff; with additional support staff such as pharmacists, radiologists, and psychosocial support to make up the rest of the team (Van Heerden et al., 2023). Generally, cancer treatments can be classified as local or systemic (Volberding et al., 2021). Surgical treatments and radiotherapy target cancers locally, i.e., directly at the site where cancer cells are located (Volberding et al., 2021). Whereas, systemic therapies, such as chemotherapy, circulate throughout the body and therefore affect all cells, and not just cancer cells (Volberding et al., 2021). Although access to timely, safe, and affordable surgery and radiotherapy is scarce in Africa, the main treatment standards for controlling and managing cancer is surgery, radiotherapy, and systemic therapies (Sharma et al., 2022). Aminoglycosides, carboplatin, vinblastine, cisplatin, etoposide, loop diuretics, and vincristine are usually part of standard chemotherapy protocol due to their proven efficacy (Lambert et al., 2008; Tillmanns et al., 2021). Alternatively, it is possible to combine surgery with other types of treatments such as radiation or chemotherapy to shrink the size of the tumour before it is removed or to treat remaining cancer cells after surgery (Volberding et al., 2021). Treatment such as cranial irradiation, is also available and can be used in parallel with other chemotherapies (Tillmanns et al., 2021). Families in LMICs may face a considerable number of

challenges regarding this treatment, as the availability of highly specialized medical resources or treatment might be difficult for them to access, especially if the family lives far away (Amayiri et al., 2023). In LMICs such as Africa, the prevalence of therapy abandonment and treatment failures due to drug toxicity or other comorbid conditions such as infections, malaria, and other childhood diseases, is quite high (Sharma et al., 2022). With all these treatments, there are risks for morbidity and mortality.

1.4. Risk factors of paediatric cancer

Researchers have found that long-term cancer survivors have a higher risk of morbidity and mortality (Oeffinger et al., 2006). With regards to morbidity, it is important to note that young children as well as children who receive higher cumulative doses of ototoxic agents have a substantially higher burden of morbidity (Landier, 2016). Oeffinger et al. (2006) for example, conducted a study which found that nearly two-thirds of childhood cancer survivors reported having at least one chronic condition, and that many had multiple and/or severe chronic conditions after cancer treatment. Mortality and morbidity may result from inadequate follow up and limited access to medication (Amayiri et al., 2023). This is especially prevalent in LMICs, where often cancer is detected at the later stages due to the lack of access to infrastructure which could provide appropriate care, which later leads to high rates of treatment being abandoned and loss to follow-up, result in a high rate of cancer-related mortality (Ehrlich et al., 2023). Morbidity factors amongst childhood cancer survivors include hearing loss, primary hypothyroidism, cardiac dysfunction, and neuro-cognitive decline (Dixon et al., 2018; Emerson et al., 2022). It has also been reported by Amayiri et al. (2023), that cognitive decline, hypothalamic-pituitary dysfunction, visual deterioration, and vasculopathy or necrosis and secondary tumours may be late-onset side effects off radiotherapy.

Additionally, survivors of childhood cancer report chronic pain in adulthood, which in turn is associated with a reduced quality of life (Dixon et al., 2018). Children in their early stages of brain development are particularly vulnerable to cognitive effects of cranial irradiation (Merchant et al., 2009). Childhood cancer survivors are also at an increased risk of developing psychological disorders, such as depression or anxiety (Dixon et al., 2018). Researchers have found that psychological distress (particularly suicidal ideation) is associated with an increased overall mortality rate in long-term survivors of childhood cancer (Brinkman et al., 2014). Attributed to the lower life expectancy of males, according to Dixton et al. (2018), there is an increased rate of mortality among male survivors (five years after diagnosis) than among female survivors. As a result, rapidly growing population of cancer survivors faces multiple risks, including recurrence and long-term adverse treatment-related effects, as well as elevated risk of physical and psychosocial comorbidities (Arem & Loftfield, 2018). Sensory effects, such as ototoxicity are also included in the morbidity outcomes of cancer treatments. Furthermore, the concurrent use of multiple ototoxic agents, can lead to greater effects of ototoxicity (Tillmanns et al., 2021).

1.5. Ototoxicity

A frequently reported complication of cancer treatment is hearing loss as a result of ototoxicity (Whelan et al., 2011). The side effects of medications like cisplatin can be significant. These side effects include nausea, vomiting, loss of appetite, kidney failure, alopecia, and hearing loss amongst few (Zand et al., 2023). Between 20% and 70% of patients suffer from cisplatin-related ototoxicity, which 28% of them have moderate to severe ototoxicity (Zand et al., 2023). Within two years after receiving cisplatin chemotherapy, it was found that nearly 50% of paediatric patients who had medulloblastoma experienced some form of hearing loss (Zand et al., 2023). Regardless of the influencing factors at play, hearing function in paediatric patients has been documented to present in a certain way. Ototoxicity is

when the hearing or balance functions of the ear are damaged by drugs or chemicals (Tillmanns et al., 2021). A permanent, sensorineural hearing loss is the result of cochlear damage, where death of the cochlear hair cells, or more specifically, the outer hair cells at the beginning of the basal turn of the cochlea occurs (Sinxadi & Blockman, 2009). The outer hair cells are destroyed by the increase in oxygen radicals that react with nitric oxide in the inner ear. The destruction of the outer hair cells therefore makes it difficult for the appropriate signals to be sufficiently transmitted to the auditory nerve, resulting in a permanent hearing loss (Sinxadi & Blockman, 2009). The current study focused on the hearing function only. There is evidence that certain cancer treatments, such as platinum agents, cranial irradiation, and brain surgery, can lead to or increase ototoxicity (Diepstraten et al., 2022). Due to the proximity of the disease to the auditory system, head and neck cancer patients are more susceptible to ototoxic side effects from chemotherapy, surgery and radiation, as the cochlea is extremely sensitive to radiation and ototoxic agents such as chemotherapy (Santucci et al., 2021). The most common types of head and neck cancers include lymphoma's, nasopharyngeal carcinoma, thyroid carcinoma and rhabdomyosarcoma (Silverman et al., 2021). Regarding head and neck cancers, hearing loss may slowly start to occur within the first six months to two years after treatment (Bass et al., 2016; Robertson et al., 2019). Furthermore, children who received cisplatin are at an increased risk for developing an asymmetrical hearing loss or late onset hearing loss. Additionally, there is an increased risk for a further decline in hearing function in children who receive a combination of radiation treatment in combination with chemotherapy, which is the main treatment option for patients with head and neck cancers (Bass et al., 2016; Robertson et al., 2019).

Ototoxicity may also be influenced by the type of medication administered, the cumulative dose, the age of the patient at the time of medication administration, the route of administration of the medication (bolus vs. infusion), the dosing regimen of the medication

administered, and concurrent use of other medications (Dillard et al., 2022; Olgun et al., 2021; Tillmanns et al., 2021; Yancey et al., 2012). With regards to the type of medication administered, hearing damage caused by chemotherapy such as carboplatin, can range from reversible tinnitus to permanent hearing loss. Furthermore, irreversible, bilateral, and progressive sensorineural hearing loss is a characteristic symptom of cisplatin ototoxicity (Whelan et al., 2011; Al-Ali et al., 2023). Carboplatin is known to be the less toxic of the two agents, but when used in combination with cisplatin, the consequences can be catastrophic in terms of hearing organ damage (Whelan et al., 2011). Although carboplatin is less ototoxic than cisplatin, it can still cause hearing loss as well as other ototoxic effects, such as vestibular dysfunction or tinnitus (Dillard et al., 2022). In relation to the cumulative dose of cisplatin, the ototoxic effects on hearing appear to be worse at high frequencies (4-8 kHz) (Yancey et al., 2012). A study by Liberman et al. (2016), found that there was no statistical relationship between gender and hearing loss in the paediatric population with cancer, although it was reported by Yancey et al. (2012) that cumulative dose and gender are the most important clinical markers for ototoxicity. Therefore, there is limited evidence to indicate the effect gender might have on this population's hearing function. Children younger than 5-years old who were treated with carboplatin, were found to have the lowest prevalence of hearing loss (Dillard et al., 2022). However, it was later found that, children under 5-years old who treated using cisplatin-based regimens had the highest prevalence of hearing loss, consistent with research indicating that young age is a risk factor for hearing loss (Dillard et al., 2022). Approximately 86% of paediatric patients on cisplatin and 33% of paediatric patients on carboplatin with different forms of cancers were found to have a hearing loss due to the ototoxic nature of these medications (Al-Ali et al., 2023).

In the paediatric population, the prevalent use of ototoxic drugs that are prescribed to treat neonatal conditions including ear infections, malaria, cancer, HIV, and drug-resistant

tuberculosis are known to cause irreversible hearing damage (Olusanya et al., 2014). Medicines may cause irreversible damage to the hair cells and inner ear via the round window membrane, the cerebrospinal fluid, or the bloodstream (Olusanya et al., 2014). Platinum-based chemotherapeutic agents, aminoglycosides, cytostatics, loop diuretics, salicylates, antiretroviral medications, and quinine are drugs known to have ototoxic effects (Zahnert, 2011; Moodley et al., 2021). More recently, in a study conducted by Waissbluth in 2020, Cyclosporine, an immunosuppressant drug or otherwise known as an anti-rejection drug for organ transplants, was found to have some ototoxic effects on the hearing organ. Additionally, biologics which are used to slow down or stop inflammation, may also have some ototoxic effects (Szczepek and Stankovic, 2021).

1.5.1. Assessment and medical management of ototoxicity

The Health Professions Council of South Africa's (HPCSA) (2018) guidelines recommend that the assessment and management of ototoxicity begins with counselling prior to treatment, about the risk of the ototoxic effects from the medication (HPCSA, 2018). Timely counselling of the patient and/or their guardian is essential to the management of ototoxicity (Crundwell et al., 2016). Additionally, Landier (2016) recommends that the patient receives baseline measures where current hearing thresholds are obtained and later used as a form of comparison with the hearing thresholds obtained during and after treatment. A comprehensive audiological assessment should be performed within 24 hours or before administration of the next dose of medication if the patient's hearing thresholds have worsened compared to their baseline thresholds (HPCSA, 2018). To assess the progress of the patient's hearing after treatment, a determination criterion (grading) should be established beforehand (HPCSA, 2018). As soon as the grading is decided upon, the severity of the shift must be assessed according to the hearing adverse event scale (HPCSA, 2018). Furthermore,

if a shift has been detected, it is recommended by the HPCSA (2018) guidelines that follow-up evaluations should be repeated once a month, until the stabilization of the hearing thresholds, and no additional changes are detected (HPCSA, 2018). In accordance with HPCSA (2018) guidelines, patient medical management and audiological management in the form of aural rehabilitation should be handled by a multidisciplinary team that is responsible for establishing a comprehensive treatment plan for the patient. According to Dillard et al. (2022), otoacoustic emissions (OAEs) are effective in detecting early onset changes in hearing after exposure to ototoxic medications. Additionally, high frequency audiometry (>8000Hz) is also recommended, above and beyond the standard clinical audiogram (250Hz-8000Hz). Due to the ototoxic damage first developing at the basal end of the cochlea, these tools are recommended as they are able to assess high frequencies which correspond with the basal end of the cochlea (Dillard et al., 2022).

Medical management of ototoxicity includes monitoring the patient's hearing during treatment to allow for early identification of changes in hearing, which could help initiate a change in the patient's treatment protocol to minimize further hearing loss from occurring (Crundwell et al., 2016). Furthermore, in order to ensure that enough evidence is collected for an adequate benefit/risk assessment, audiologists, physicians, and pharmaceutical companies should significantly increase their efforts to develop non-ototoxic therapeutic agents (Khoza-Shangase, 2017). It is also important to expand the evidence base for otoprotective agents that can prevent ototoxicity when ototoxic drugs cannot be avoided. Restorative treatment, which involves the use of neurotrophins to regenerate hair cells damaged by ototoxic drugs, also needs to be carefully considered (Khoza-Shangase, 2017). Particularly in LMICs, such as South Africa, these strategies are critical to achieve strategic long-term financial savings, as the economic impact associated with the resulting unemployment of affected individuals

results in the elimination of potential litigation costs, amplification device costs, rehabilitation costs, and social grants costs (Khoza-Shangase, 2017).

1.6. Hearing loss in the paediatric cancer population

Castelán-Martínez et al. (2014), found that about 50% of children treated with cisplatin develop some form of permanent hearing loss, and the incidence reaches 90% in children receiving a cumulative dose of 400 mg/m2 or more of cisplatin. Regarding age at the time medication is administered, a study by Konrad-Martin et al. (2005), reported that individuals may also be susceptible to ototoxicity based on their age. For example, Olgun et al. (2021) found that children under 5 years of age have a 15-20 times higher risk of developing ototoxicity. With regards to dosing schedules of administration of medication, Yancey et al. (2012), reported that various doses and dosing regimens seem to have varying propensities to cause ototoxicity. For example, Wei and Yuan (2019), reported that there is a significantly increased risk of ototoxicity in paediatric patients with cancer when a single maximum dose is administered.

As far as the description of hearing function of paediatric patients with cancer is concerned, Clemens et al. (2017) characterized the hearing loss as a high frequency sensorineural hearing loss. Furthermore, Landier (2016) reported that when continuously exposed to an ototoxic agent, hearing threshold shifts begin at high frequencies (>4000 Hertz) and progresses gradually to lower frequencies with ototoxic hearing loss. Hearing loss, as a complication, is not only a functional limitation for survivors, but can also affect areas such as speech and language development, educational attainment, social-emotional development, and quality of life in the paediatric population (Whelan et al., 2011; Smith et al., 2017). Furthermore, with regards to language and communication skills, children who acquire a hearing loss are at an increased risk of learning at a slower pace than their peers,

therefore resulting in a delay in the development of their receptive and expressive communication skills, which could ultimately lead to these children developing learning problems and having reduced academic achievement. In general, children with hearing losses struggle with their communication skills, which can lead to poor self-esteem and social isolation (Shojaei, Jafari, & Gholami., 2016). All these factors necessitate careful assessment and management of paediatric patients on cancer treatments.

1.7. Audiological management of hearing loss in the paediatric population

As far as audiological management is concerned, 40% of the children who acquire late auditory onset effects eventually require hearing aids (Diepstraten et al., 2022). Implementing an appropriate aural rehabilitation programme for patients who acquire a disabling hearing loss as well as ensuring that assistive listening devices and/or amplification devices are provided is crucial to the audiological management of ototoxicity (Crundwell et al., 2016; HPCSA, 2018). Speech reading or compensatory strategies, and/or sign language may be used as alternative viable options to reduce the impact hearing loss might have on this population, where amplification is not available or feasible (Dillard et al., 2022).

At the long-term follow-up (two years post-treatment) an auditory assessment is usually recommended for patients with a history of receiving platinum chemotherapy treatment (Landier, 2016). Due to the potential for progression of hearing loss over time, ongoing audiological monitoring every five years is advised for patients who have received chemotherapy (Landier, 2016). Ensuring the prevention of any form of hearing loss through monitoring hearing acuity is important for the quality of life of these patients (Dillard et al., 2022). By identifying at-risk patients early, counselling them, monitoring, and managing them appropriately through a logical and systematic approach, ototoxicity monitoring and management programmes can greatly reduce the incidence of hearing loss and its associated

reduced quality of life, especially in the lives of childhood cancer survivors, who face multiple risks due to the treatment they received, that could affect their future quality of life (Dillard et al., 2022; Santucci et al., 2021).

1.8. Research Rationale

The literature reviewed revealed limited evidence around the relationship between age at diagnosis, race and gender and hearing function, dosage of cancer treatment and hearing function, factors such as type and duration of cancer and hearing function, and finally treatment factors, such as different treatment options and hearing function, particularly within the South African context. Majority of studies reviewed are from high income countries where the treatment protocols, regimens and modalities may be different to the South African context (Whelan et al., 2011; Smith et al., 2017; Wei & Yuan., 2019; Olgun et al., 2021). Furthermore, most of these studies focus on the effects of platinum-based chemotherapies on the hearing function (Brock et al., 2012; Castelán-Martínez et al., 2014; Landier et al., 2014; Santucci et al., 2021). Therefore, the aim of this study was to describe the hearing function in a group of children with a history of cancer who underwent chemotherapy treatment in Johannesburg, South Africa, with specific objectives aimed at determining the potential relationships between various factors and hearing function. Findings from the study will potentially contribute to knowledge on assessment and management of this population within the South African context.

CHAPTER TWO

METHODOLOGY

2.1 Aim and specific objectives

2.1.1. Main aim

The main aim of the study was to investigate the hearing function of paediatric patients with cancer in Johannesburg, South Africa. To attain the study's main aim, specific objectives and to test the hypotheses, statistical analyses were implemented using a statistical software such as IBM SPSS Statistics v26.0 software. To indicate any patterns within the main aim, specific objectives and the hypotheses, descriptive and inferential statistics were used (Kumar et al., 2019).

2.1.2. Specific objectives

The specific objectives of the study were:

1. To describe the hearing function of paediatric patients with cancer.
2. To determine factors that influenced the hearing function in this population.
3. To explore the relationship between demographic factors such as age, race and gender and hearing function findings in this population.
4. To investigate the relationship between diagnostic factors such as type of cancer and duration of cancer treatment and hearing function findings in this population.
5. To study the relationship between treatment factors such as different treatment options and hearing function findings.

Initially the relationship between treatment factors such as the dosage of different treatment options and the hearing function findings were going to be analysed as outlined in

objective five of this study, however due to the fact that all of the medications documented in patients' records had different metric systems for the medication dosages, this objective had to be amended to just include treatment options, as converting the medications to be on the same scale would have been beyond the scope of the current study.

2.2. Hypotheses

Null Hypothesis (H_0): The hearing function of paediatric patients with cancer is not influenced by the type of cancer, the type of treatment, the age of the patient, the gender and race of the patient.

Alternative Hypothesis (H_1): The hearing function of paediatric patients with cancer is influenced by the type of cancer, the type of treatment, the age of the patient, the gender and race of the patient.

2.3. Research Design

A descriptive retrospective record review, using two sources of data, was used in this study as it allowed for questions to be answered relating to the population that was being studied, which was a vulnerable population which was exposed to harmful agents, and it allowed for longitudinal research to be conducted (Buxton, 2021). The two sources of data were hospital medical records from: 1) Chris Hani Baragwanath Academic Hospital (CHBAH), and 2) Charlotte Maxeke Johannesburg Academic Hospital (CMJAH).

The advantages of conducting a retrospective record review includes the use of existing data which is relatively inexpensive less time-consuming (Hess, 2004; Gearing et al., 2006; Buxton, 2021). In addition, the initial assessments, investigations, and treatments were administered by different healthcare professionals at different times, this may result in difficulty managing biases and confounders, therefore bringing into question the reliability and validity of the existing data (Hess, 2004), however, it can be assumed that the healthcare

professionals who assessed these patients were HPCSA registered, thus appropriately skilled to assess patients in a reliable and valid manner.

The disadvantages of conducting a retrospective record review include: less control over sampling methods and sample sizes (Mann, 2003); and a lack of complete documentation and limited access to records, which included missing medical records, and differences in the quality of information recorded by different healthcare professionals (Gearing et al., 2006; Buxton, 2021).

The use of a retrospective record review study in this case was warranted since it would be impractical to conduct a study relating to the variables of interest for a master's level degree (Kavallieratos, 2012; McBurney & White, 2013), as a result of the long-term nature of and the high cost of employing a prospective observational longitudinal study design for this study and the mortality rate of the patients being studied being high. Therefore, for this study, a retrospective record reviewed was considered appropriate (Kavallieratos, 2012; McBurney & White, 2013).

2.4. Study Population

Files of paediatric patients with cancer whose hearing was assessed at CHBAH or CMJAH over a five period between 2018-2022, formed the participants for this study. The five-year range was aimed at preventing an overload of data from being collected (Hewitt et al., 2003), which was found to be a limitation in the end, due to the lack of files and information found in some of the files. Children with cancer may require an age-appropriate audiologic monitoring different from those with different conditions. This is because the reliability of behavioural testing in young children, particularly those with cancer can be limited due to their impaired neurological status and fatigue (Meijer et al., 2021). With children younger than 5-years-old, it would have only been feasible to conduct non-behavioural tests such as

OAEs and auditory brainstem responses (ABRs); but detecting changes in the auditory function is challenging in this age group as they can become easily distracted and agitated, therefore audiological results may have been limited with this age group (Meijer et al., 2021). Therefore, participants had to be between the ages of five to 18 years old. Regarding the feasibility of this study, this age range (five to 18 years old) was chosen as behavioural pure tone testing could have been confusing and tiresome for participants younger than five at the time hearing function was assessed, which in turn could have affected the reliability of the results (Khoza-Shangase & Lau, 2021).

Table 1 depicts the demographic profile of the participants in the current study. There were 47 patient records reviewed (21 females and 26 males) in this study. The patient ages ranged from five years to 17 years old, with a median age of 12 years old.

Table 1:

Demographic profile of participants (N=47)

	Total (N=47)
Age of Diagnosis	
Median (Q_1, Q_3)	12.00 (10.00; 14.00)
Min	5.00
Max	17.00
Gender	
Female	21 (44.7%)
Male	26 (55.3%)

2.5. Sampling method

Non-proportional quota sampling, a form of non-probability sampling, was used in this study (Etikan & Bala, 2017). This type of sampling technique allows the researcher to have easy access to the sample population and is a technique with minimal restriction as the researcher

was able to be guided by the characteristics of the population, such as sex or race (Etikan & Bala, 2017). Whilst adhering to the inclusion criteria that was set out for this study, the sample was limited to patient records which were found at CHBAH and CMJAH audiology and oncology units, where 47 patient records could be reviewed for this study. and A limitation of this type of sampling method was that random selection had not been used to select the sample, therefore making it difficult to establish possible sampling errors. There was also a high possibility of sampling bias (Sharma, 2017). This type of sampling method also makes it impossible to make generalizations such as statistical inferences, from the sample to the population, which can in turn lead to problems of external validity (Sharma, 2017).

2.6. Sample size and study settings

Data was collected and reviewed from 47 patient records, which consisted of both male and female patient records, who met the inclusion criteria set out. These patient records were reviewed from the CHBAH and CMJAH audiology and oncology units in Johannesburg, South Africa. Situated in Soweto, Johannesburg and fondly known as “Bara”, CHBAH is the largest hospital in South Africa and the African continent; and formally known as Johannesburg General Hospital, CMJAH is situated in Parktown, Johannesburg (Research Unit, 2022). Both CHBAH and CMJAH are tertiary hospitals which primarily serve the greater Johannesburg and North West province, as well as provide tertiary services to a large region of northeast and central South Africa (Goolam et al., 2018). These facilities both serve as teaching hospitals for the University of the Witwatersrand’s Faculty of Health Sciences (Govender et al., 2022; Research Unit, 2022). They both receive referrals from several hospitals in their catchment areas (Research Unit, 2022). Paediatric patients with various types of cancers are referred to the paediatric oncology units, which coordinate their multidisciplinary management with various primary healthcare workers; therefore, these

facilities were appropriate for reviewing the hearing function of the paediatric population with cancer (Goolam et al., 2018). The research sites were chosen due to their proximity to the university and due to the existence of paediatric oncology clinics and the existing paediatric cancer patient audiological files in these institutions. These patients would have been seen as either referrals from the oncology unit or as self-referrals in the audiology department for a hearing assessment.

After obtaining ethical clearance (Protocol Number: M221128) in April 2023, data collection subsequently began in May 2023 until all possible data could be collected. The number of patient records found was smaller than the proposed sample size of 111 patient records due to factors such as the limited number of records and incomplete data found in the files obtained by the researcher, records that did not meet the inclusion criteria, records of patients who did not come to follow-up appointments due to reasons such as death, patients defaulting treatment or being too ill to attend sessions, and excessive data missing from the files which would limit the analysis of the study.

To determine the sample size required for this study, the G-Power sample size calculator was used (Faul et al., 2007). The sample size calculator is a widely used calculator that can be used to calculate the minimum effective sample size required for a study (Faul et al., 2007; Mayr et al., 2007). Using an alpha value of 0.05, an effect size $|p|$ of 0.3 and a power value of 0.95, the required sample size for this study was 111 participant files.

2.7. Inclusion and exclusion criteria

Patient records that were included in this study had to meet the following criteria:

2.7.1. Inclusion criteria

- Patient records needed to be of paediatric patients whose ages ranged between five to18 years old. The Child Care Act 74 of 1983 defines a child as anyone under 18 years of age (*CHILD CARE ACT 74 OF 1983*, 1983).
- Patient records with confirmed medical diagnosis of any form of cancer, who received treatment or were receiving treatment at the time the hearing function was assessed over the five-year period of 2018-2022.
- Only patient records who had their hearing function assessed at Chris Hani Baragwanath Academic Hospital or Charlotte Maxeke Johannesburg Academic Hospital during their cancer treatment.
- Only records with at least two audiologic assessment sessions for progression of the hearing status description. These audiological assessments had to include an otoscopic examination, tympanometry, pure tone audiometry and/or distortion product otoacoustic emissions (DPOAE) results. Majority of the files reviewed had an average of about two to four weeks between each session.
- The patients associated with the patient records found had to be discharged or no longer being followed up at the clinics when the files were being reviewed.
- If a file of a patients file was found to have been tested with objective audiological assessment (i.e., diagnostic ABR and DPOAEs), due to the possibility of them not being able to cope with behavioural audiological assessments, they would be included if the results yield reliable results, included a threshold estimated audiogram and there were two or more of these assessments done subsequently.

2.7.2. Exclusion Criteria

- Patient records who were found to be younger than five years old were excluded from the study, due to the possibility of behavioural pure tone testing being confusing and tiresome for participants younger than five at the time hearing function was assessed, which in turn could affect the reliability of the results (Khoza-Shangase & Lau, 2021).
- Patient records with any cognitive impairments, which may have affected the reliability of results obtained during pure tone audiometry, were excluded. The perceived difficulties that may be caused by cognitive impairments may influence any audiological or auditory assessment result negatively (Tomlin et al., 2015).
- Furthermore, patient records which did not have any audiological assessment results or those that had less than two audiological assessment results were excluded from the study.

2.8. Data Collection

Prior to the data collection for the study, permission to conduct the study was obtained from the University of the Witwatersrand's Medical Human Research Ethics Committee (**Appendices A-C)**, with ethics approval protocol number M221128. Approval (**Appendices D-H)** from all relevant management structures at the research sites was also obtained as part of the ethics application process.

Patient records were reviewed, and relevant data was captured using a data capturing form (**Appendix J)** as well as a number coding system to differentiate between patient records. The data capturing form included age at diagnosis, gender, race, type of cancer, treatment protocol used, duration of treatment, cumulative doses of treatment administered, administration of aminoglycoside antibiotic (gentamicin, tobramycin, and/or amikacin) at any time during treatment as well as an audiological assessment results, any history of hearing

difficulties, symptoms of hearing loss, and suspected hearing difficulties (Orgel et al., 2012; Khoza-Shangase & Lau, 2021). Furthermore, the data capturing form also included a section to report any other management the patient records may have noted such as hearing aid evaluations and/or fittings, cochlear implant evaluations and/or fittings, aural rehabilitation, a referral to any other discipline or profession and an "other" option. Hearing function was captured on a separate data capturing form (**Appendix K).** Hearing function was presented through audiological results such as otoscopy, tympanometry, acoustic reflex thresholds (ARTs), Distortion Product OAES (DPOAEs) and Pure Tone Audiometry (from 250Hz-20 000Hz, for some sites). The data capturing forms included a not applicable (N/A) option for missing or undocumented information as well as section to take note of any existing comorbidities. Comorbidity is defined as having a long-term health condition in addition to a primary disease (i.e., cancer), such as diabetes (Fowler et al., 2020). Patients with several comorbid diseases may have a poorer prognosis for their primary illness. Furthermore, the timing of their cancer diagnosis may either be influenced positively or negatively by existing comorbidities, i.e., a patient's comorbidity could either lead to an early diagnosis or a delayed diagnosis (Fowler et al., 2020). According to Fowler et al. (2020), chronic obstructive pulmonary disease, diabetes, cerebrovascular disease, congestive heart failure and peripheral vascular disease were among the most recorded comorbid conditions among cancer patients (Fowler et al., 2020). Comorbidity factors were carefully documented, if any were noted, to ensure that they were taken into cognisance during the analysis and interpretation of the findings.

2.9. Hospital Audiological Testing Procedures

According to the ASHA website, hearing loss can be identified and diagnosed by a variety of tests, for which the methods used are dependent on the patients age and other factors (ASHA, 2024). These tests include Pure Tone Audiometry, Speech Testing, Tympanometry, ABR,

and OAEs. Each unit at CHBAH and CMJAH used their own standardized audiological protocols to monitor their patients hearing function.

At CHBAH and CMJAH patients were either referred by the oncology unit or self-referred to the audiology department for assessments of their hearing function. Both CHBAH and CMJAH follow the same testing protocols for their patients. The assessment begins with the case history of the patient being documented followed by otoscopic examination. Tympanometry and ipsilateral acoustic reflex testing are then performed, followed by DPOAE testing. Finally conventional and high frequency pure tone audiometry is conducted. CHBAH used the following equipment to assess their patients: a KaWe otoscope, GSI 39 Auto Tympanometer to perform acoustic immittance and tympanometry, the Path Sentiero DPOAE machine to conduct DPOAE testing and the GSI Audiostar audiometer and the GSI 61 Clinical audiometer to conduct conventional and high frequency pure tone audiometry. The equipment used at CMJAH during the period when the data was collected was not noted as the audiology department had upgraded their equipment over the five-year period and could not be certain exactly which equipment was used for the testing of their patients. However, it was diagnostic equipment that met all the ANSI standards and was annually calibrated as standard protocol.

Case history establishes the basis of an audiological assessment. During case history taking, the audiologists must analytically and thoughtfully collect and examine all relevant information regarding their patient's medical history and hearing history (Beck, 2014). Both CHBAH and CMJAH utilize the subjective, objective, assessment, and plan (SOAP) format of case history taking (Beck, 2014). The researcher reviewed the case history notes of the audiological evaluation in the patient records and excluded the patient records that did not meet the inclusion criteria (i.e., those with cognitive impairments, not meeting the age range

and those with less than two hearing assessments available in their records), and the records considered suitable according to the inclusion criteria were included (Kavallieratos, 2012).

Audiologists used an otoscope to examine the ear canal, determine if the colour, shape, and general appearance of the structures of the tympanic membrane appeared normal and were intact (Hunter & Standford, 2014; Kramer et al., 2018). An otoscope helped to determine if there was any discernible signs of disease, malformations, fluids or drainage, tympanic membrane perforations, collapsed ear canals or blockages from atresia, stenosis, foreign bodies, cerumen, or debris (Diefendorf, 2014; Hunter & Standford, 2014). Furthermore, it was crucial to visually inspect the external auditory canal to verify if there were any contraindications within the canal that would have interfered with several audiological assessments which required the placement of a probe in the canal (Diefendorf, 2014).

Immittance audiometry measured how much sound energy was transmitted through the outer and middle ear systems (Kramer et al., 2018). As objective diagnostic measures, immittance testing aids the audiologists in identifying specific areas of dysfunction in the auditory system during routine examination of the middle ear system (DeBonis & Donohue, 2020). Acoustic immittance can either refer to acoustic impendence or acoustic admittance, or both (DeBonis & Donohue, 2020).Tympanometry and acoustic reflex thresholds tests are the two main assessments that make up the test battery of acoustic admittance (DeBonis & Donohue, 2020). Used to measure the acoustic admittance as a function of variations in the external auditory canal air pressure, tympanometry automatically delivers various pressure levels using a tympanometer in the canal. and Tympanometry is an objective physiological measurement of the middle ear's acoustic admittance in relation the air pressure within a sealed ear canal (Hunter & Standford, 2014). The main aim of tympanometry is to determine what is the point (measured in daPa) where the middle ear pressure equals the pressure in the

ear canal (DeBonis & Donohue, 2020). When the ear canal pressure is equal to the middle ear pressure, the acoustic admittance of the middle ear system will be maximized (DeBonis & Donohue, 2020). The changes in sound pressure, measured with a 226Hz probe tone, can be described using tympanometric types (Table 2), which was developed by Jerger (1970), and is a method used by many audiologists around the world, including South Africa (DeBonis & Donohue, 2020).

Table 2

Tympanometric Types (adapted from DeBonis & Donohue, 2020)

Type	Description
A	Normal middle ear function, i.e., Normal middle ear pressure and admittance.
As	Normal middle ear pressure with a decreased admittance, i.e., stiffness in middle ear system (e.g., Tympanosclerosis or otosclerosis)
Ad	Normal middle ear pressure with a significantly increased admittance, i.e., flaccid, or hypermobile middle ear system (e.g., ossicular discontinuity)
B	Flat across the pressure range with no identifiable point of maximum admittance, i.e., extreme stiffness of outer and/or middle ear systems (e.g., otitis media or impacted cerumen)
C	Negative pressure accompanied with normal or near normal admittance (e.g., Eustachian tube dysfunction)

ARTs are involuntary responses of the stapedius muscle to the sounds that are produced by an external stimulus (DeBonis & Donohue, 2020). The ear's immittance is altered due to the reflexive muscle contraction stiffening the conductive mechanism via the stapedial tendon (Gelfand, 2016). ARTs can be determined clinically by audiologists, and they can indicate the lowest intensity level at which the reflex is detectable or can produce a reflex response (Gelfand, 2016; DeBonis & Donohue, 2020). Audiologists can use this information to determine whether the middle ear is functioning normally (i.e., whether it is a cochlear or retrocochlear pathology) (DeBonis & Donohue, 2020). Adapted from Clark

(n.d.), Table 3 depicts the interpretation of acoustic threshold assessments. They can either be described as Present, Partial or Elevated, or Absent (Gelfand, 2016).

Table 3

Interpretation of acoustic reflex thresholds (Clark, n.d.).

Interpretation	Description
Present	Reflexes within normal limits, therefore consistent with normal middle ear and brainstem function, therefore indicating sufficient auditory sensitivity.
Partial or elevated	Could be indicative of the presence of a hearing loss, especially at the frequencies where they are absent.
Absent or elevated	Reflexes suggestive of a middle ear disorder, hearing loss or interruption of the neural pathway. Additionally, can be observed in children with normal or near-normal hearing. This may be indicative of a middle ear disease or neurological involvement of the 8th or 7th cranial nerves.

Sounds which are generated in the cochlea and measured in the ear canal is what an OAE can be defined as. OAEs are exhibited in response to stimuli being presented to healthy ears but are not observed in ears with moderate or greater cochlear hearing losses (DeBonis & Donohue, 2020). In the cochlea, the outer hair cells generate the mechanical energy known as OAEs, from a cochlear source related to sensory cell activity. Spontaneous and evoked OAEs are the two major types of OAEs used. In the absence of a sound stimulus, spontaneous OAEs are sounds generated by the cochlea and recorded in the ear canal and are usually found in individuals with normal hearing (DeBonis & Donohue, 2020). On the contrary, an evoked OAE is a sound produced by the cochlea that is recorded in the ear canal in response to stimulus (DeBonis & Donohue, 2020). Dependent on the type of stimulus that elicits them, different types of OAEs can be named after the stimuli used to elicit them, i.e., transient or distortion products. Hall and Swanepoel (2010), categorized OAE findings into

three potential categories; namely: normal, present but abnormal, and or absent. The researcher used a pass or refer criteria based on Hall and Swanepoel's (2010) criteria for this study as depicted in Table 4.

Table 4

Criteria for interpreting DPOAEs results (adapted from Hall & Swanepoel, 2010)

Criteria	Description
Normal	Emissions at a minimum of 6dB more intense than ambient noise. A person with a hearing loss is unlikely to produce these emissions
Present, but abnormal	Emissions at a minimum of 6dB, although their amplitude indicates that a person with normal hearing did not produce them.
Absent	Emissions not a minimum of 6dB more intense than ambient noise.

Normal function in both the middle ear and cochlea is shown by the presence of an OAE across the frequency range; whereas a sensory hearing loss can be implied by the absence of an OAE, where there is no middle ear pathology or acoustic obstruction (Jachova & Ristovska, 2023). The presence of middle ear fluid as well as in the case of negative middle ear pressure without the presence of a hearing loss, can have significant impact on the results of a DPOAE (Jachova & Ristovska, 2023). With regards to a child's hearing and auditory function, OAE results should be analysed in conjunction with other results that may have been collected. The benefits of OAEs are that:

- They provide audiologists the ability to distinguish between cochlear (sensory) and neural involvement.
- For patients who are unable to give reliable behavioural responses to audiological stimuli, OAEs provide information about the cochlear status and estimate their hearing function.

- Changes in cochlear function can be monitored (DeBonis & Donohue, 2020).

One of the most commonly used methods to assess hearing is through conventional pure tone threshold (PTT) assessments, which has a frequency range that operates between 0.125-8000Hz, which are the most relevant frequencies for speech sounds (Jachova & Ristovska, 2023; Škerková et al., 2021). Conventional PTT involves establishing the lowest sound pressure levels for various frequencies in which the patient can hear (Jachova & Ristovska, 2023). To obtain behavioural thresholds, clinical audiometers, which had the capabilities of assessing high frequencies, at each audiology departments, were used on each patient. Visual Reinforcement Audiometry (VRA), Conditioned Play Audiometry (CPA), and Speech Audiometry are methods in which hearing thresholds can be assessed and are dependent on the age of the child. VRA is usually conducted on infants around 5-6 months and relies on the infant's natural tendency to turn to a sound source. CPA can be used to assess children from the age of 24 months but is more reliable on children between 2-3 years of age and relies on a child responding to a sound using an activity. Conventional audiometry is usually appropriate for developing children who are age 4 years and older (Jachova & Ristovska, 2023). Hearing thresholds in the frequency range of 8000-20 000Hz, which are frequencies where damage to the hearing threshold can first be observed, can be assessed using high frequency audiometry (HFA) (Škerková et al., 2021). The same procedures used to assess conventional PTT can be used to assess HFA. Hearing impairments caused by ototoxicity, noise exposure, and acoustic traumas, or tinnitus assessments can be effectively assessed using HFA, as the frequency area 8000-20 000Hz is more sensitive to the effects of external factors such as medications and loud noises relative to the low and mid frequencies (Interacoustics, 2022); therefore, patients treated with significant dosages of ototoxic medication are left vulnerable to a significant decrease in their high frequency thresholds

(Kavallieratos, 2012). According to Vielsmeier et al. (2015), cochlear damage is not reliably ruled out by conventional PTT and that conventional PTT cannot detect damage to the hair cells that code for frequencies between the tested frequencies or above 8000Hz.

2.9. Analyses of data and statistical procedures.

To indicate any patterns the data may assume and to summarise the data collected, descriptive and inferential statistics was used (Kumar et al., 2019). A total of 47 patient records were reviewed for this study, where each patient had at least two appointments reviewed. In quantitative analysis, researchers aim to use descriptive statistics to identify the basic characteristics of variables by offering simple summaries of the sample and measurements (Trochim, 2002). Central tendency measures, such as mean, mode, and median, provided a clear picture of where most of the data would fall (Kumar et al., 2019), and these measures were adopted in the study for analysis of the data for objectives one and two. The use of inferential statistics, adopted for analysis of data for objectives three, four, and five, allowed for inferences beyond the immediate data using a more mathematical method (Trochim, 2002).

The independent variables in the study were as follows: gender, age, race, type of cancer, type of treatment, duration of treatment. Hearing function of the sample, using ear-specific information such as tympanograms, acoustic reflexes, DPOAEs and Pure Tone Average (PTA) were used to measure the degree of hearing loss based on the (a)symmetrical hearing status of the patient records. These were described using descriptive statistics. Additionally, the researcher took note of any audiological changes that may have occurred. When an asymmetry is found in a hearing loss, the degree of hearing loss varies from each ear in a bilateral hearing loss. A bilateral hearing loss can be defined as a hearing loss in both ears, whereas a unilateral loss is usually when a hearing loss is found in one ear (DeBonis & Donohue, 2020). With regards to DPOAE results, assessments were conducted for both the

right and left ears at each frequency at each patient's initial audiological assessment and at their follow-up session. The DPOAE results were summarized descriptively as an overall pass or refer for both the left and right ears.

There are various ways to categorizing a hearing loss, such as type, degree, and configuration (Brewer et al., 2024). There are three common types of hearing loss, namely: sensorineural hearing loss, conductive hearing loss and mixed hearing loss (Brewer et al., 2024). The level of severity is referred to as the degree of hearing loss, which can have a significant impact on an individual's quality of life (Brewer et al., 2024). Haggard and Primus (1999), Downs (1976) and Northern and Downs (2002) had proposed a more precise scale for children which would be used to classify the categories using descriptive terminology. They were concerned that a low threshold such as 25dB hearing loss, which is often applied to adults, is too high for children, and they recommended that a fence of 15dB hearing loss would be more appropriate for children (Haggard & Primus, 1999). As a result, Clark (1980), proposed a similar hearing loss classification scale for children with hearing loss as Goodman (1965), but with an extended threshold to include an additional category of slight hearing loss for PTAs between 15dB and 25dB hearing loss. This scale is widely used by many audiologists around the world for children and was therefore used to clinically describe the PTA results in the current study (Haggard & Primus, 1999). The PTA was descriptively described as a degree of hearing loss for both the left and right ears, using these existing scales as is depicted in Table 5 (Clark, 1980). Furthermore, the symmetry, laterality, type, and configuration of the patient records hearing function in session one and session two will be discussed in conjunction with the degree of the hearing loss if one is present.

Table 5

Scale of hearing impairment

Scale of hearing impairment (Clark, 1980)	
PTA in decibels (dB HL)	**Classification Term**
<15	Normal
15-25	Slight
26-40	Mild
41-55	Moderate
56-70	Moderately-Severe
71-90	Severe
>90	Profound

To examine the relationship between hearing function (tympanograms, acoustic reflexes, DPOAEs and PTA) and the independent variables, a logistic regression was performed (Armitage et al., 2002). Binary logistic regression was used to examine the relationship between the hearing function (hearing loss or normal hearing) and the above-mentioned factors, where hearing function was on a nominal scale (categorical), and factors on a continuous scale (age) and a nominal scale (gender, race, type of cancer, type of treatment and the duration of treatment). Therefore, the study investigated whether age, gender, race, type of cancer, type of treatment and the duration of treatment would have a substantial impact on the tympanograms, acoustic reflexes, DPOAEs and PTA results of the paediatric population with cancer. As a result, age, gender, race, type of cancer, type of treatment and the duration of treatment are the independent variables, whereas the tympanograms, acoustic reflexes, DPOAEs and PTA results are the response variables.

Researchers use P values to establish whether a sample estimate differs significantly from a hypothesized value (Shreffler & Huecker, 2022). According to the null hypothesis the hearing function of paediatric patients with cancer was not influenced by the type of cancer, the type of treatment and its duration, the age of the patient and the gender and race of the patient. The alternative hypothesis stated that the hearing function of paediatric patients with

cancer was influenced by the type of cancer, the type of treatment and its duration and dosage, the age of the patient and the gender and race of the patient. P-values indicate the likelihood that the observed effect within the study would have occurred by chance if there was no true effect, in reality (Shreffler & Huecker, 2022). Typically, in order to be considered statistically significant, data should yield a $p<0.05$ (Shreffler & Huecker, 2022). In other words, all the hypotheses were tested at a 5% significant value and 95% confidence level would be present (Shreffler & Huecker, 2022). Therefore, the null hypotheses are rejected if they have a p-value which is lower than 0.05 (Shreffler & Huecker, 2022).A statistician was consulted for the inferential statical analysis of this study.

Statistically, R-squared (R^2 or the coefficient of determination) is a statistical measure in a regression model that measures how much proportion of a variance can be explained by an independent variable based on the dependant variable (Taylor, 2020; Gao, 2023). R^2 is frequently used to assess things such as the preventability of disease, the effectiveness of treatments, whether genetic factors could be a contributing variable to diseases etc., which in the case of this study, the researcher's aim was to determine the relationship between the hearing function of the paediatric population and independent variables such as age, treatment, and type of cancer amongst some of the selected variables (Gao, 2023). With degrees of freedom corresponding to the number of new variables introduced, the R^2 test follows an asymptotic chi-squared distribution (Kim, 2023). To determine the fit and effectiveness of regression models, R^2 is a commonly used statistical measure in empirical research (Gao, 2023; Kim, 2023). With a range from zero (no explanatory power) to one (perfect fit), R^2 measures how well independent variables explain a dependent variable's variance (Gao, 2023; Kim, 2023). R^2 is commonly used to take the degrees of freedom into account using the sample size (n) and the number of independent variables(k), as well as a

constant if needed(Gao, 2023; Kim, 2023). Therefore, the adjusted R^2 can be calculated using the following equation (Kim, 2023):

$$R^2 = 1 - \frac{n-1}{n-k}(1 - R^2) \cdot$$

The multivariable logistic regression which was calculated using the regression formula to obtain the R^2 score will explore the factors associated with hearing loss.

2.10. Reliability and Validity

The researcher compiled and reviewed the patient records personally to ensure data collection remained consistent. To increase the reliability and validity of the study, certain conditions were taken into account when utilizing the data. The reviewed patient files were collected from the audiology and oncology units at Chris Hani Baragwanath Academic Hospital and Charlotte Maxeke Johannesburg Academic Hospital. When the data was originally collected, both oncology and audiology teams consisted of qualified professionals, who followed the protocols of their departments to ensure that the data collected met the standards of their established protocols at each hospital. Strictly following the test procedure protocols, ensured the reliability of the data collection.

Repeated measures served as the basis for the audiological assessments that the patients regularly underwent. The frequent testing resulted in a decrease in false-positive results, which in turn improved the study's reliability. When the feasibility of selecting a random or large sample number is low, a valuable feature to have is repeated measures (Kavallieratos, 2012). Due to the patient's information being obtained from their audiological and medical records, their information can therefore be deemed reliable (Kavallieratos, 2012). External validity, in its most basic form, depicts the range to which inferences obtained from a study's sample may be applied to broader populations or the general populations (Findley et al., 2021). Generalizability is therefore used as the term to describe

the inferences that relate to a broader population of a predefined sample, which in this case would be the paediatric population with cancer in South Africa (Findley et al., 2021). Furthermore, due to the availability of repeated measures in this study on the same participants and the sample being representative of the population in the area, the external validity and generalization is improved and strengthened (Kavallieratos, 2012).

2.11. Ethical considerations

When information about patients is requested for educational or research purposes, it is the responsibility of both the health care professionals and the researcher to protect and respect the privacy and autonomy of the patients (Health Professions Council of South Africa, 2021). This was adhered to by the researcher of this study by ensuring no personal identifying information was reported on or documented. Given that this study was a retrospective study and obtaining the consent of patients would been impractical in some cases, the data was anonymized, and the research ethics committee informed as per the Health Professions Council of South Africa's guidelines (2021). Additionally, with a five-year survival rate of 10-55% in LMIC's, there would have been an increased probability that several of the cancer patients would have passed away due to the severity of their disease (WHO Global Initiative for Childhood Cancer, 2021; Ehrlich et al., 2023).

Permission was obtained from all the relevant management structures from CHBAH and CMJAH. The following conditions were adhered to and followed for data collection:

i. Obtained ethical approval from the relevant administrative authorities as well as the University of Witwatersrand Ethical Committee (Medical) for this study (Protocol Number: M221128) (Appendix A).
ii. Approval from CMJAH and CHBAH's medical manager and/or CEO was obtained (Appendices D and G).

iii. Approval from CMJAH's ethics committee was obtained (Appendix G).

iv. Approval from CHBAH's Medical Advisory Committee was obtained (Appendix D).

v. Approval from the departmental HOD or supervisor of the audiology departments was given from both CMJAH and CHBAH (Appendices F and I).

vi. Approval from the departmental HOD or supervisor of the oncology departments was given from both CMJAH and CHBAH (Appendices E and H).

vii. Both hospitals will have access to the results of the research study.

Before any study may proceed, risks to human subjects must be carefully considered and evaluated. Ethical considerations are of the utmost significance in the field of research. The difference between right and wrong may boil down to a set of principles known as ethics (Beshty, 2015). The ethical principles of the Declaration of Helsinki were adhered to throughout this study as they were essential to the practice of healthcare and guided the research (World Medical Association, 2015).

Autonomy

This principle entails respect for the participants personal information. Research that involves human subjects must respect the dignity, well-being, and safety interests of all participants (du Toit et al., 2015). This was safeguarded by only extracting and coding information which was only required for answering the research question from the participant records. Additionally, before further analysis was conducted, any form of identifying information from the data set was removed (Sarkar & Seshadri, 2014). Participant records were coded

using numerical formats to conceal their identity, i.e., each participant record was given a unique number (Sarkar & Seshadri, 2014).

Beneficence and non-maleficence

A researcher's ethical obligation is to maximize benefit while minimizing harm. The deliberate infliction of harm on persons is strictly prohibited (du Toit et al., 2015). As medical and audiological records in this study were reviewed and participants were not directly involved in the study, the participants did not experience any potential economic, social, legal, physical, or psychological or physical harm or risks, nor did they receive any direct benefits (du Toit et al., 2015).

Justice

This pertains to participant records right to privacy and fair treatment. In the case of this study, as far as the right to fair treatment, it would have been to ensure that no group is excluded from the study, and to be representative of the overall target population, the types of participants selected should be guided by research questions and requirements provided. The specified inclusion and exclusion criteria were adhered to ensure justice, and the right to privacy was ensured by all shared information being kept confidential by the researcher (Barrow et al., 2021)**.**

Confidentiality

During this the data collection in this study no personal identifying information was collected. The research ensured that no personally identifiable information that could link any reviewed participant record to an individual participant was collected. Personal identifiable information such as names, hospital numbers, cell phone numbers, identification numbers or email addresses were not collected. Hospital numbers were coded for data collection and analysis processes, and the codes were only accessible to the researcher and the supervisor.

Confidentiality was of the utmost importance when extracting data from the patient records. Only authorized researcher had access to this information (Sarkar & Seshadri, 2014).

Data safety monitoring

Collected data was secured in a code-encrypted Microsoft Excel document, in a computer (Huawei intel core i5 processor computer) that is password-protected. The digital data does not have any information that can identify the participants and have been stored in an encrypted Microsoft Excel sheet which have been backed up on both a code-encrypted external hard drive and code-encrypted online google drive for statistical analysis. Hard copy data capture forms have been stored in a locked cupboard in the researcher's home. According to Wits Ethics Committee information sheet, if a scientific publication would arise from the study, all data collected throughout the study will be securely retained for two years and for six years if no publication occurs (*Ethics Committees - Wits University*, 2022). Thereafter, the data will be destroyed and/or deleted.

CHAPTER THREE

RESULTS

3.1. Introduction

The findings from the study into the hearing function of the paediatric population with cancer, who were treated at either Chris Hani Baragwanath Hospital or Charlotte Maxeke Academic Hospital are presented in this chapter in line with the main aim of the study, and its specific objectives. The main aim of the study was to investigate the hearing function of paediatric patients with cancer in Johannesburg, South Africa; with the specific objectives being 1) to describe the hearing function of paediatric patients with cancer; 2) to determine factors that influenced the hearing function in this population; 3) to explore the relationship between demographic factors such as age, race and gender and hearing function findings in this population; 4) to investigate the relationship between diagnostic factors such as type of cancer and duration of cancer treatment and hearing function findings in this population; and 5) to study the relationship between treatment factors such as different treatment options and hearing function findings.

3.2. Description of the sample

3.2.1. Demographics

Table 6 below depicts the demographic profile of the total sample, where the study consisted of 47 participants. The demographic profile includes the participants' gender, race, and the hospitals where the patient records were obtained for review. The total sample was made up of majority male participants (55.3%), with female participants being the least prevalent of the total sample (44.7%). The most common race that made up the total sample was the African race (91.5%), with majority of the participants being obtained from the CHBAH Paediatric Oncology Unit and Audiology department (68.1%).

Table 6

An analysis of the demographic profile of participants (N=47)

	Total (N=47)
Gender; n (%)	
Female	21 (44.7)
Male	26 (55.3)
Race; n (%)	
African	43 (91.5)
White	1 (2.1)
Coloured	2 (4.3)
Indian	1 (2.1)
Hospitals; n (%)	
CHBAH	32 (68.1)
CMJAH	15 (31.9)

3.2.2. Medical profile of patient records

Table 7 below depicting the medical profile of the sample reveals the treatment durations (days), the various types of cancer, and the cancer treatments documented in this sample. The most prevalent treatment duration was 0-50 days (72.3%), with only 2 participants having received treatment for longer than 100 days. As far as type of cancer was concerned, osteosarcoma was the most prevalent cancer diagnosis (42.6%); with Doxorubicin, otherwise known as Adriamycin (29.8%), and Vincristine (20.5%) being the most prescribed treatments.

Table 7

Medical profile of participants (N=47)

	Total (N = 47)
Treatment duration (days)	
0-50 days	34 (72.3%)
51-100 days	11 (23.4%)

	Total (N = 47)
>100 days	2 (4.3%)
Type of cancer	
Brain Cancer	4 (8.5%)
Embryonal Cancer	3 (6.4%)
Hodgkin's Lymphoma	4 (8.5%)
Leukaemia	1 (2.1%)
Medulloblastoma	3 (6.4%)
Nasopharyngeal Carcinoma	7 (14.9%)
Neuroblastoma	2 (4.3%)
Osteosarcoma	20 (42.6%)
Pelvic germ cell tumour	1 (2.1%)
Rhabdomyosarcoma	1 (2.1%)
Testicular tumour	1 (2.1%)
Cancer treatments	
5fu (Fluorouracil)	1 (2.3%)
Adriamycin/Doxorubicin	14 (29.8%)
Carboplatinum	1 (2.3%)
Cisplatin	9 (19.1%)
Cyclophosphamide	1 (2.3%)
Dexamethasone	1 (2.3%)
Etoposide	1 (2.3%)
Gemcitabine	1 (2.3%)
Ifosfomide	3 (6.8%)
VP16	2 (4.5%)
Vinblastine	1 (2.3%)
Vincristine	9 (19.1%)

3.3. Description of the hearing function of paediatric patients with cancer

a) *Auditory status*

In accordance with the sample size, the researcher was 95% confident that the true prevalence of the hearing loss in the sample would be between 23.5% and 51.1% (95% CI: 23.5 – 51.1). With a prevalence of 36.2% of hearing loss the auditory status of the paediatric patients with cancer is portrayed in Table 8 below. In this study, 47 patient records were reviewed, with 17 of these participants attending at least two sessions or more. As portrayed in Table 8, four participants (23.5%) presented with a hearing loss in session one. In the second session, it

was found that this number more than doubled to nine participants (52.9%), presenting with a hearing loss. This increase in hearing loss is evidence that there are factors that may have an impact on the hearing function of this population. The most prevalent type of hearing loss that was found in session one was a conductive hearing loss (75.0%), but by the second session the most prevalent type of hearing loss was found to be a sensorineural hearing loss (55.6%), with a conductive hearing loss following closely behind (44.4%). In session one it was found that most participants presented with a unilateral, and therefore asymmetrical hearing loss (75% respectively). Whereas session two revealed that most of the hearing losses were bilateral and symmetrical (55.6% respectively). Furthermore, it was found that none of the participants presented with a mixed hearing loss. The most prevalent degree of impairment was a mild hearing loss (17.6%) in session one, with a mild to profound hearing loss (5.9%) being the least type of hearing loss. Session two revealed that the most prevalent degree of impairment was a moderate hearing loss (17.6%), with the least type of hearing losses being a slight, mild to moderate, mild to profound or profound hearing loss (5.9% respectively). In both sessions a high-frequency hearing loss was found to be the most prevalent configuration, with 75.0% of the participants presenting with this type of configuration in session one, with an increase to 88.9% in session two.

Table 8

Characteristics of auditory status among participants– among those who had <u>two appointments (n=17)</u>

	Session 1; n (%)	**Session 2; n (%)**
Participants with hearing loss	4 (23.5)	9 (52.9)
Degree of hearing		
Normal	13 (76.5)	8 (47.0)
Mild	3 (17.6)	2 (11.8)
Slight	0	1 (5.9)
Slight to moderate	0	0
Mild to moderate	0	1 (5.9)

Mild to profound	1 (5.9)	1 (5.9)
Moderate	0	3 (17.6)
Moderately severe	0	0
Severe to profound	0	0
Profound	0	1 (5.9)
Laterality		
Unilateral	3 (75.0)	4 (44.4)
Bilateral	1 (25.0)	5 (55.6)
Symmetry		
Symmetrical	1 (25.0)	5 (55.6)
Asymmetrical	3 (75.0)	4 (44.4)
Type		
Sensorineural Hearing Loss	1 (25.0)	5 (55.6)
Conductive Hearing Loss	3 (75.0)	4 (44.4)
Mixed Hearing Loss	0	0
Configuration		
Sloping	1 (25.0)	1 (11.1)
High Frequency	3 (75.0)	8 (88.9)

b) *Otoscopic Examination, Tympanograms, Acoustic Reflexes and DPOAEs*

Table 9 shows the audiological results among the participants. In session one, the majority of the participants presented with a conductive hearing loss (75%). Table 9 below shows that about 23,5% of the participants presented with occluding wax in at least one or both of their ears. Additionally, Table 9 shows that 18.7% of the participants obtained a Type B tympanogram, indicating a stiff tympanic membrane or abnormal middle ear function. However, about 13.3% of the participants presented with an absent ARTs result and about 7.1% of the participants obtained a refer result for their DPOAE assessment, suggesting that a small threshold of participant's middle ear function was abnormal, with the remainder of the participants having a possible normal middle ear function and cochlear function. Nonetheless, the otoscopy and tympanogram results correlate with the auditory status of the participants.

The number of participants who presented with a hearing loss increased by 29.4% in session two. However, session two saw 55.6% of the participants presenting with a sensorineural loss

as compared to 44.4% with a conductive hearing loss. As can be seen in Table 9, approximately 87.5% of the participants presented with normal, Type A tympanograms, with the remainder presenting with abnormal tympanogram results (12.5%) in session two. Around 6.7- 26.7% of the participants presented with either a partially present, absent, or elevated ARTs result, with the remaining 46.6% of the participants presenting with a present result. Moreover, approximately 85.7% of the participants presented with a pass DPOAE result, with the remaining 14.3 presenting with a refer in session two.

Table 9

Audiological results among the participants

Otoscopy (n=17)				
Result	**Session 1; n (%)**		**Session 2; n (%)**	
	Left	**Right**	**Left**	**Right**
No abnormalities detected (NAD)	12 (70.6)	13 (76.5)	12 (70.6)	13 (76.5)
Dull tympanic membrane (DTM)	1 (5.9)	2 (11.7)	1 (5.9)	3 (17.6)
Occluded wax (OW)	4 (23.5)	1 (5.9)	4 (23.5)	0
Partially occluded wax (POW)	0	1 (5.9)	0	1 (5.9)

Tympanometry (n=16)				
Type	**Session 1; n (%)**		**Session 2; n (%)**	
	Left	**Right**	**Left**	**Right**
A	13 (81.3)	14 (87.5)	14 (87.5)	14 (87.5)
As	0	1 (6.3)	0	1 (6.3)
Ad	0	0	0	0
B	3 (18.7)	0	2 (12.5)	1 (6.3)
C	0	1 (6.3)	0	0

Acoustic Reflex Thresholds (n=15)				
Result	**Session 1; n (%)**		**Session 2; n (%)**	
	Left	**Right**	**Left**	**Right**
Present	6 (40)	8 (53.4)	7 (46.6)	7 (46.6)
Partially present	7 (46.6)	5 (33.3)	4 (26.7)	4 (26.7)
Absent	1 (6.7)	2 (13.3)	3 (20)	2 (13.3)
Elevated	1 (6.7)	0	1 (6.7)	2 (13.3)

DPOAE (n=14)				
Result	**Session 1; n (%)**		**Session 2; n (%)**	
	Left	**Right**	**Left**	**Right**

Pass	13 (92.9)	13 (92.9)	12 (85.7)	12 (85.7)
Refer	1 (7.1)	1 (7.1)	2 (14.3)	2 (14.3)

3.4. Establishing factors that influenced the hearing function in this population

In this study, the prevalence of hearing loss was 36.2% (95% CI: 23.5 – 51.1). As a result, the researcher was 95% confident that the true prevalence of hearing loss in the population in which the sample was drawn would fall between 23.5% and 51.1%. As discussed in the methodology chapter, the fit and effectiveness of regression models is determined using R^2 which is a commonly used statistical measure in empirical research (Gao, 2023; Kim, 2023). With a range from zero (no explanatory power) to one (perfect fit), R^2 measures how well independent variables explain a dependent variable's variance (Gao, 2023; Kim, 2023). As seen in Table 10, the value of R^2 was 0.09, indicating that the independent variables had minimal effect on the dependent variable. Therefore, the alternative hypothesis was rejected, and the null hypothesis proven true for these objectives. Furthermore, to be considered statistically significant, in this analysis, the data would have to yield a $p<0.05$ alpha value (Shreffler and Huecker, 2022). Essentially, p-values indicated the likelihood that the observed effect within the study would have occurred by chance if there was no true effect, in reality (Shreffler and Huecker, 2022). Thus, factors such gender, age of diagnosis and the total treatment days had no statistical or significant impact on the hearing function of the paediatric population with cancer, as these factors yielded p-values which were all greater than $p<0.05$, as indicated in Table 10.

Table 10

Multivariable logistic regression exploring factors associated with hearing loss

Predictor variables	Odds ratio	p value (α = 0.05)	95% confidence interval	
			Lower	Upper
Gender [a]	3.09	*0.095*	0.822	11.61
Age of diagnosis (Years)	0.87	*0.167*	0.710	1.061

Total treatment days	1.0	*0.272*	0.967	1.009

Regression calculated with n = 47, $R^2 = 0.09$

[a] Reference category = female

Below, Table 11 indicates the independent variables and their effects on the dependent variable, being the hearing function of this population. As it was stated above, the null hypotheses are rejected when $p<0.05$. Table 11 indicates that the only independent variable or objective that is true to the alternative hypothesis and therefore the null hypothesis rejected, is the type of cancer, with a p-value of 0.027.

To statically describe the significance of the PTA degree of impairment in the total sample (N=47) from session 1 to session 2, Chi-square analysis was used (Table 11) and Multivariable logistic regression (Table 10). The Multivariable logistic regression was found to statistically non-significant for the overall objectives set out for hearing loss, with a score R^2 score of 0.09. According to Table 11, the most statistically significant objective was the relationship between the type of cancer and hearing loss, with a p-value less than 0.05 (p=0.027). Therefore, the most significant changes in hearing were found to be within this objective. On the contrary, the statistically non-significant objectives were treatment duration in days (p=0.915) and race (0.479), with p-value scores which were greater than 0.05. In this study, it was found that each participant had a combination of up to five treatment options in their treatment regimen. As discussed above, Doxorubicin and Vincristine were the most used treatment options amongst this population. According to Table 11, all the treatment options, from Treatment one through to five, were statistically non-significant with p-values ranging from 0.357 to 0.827; all of which are greater than 0.05.

Table 11

Association between hearing loss and diagnostic and demographic characteristics, Chi-square analysis (p = 0.05)

	Normal (N = 30)	Hearing loss (N = 17)	p-value
Age of diagnosis			0.341
Median (Q1, Q3)	13.0 (10.0, 14.0)	11.0 (8.0, 14.0)	
Min, Max	7.0, 16.0	5.0, 17.0	
Gender			0.113
Female	16 (76.2%)	5 (23.8%)	
Male	14 (53.8%)	12 (46.2%)	
Race			0.479
Black	26 (60.5%)	17 (39.5%)	
Coloured	2 (100.0%)	0 (0.0%)	
Indian	1 (100.0%)	0 (0.0%)	
White	1 (100.0%)	0 (0.0%)	
Type of cancer			0.027
Brain Cancer	2 (50.0%)	2 (50.0%)	
Embryonal Cancer	3 (100.0%)	0 (0.0%)	
Hodgkin's Lymphoma	3 (75.0%)	1 (25.0%)	
Leukaemia	1 (100.0%)	0 (0.0%)	
Medulloblastoma	2 (66.7%)	1 (33.3%)	
Nasopharyngeal Carcinoma	0 (0.0%)	7 (100.0%)	
Neuroblastoma	2 (100.0%)	0 (0.0%)	
Osteosarcoma	15 (75.0%)	5 (25.0%)	
Pelvic germ cell tumour	1 (100.0%)	0 (0.0%)	
Rhabdomyosarcoma	0 (0.0%)	1 (100.0%)	
Testicular tumour	1 (100.0%)	0 (0.0%)	
Treatment duration (days)			0.915
0-50 days	22 (64.7%)	12 (35.3%)	
51-100 days	7 (63.6%)	4 (36.4%)	
>100 days	1 (50.0%)	1 (50.0%)	
Treatment 1			0.357
5fu (Fluorouracil)	0 (0.0%)	1 (100.0%)	
Adriamycin/Doxorubicin	11 (78.6%)	3 (21.4%)	
Carboplatinum	1 (100.0%)	0 (0.0%)	
Cisplatin	4 (44.4%)	5 (55.6%)	
Cyclophosphamide	1 (100.0%)	0 (0.0%)	
Dexamethasone	0 (0.0%)	1 (100.0%)	
Etoposide	1 (100.0%)	0 (0.0%)	
Gemcitabine	0 (0.0%)	1 (100.0%)	

	Normal (N = 30)	Hearing loss (N = 17)	p-value
Ifosfomide	1 (33.3%)	2 (66.7%)	
VP16	2 (100.0%)	0 (0.0%)	
Vinblastine	1 (100.0%)	0 (0.0%)	
Vincristine	7 (77.8%)	2 (22.2%)	
Treatment 2			0.398
5-Fluorouracil	0 (0.0%)	4 (100.0%)	
Actinomycin D	1 (100.0%)	0 (0.0%)	
Adriamycin/Doxorubicin	5 (83.3%)	1 (16.7%)	
Bleomycin	1 (100.0%)	0 (0.0%)	
Carboplatinum	4 (80.0%)	1 (20.0%)	
Cisplatin	11 (68.8%)	5 (31.2%)	
Cyclophosphamide	3 (75.0%)	1 (25.0%)	
Etoposide	1 (50.0%)	1 (50.0%)	
MTX	1 (100.0%)	0 (0.0%)	
Mesna	1 (50.0%)	1 (50.0%)	
VP16	0 (0.0%)	1 (100.0%)	
Vincristine	1 (100.0%)	0 (0.0%)	
Treatment 3			0.493
Adriamycin/Doxorubicin	2 (66.7%)	1 (33.3%)	
Bleomycin	4 (100.0%)	0 (0.0%)	
Carboplatinum	1 (50.0%)	1 (50.0%)	
Cisplatinum	2 (66.7%)	1 (33.3%)	
Cyclophosphamide	1 (100.0%)	0 (0.0%)	
Dacarbazine	1 (100.0%)	0 (0.0%)	
Etoposide	2 (100.0%)	0 (0.0%)	
MTX	13 (76.5%)	4 (23.5%)	
VP16	2 (66.7%)	1 (33.3%)	
Vincristine	0 (0.0%)	1 (100.0%)	
Treatment 4			0.827
Adriamycin/ Doxorubicin	1 (100.0%)	0 (0.0%)	
Carboplatinum	1 (100.0%)	0 (0.0%)	
Cisplatin	4 (80.0%)	1 (20.0%)	
Cyclophosphamide	1 (100.0%)	0 (0.0%)	
Cytosar	1 (100.0%)	0 (0.0%)	
D7IC	1 (100.0%)	0 (0.0%)	
Etoposide	1 (100.0%)	0 (0.0%)	
IT M/H/C	0 (0.0%)	1 (100.0%)	
Ifosfomide	1 (50.0%)	1 (50.0%)	
MTX	1 (50.0%)	1 (50.0%)	
Neupogen	1 (50.0%)	1 (50.0%)	
VP16	2 (100.0%)	0 (0.0%)	
Vincristine	1 (100.0%)	0 (0.0%)	
Treatment 5			0.407
Carboplatinum	1 (100.0%)	0 (0.0%)	

	Normal (N = 30)	Hearing loss (N = 17)	p-value
Cisplatin	3 (75.0%)	1 (25.0%)	
Cyclophosphamide	3 (75.0%)	1 (25.0%)	
Laspar	1 (100.0%)	0 (0.0%)	
MTX	0 (0.0%)	1 (100.0%)	
Mesna	1 (50.0%)	1 (50.0%)	
Procarbazine	1 (100.0%)	0 (0.0%)	
VP16	2 (100.0%)	0 (0.0%)	

3.5. Exploring the relationship between demographic factors such as age, race, gender, and hearing function findings in this population

To be considered statistically significant, data should yield a p-value that is less than 0.05 (Shreffler and Huecker, 2022).

As far as the relationship between age and hearing function findings is concerned as seen in Table 12, the p-value for age is greater than 0.05, with a score of 0.167. Similarly, the p-value for gender is greater than 0.05 at 0.095. Therefore, this indicates that the relationship between these variables and hearing function findings are statistically non-significant, indicating that the likelihood that age and gender have a significant effect on the hearing function of this population is small. Table 12 indicates that the p-value for race is 0.479, which also indicates a statistically non-significant relationship between race and hearing function in this sample. These results could, however, have also been influenced by the size of the sample, as the small size may have had a negative effect on drawing up well-rounded inferences on this study.

Table 12

Association between hearing loss and demographic characteristics, Chi-square analysis (p = 0.05)

	Normal (N= 30)	Hearing loss (N = 17)	p-value
Age of diagnosis			0.341
Median (Q1, Q3)	13.0 (10.0, 14.0)	11.0 (8.0, 14.0)	
Min, Max	7.0, 16.0	5.0, 17.0	
Gender			0.113
Female	16 (76.2%)	5 (23.8%)	
Male	14 (53.8%)	12 (46.2%)	
Race			0.479
Black	26 (60.5%)	17 (39.5%)	
Coloured	2 (100.0%)	0 (0.0%)	
Indian	1 (100.0%)	0 (0.0%)	
White	1 (100.0%)	0 (0.0%)	

3.6. Investigating the relationship between diagnostic factors such as the type of cancer, duration of cancer treatment and hearing function in this population.

With a p-value of 0.027, which is less than 0.05, the relationship between the type of cancer and hearing function was found to be statistically significant in this study according to Table 13

According to Table 13, participants with brain cancer had an equal possibility of acquiring a hearing loss, with 50% of the participants with cancer having hearing within normal limits and 50% of the participants acquiring a hearing loss. Participants with embryonal cancer were less likely to acquire a hearing loss, along with patients who had leukaemia, pelvic germ cell cancer, neuroblastoma, and testicular cancer as 100% of these participants had normal hearing.

According to Table 13, 75% of the participants with Hodgkin's lymphoma and osteosarcoma (where most participants presented with normal hearing), presented with normal hearing, as compared to 25% of these participants who presented with a form of

hearing loss after their second hearing assessment. A percentage of 66.7% of patient records were found to have normal hearing for participants diagnosed with medulloblastoma, as compared to 33.3% who acquired a hearing loss. Lastly, 100% of the patient records who were diagnosed with rhabdomyosarcoma were found to have a hearing loss.

As far as the relationship between treatment duration and hearing function, according to Table 13, 72.3% of the participants underwent treatment over the span of 0-50 days, with the remaining 23.4% and 4.3% undergoing treatment over 51-100 days and more than 100 days respectively. Table 13 indicates a p-value of 0.915, which is a score higher than 0.05, and therefore indicating a relationship that is statistically non-significant. Thus, the duration of the cancer treatment likely had no effect on the hearing function of this population.

Table 13

Association between hearing loss and diagnostic characteristics, Chi-square analysis (p = 0.05)

	Normal (N= 30)	Hearing loss (N = 17)	p-value
Type of cancer			0.027
Brain Cancer	2 (50.0%)	2 (50.0%)	
Embryonal Cancer	3 (100.0%)	0 (0.0%)	
Hodgkin's Lymphoma	3 (75.0%)	1 (25.0%)	
Leukaemia	1 (100.0%)	0 (0.0%)	
Medulloblastoma	2 (66.7%)	1 (33.3%)	
Nasopharyngeal Carcinoma	0 (0.0%)	7 (100.0%)	
Neuroblastoma	2 (100.0%)	0 (0.0%)	
Osteosarcoma	15 (75.0%)	5 (25.0%)	
Pelvic germ cell cancer	1 (100.0%)	0 (0.0%)	
Rhabdomyosarcoma	0 (0.0%)	1 (100.0%)	
Testicular cancer	1 (100.0%)	0 (0.0%)	
Treatment duration (days)			0.915
0-50 days	22 (64.7%)	12 (35.3%)	
51-100 days	7 (63.6%)	4 (36.4%)	
>100 days	1 (50.0%)	1 (50.0%)	

3.7. Analysing the relationship between treatment factors such as different treatment options and hearing function findings in this population

As discussed above, each participant had a combination of at least five treatment options administered to assist in the treatment of their cancer. Data would need to produce a p-value which is less than 0.05 in order to be considered statistically significant (Shreffler & Huecker, 2022).

As far as the relationship between the different treatment options and hearing function findings is concerned as seen in Table 14, there are five different treatment combinations. The p-value for all the treatment options is greater than 0.05, with a score of 0.357 for Treatment one, 0.398 for Treatment two, 0.493 for Treatment three, 0.827 for Treatment four and 0.407 for Treatment five. Therefore, this indicates that the relationship between these variables and hearing function findings are statistically non-significant, indicating that there is a minimal likelihood that the different treatment options have a significant effect on the hearing function of this population.

Table 14

Association between hearing loss and treatment options

	Normal (N = 30)	Hearing loss (N = 17)	p-value
Treatment 1			0.357
5fu (Fluorouracil)	0 (0.0%)	1 (100.0%)	
Adriamycin/Doxorubicin	11 (78.6%)	3 (21.4%)	
Carboplatinum	1 (100.0%)	0 (0.0%)	
Cisplatin	4 (44.4%)	5 (55.6%)	
Cyclophosphamide	1 (100.0%)	0 (0.0%)	
Dexamethasone	0 (0.0%)	1 (100.0%)	
Etoposide	1 (100.0%)	0 (0.0%)	
Gemcitabine	0 (0.0%)	1 (100.0%)	
Ifosfomide	1 (33.3%)	2 (66.7%)	
VP16	2 (100.0%)	0 (0.0%)	
Vinblastine	1 (100.0%)	0 (0.0%)	
Vincristine	7 (77.8%)	2 (22.2%)	

	Normal (N = 30)	Hearing loss (N = 17)	p-value
Treatment 2			0.398
5-Fluorouracil	0 (0.0%)	4 (100.0%)	
Actinomycin D	1 (100.0%)	0 (0.0%)	
Adriamycin/Doxorubicin	5 (83.3%)	1 (16.7%)	
Bleomycin	1 (100.0%)	0 (0.0%)	
Carboplatinum	4 (80.0%)	1 (20.0%)	
Cisplatin	11 (68.8%)	5 (31.2%)	
Cyclophosphamide	3 (75.0%)	1 (25.0%)	
Etoposide	1 (50.0%)	1 (50.0%)	
MTX	1 (100.0%)	0 (0.0%)	
Mesna	1 (50.0%)	1 (50.0%)	
VP16	0 (0.0%)	1 (100.0%)	
Vincristine	1 (100.0%)	0 (0.0%)	
Treatment 3			0.493
Adriamycin/Doxorubicin	2 (66.7%)	1 (33.3%)	
Bleomycin	4 (100.0%)	0 (0.0%)	
Carboplatinum	1 (50.0%)	1 (50.0%)	
Cisplatinum	2 (66.7%)	1 (33.3%)	
Cyclophosphamide	1 (100.0%)	0 (0.0%)	
Dacarbazine	1 (100.0%)	0 (0.0%)	
Etoposide	2 (100.0%)	0 (0.0%)	
MTX	13 (76.5%)	4 (23.5%)	
VP16	2 (66.7%)	1 (33.3%)	
Vincristine	0 (0.0%)	1 (100.0%)	
Treatment 4			0.827
Adriamycin/ Doxorubicin	1 (100.0%)	0 (0.0%)	
Carboplatinum	1 (100.0%)	0 (0.0%)	
Cisplatin	4 (80.0%)	1 (20.0%)	
Cyclophosphamide	1 (100.0%)	0 (0.0%)	
Cytosar	1 (100.0%)	0 (0.0%)	
D7IC	1 (100.0%)	0 (0.0%)	
Etoposide	1 (100.0%)	0 (0.0%)	
IT M/H/C	0 (0.0%)	1 (100.0%)	
Ifosfomide	1 (50.0%)	1 (50.0%)	
MTX	1 (50.0%)	1 (50.0%)	
Neupogen	1 (50.0%)	1 (50.0%)	
VP16	2 (100.0%)	0 (0.0%)	
Vincristine	1 (100.0%)	0 (0.0%)	
Treatment 5			0.407
Carboplatinum	1 (100.0%)	0 (0.0%)	
Cisplatin	3 (75.0%)	1 (25.0%)	
Cyclophosphamide	3 (75.0%)	1 (25.0%)	
Laspar	1 (100.0%)	0 (0.0%)	
MTX	0 (0.0%)	1 (100.0%)	

	Normal (N = 30)	Hearing loss (N = 17)	p-value
Mesna	1 (50.0%)	1 (50.0%)	
Procarbazine	1 (100.0%)	0 (0.0%)	
VP16	2 (100.0%)	0 (0.0%)	

The results from this study indicate that the null hypothesis was accepted by majority of the objectives set out. The relationship between the type of cancer and the hearing function of this population was the only objective found to have rejected the null hypothesis.

CHAPTER FOUR

DISCUSSION

According to Whelan et al., (2011), a complication that is frequently reported from cancer treatment is hearing loss which is a result of ototoxicity. Furthermore, research supports that there is a relationship between age that medication was administered, dosage of medication, type of cancer and treatment used, as well as concurrent use of other ototoxic medications (Yancey et al., 2012; Castelán-Martínez et al., 2014; Olgun et al., 2021). This study investigated the hearing function of paediatric patients with cancer in Johannesburg, South Africa; with the specific objectives being 1) to describe the hearing function of paediatric patients with cancer; 2) to determine factors that influenced the hearing function in this population; 3) to explore the relationship between demographic factors such as age, race and gender and hearing function findings in this population; 4) to investigate the relationship between diagnostic factors such as type of cancer and duration of cancer treatment and hearing function findings in this population; and 5) to study the relationship between treatment factors such as different treatment options and hearing function findings. This chapter will present a discussion of the findings in accordance with these stated specific objectives, starting with a discussion of the demographic and medical profile of the sample.

Spector et al. (2015), indicated that the incidence of childhood cancer varies according to age, sex, race, or ethnicity, therefore, it may be assumed that the hearing function of this population might also vary according to these factors. With a sample size of 47 patient records, the demographic profile of the current sample indicates that the proportion of male (55.3%) and the female (44.7%) participants were not similar, with the percentage of males being slightly higher than that of the females. Therefore the effects gender could not be equally discussed in this study. Furthermore, as it was found in the results above, that the p-value for gender was found to be statistically non-significant, therefore the effects that gender would have on the hearing function of this population would be minimal. These findings are consistent with Liberman et al. (2016) who indicated the lack of a statistical relationship between gender and hearing function in this population.

As far as the description of the participants in the current study is concerned, current findings revealed that most of the participants were of the African Population. Therefore, the current sample can be argued to be a fair representation of the general paediatric population living with cancer in South Africa. Although the sample may be considered fair as a representation of the South African population, generalizability of the findings may be difficult to obtain for the other racial groups, which may lead to insufficient data being collected on the effects factors such as race and cancer may have on the hearing function of these other racial groups. Furthermore, it may be difficult to understand how other racial groups may react or respond to interventions, if only one racial group is represented the most. This is an important methodological design that must be taken into cognisance when analysing and interpreting the current findings.

As far as the medical profile findings of this study the most prevalent treatment duration was 0-50 days (72.3%), with only 2 participants having received treatment for longer than 100 days. Current findings found in the NICD (2021) reported that in South

Africa the treatment of childhood cancers involves a six or nine-month intensive chemotherapy phase, i.e., nearly 182 to 273 days, followed by a two- or three-year maintenance phase. With the current sample having a prevalent treatment duration of 0-50 days, it can be argued this is inconsistent with the data found on the average treatment days. With an incidence of childhood cancer of approximately 1%, about 800-1000 children are diagnosed with cancer in South Africa annually (Smith et al., 2017; NICD, 2021). Furthermore, there is a high prevalence of leukaemia, lymphoma and CNS neoplasms amongst many other childhood cancers in South Africa (Otoo et al., 2020). In this current study, as far as type of cancer was concerned, osteosarcoma was found to be the most prevalent cancer diagnosis (42.6%), followed by Nasopharyngeal Carcinoma (14.9%); with Leukaemia, Pelvic germ cell tumour, Rhabdomyosarcoma and Testicular cancer being the least prevalent cancer diagnoses in this current study. Otoo et al's (2020) study is supported by the NICD (2021), who found that in South Africa, leukaemia, lymphoma, brain and spinal cord tumours, kidney cancer (Wilms tumour) and soft tissue sarcomas are the most common cancers in children. When comparing to documented evidence, current findings are not consistent with the data found as it was expected that there would be higher number of participants with leukaemia, lymphoma or CNS neoplasms represented in this study population. This difference could just be a feature of the sample and sample size in this study.

Regarding the treatment used to treat cancer in this population, Doxorubicin, otherwise known as Adriamycin (29.8%), and Vincristine (20.5%) were the most prescribed treatment modalities in this study. According to Johnson-Arbor and Dubey (2023), Doxorubicin can be used to treat leukaemia and Hodgkin lymphoma, as well as soft tissue and bone sarcomas; whereas, Vincristine is generally used to treat leukaemia, lymphoma, as well as neuroblastoma; and is suspected to be a contributing risk factor to hearing loss in combination with platinum-based chemotherapy such as cisplatin and carboplatinum

(Awosika et al., 2023; Strebel et al., 2023). According to Zand et al. (2023) and Smith et al. (2017), the standard treatment in South Africa is platinum compounds such as cisplatin and carboplatinum, with cisplatin being the most common medication to be used. Although a few participants in this study were treated with Cisplatin or Carboplatinum, doxorubicin and vincristine were still the most prevalently used treatment options. With limited research on the effects that these two treatment protocols have on the hearing function of this population, inferences on their effects could not be compared to any past evidence.

Current findings indicated that the researcher was 95% confident that the true prevalence of hearing loss in the paediatric population with cancer would fall between 23.5% and 51.2%. The prevalence of hearing loss was 36.2% as expected. This is consistent with Castelán-Martínez et al.'s (2014) study, where it highlighted that approximately 50% of children treated with cisplatin develop some form of permanent hearing loss. Furthermore, in a study by Zand et al. (2023), it was found that up to 70% of patients suffer from cisplatin-related ototoxicity, with 28% of them having a moderate to severe form of ototoxicity. Moreover, in as far as the hearing function of paediatric patients with cancer in this study was concerned, current findings on the prevalence of hearing loss in the second session (52.9%) was found to have more than doubled than that in the first session (23.5%), which showed that there were contributing factors that influenced the hearing function of this population. This increased prevalence is supported by previous findings by Whelan et al. (2011); Dixon et al. (2018); Tillmanns et al. (2021); and Emerson et al. (2022),who found that a common morbidity factor amongst childhood cancer survivors is hearing loss, which is most commonly caused by the concurrent use of multiple ototoxic agents, which can eventually lead to ototoxicity in the cochlea.

The current findings on the type of hearing loss in the first session showed a higher rate of conductive hearing losses (75.0% in session one versus 44.4% in session two), as

compared to the second session where most of the participants with a hearing loss had a sensorineural hearing loss (25.0% in session one versus 55.6% in session two). According to Zahnert (2011), about 10-30% of children suffer from transient conductive hearing loss that are caused by otitis media with effusion or obstructions such as impacted wax in the ear canal. In the current study, it was found that about 23,5% of the participants presented with occluding wax in at least one or both of their ears, which may have acted as a form of an obstruction for sound to travel through the middle ear cavity to the cochlear in these participants, resulting in a conductive hearing loss (Diefendorf, 2014; Hunter & Standford, 2014). Furthermore, it was found that approximately 18.7% of the participants obtained a Type B tympanogram, which is indicative of abnormal middle ear function and is suggestive of a conductive hearing loss (Kemp, 2002; DeBonis & Donohue, 2020). In terms of the ARTs results about 13.3% of the participants presented with an absent acoustic reflex result, which according to Clark (n.d.), is suggestive of a middle ear disorder, a hearing loss or interruption of the neural pathway; and about 7.1% of the participants obtained a refer result for their DPOAE assessment, suggesting that a small number of participants presented with abnormal middle ear functioning, with the remainder of the participants having a possible normal middle ear function and cochlear function (Jachova & Ristovska, 2023). The increase in sensorineural hearing losses in session two is evidence that more participants possibly had damage to their cochlea due to one of the factors this study sought to investigate. The increase in sensorineural hearing losses is supported by Krug et al. (2016) and Liddle et al. (2022), who reported that cancers can cause permanent hearing loss. More specifically, Whelan et al. (2011) and Al-Ali et al. (2023), reported that irreversible, bilateral, and progressive sensorineural hearing loss is a characteristic symptom of cisplatin ototoxicity, which is the medication used to treat cancer.

Ototoxic hearing losses are characterized by a high frequency sensorineural hearing loss (Clemens et al., 2017). In session two majority of the participants presented with Type A tympanograms (87.5%), which is characteristically seen in many patients who have a sensorineural hearing loss, as this indicates normal middle ear function, which would be expected in individuals who have cochlear damage (DeBonis & Donohue, 2020). About 26.7% of the participants in session two had partially present ARTs. This result could be indicative of the presence of a hearing loss, especially at the frequencies where they are absent Clark (n.d.). According to Jachova and Ristovska (2023), a sensory hearing loss can be implied by the absence of an OAE, granted there is no middle ear pathology or acoustic obstruction. In this current study approximately 14.3% of the participants presented with a refer result for their DPOAE assessment.

In session one, most participants had a mild form of a hearing loss (17.6%), whereas in session two, most participants presented with a moderate hearing loss (17.6%). The progression of the degree of impairments is a typical attribute of an ototoxic hearing loss, as indicated by Whelan et al. (2011) and Al-Ali et al. (2023), who reported that ototoxicity is characterised by an irreversible, bilateral, and progressive sensorineural hearing loss. As for the configuration of the hearing loss in these participants, it was found that in both session one and two, participants presented with a high-frequency hearing loss. The presence of a high-frequency hearing loss is supported by Dillard et al. (2022), who recommended high-frequency audiometry be performed on populations such as the one in this current study, as ototoxic damage first develops at the basal end of the cochlea, where high frequencies are measured. Furthermore, Clemens et al. (2017), characterized this type of hearing loss as a high frequency sensorineural hearing loss. Additionally, Landier (2016) reported that when individuals are exposed to an ototoxic agent repeatedly, hearing threshold begin to shift at the higher frequencies (>4000 Hertz) and progress gradually to the lower frequencies. The

implications of a hearing loss in this population are that patients are left susceptible to a decline in areas such as speech and language development, educational attainment, social-emotional development, and their overall quality of life may also be affected (Amayiri et al., 2023; Dixon et al., 2018; ; Whelan et al., 2011; and Smith et al., 2017).

When exploring factors that influenced the hearing function in this study, current findings of the value R^2 which was 0.09, is indicative that the independent variables had minimal effect on the dependent variable, and therefore rejected the alternative hypothesis. The alternative hypothesis was that the hearing function of paediatric patients with cancer would be influenced by 1) the hearing function of paediatric patients with cancer; 2) factors that influenced the hearing function in this population; 3) demographic factors such as age, race and gender and hearing function findings in this population; 4) diagnostic factors such as type of cancer and duration of cancer treatment and hearing function findings in this population; and 5) treatment factors such as different treatment options and hearing function findings; while the null hypothesis was proven true. Additionally, it was determined in the current study that to be considered statistically significant the data would have to yield a $p<0.05$ alpha value. Therefore, in the current study it was found that factors such gender, age of diagnosis and the total treatment days had no statistically significant impact on the hearing function of the paediatric population with cancer, as these factors yielded p-values which were all greater than $p<0.05$. These findings are contrary to what Dillard et al. (2022); Olgun et al. (2021); Tillmanns et al. (2021); and Yancey et al. (2012) found, where they state that factors such as the age of the patient at the time of medication administration and the dosing regimen of the medication administered could have an influence on ototoxicity. Furthermore, in Dillard et al.'s (2022) study, it was found that children under 5-years old who were treated using cisplatin-based regimens had the highest prevalence of hearing loss, consistent with research indicating that young age is a risk factor for hearing loss.

With regards to the total treatment days, Yancey et al. (2012), reported that various doses and dosing regimens seem to have varying susceptibilities to cause ototoxicity. The effects the dosing scheduling had on the hearing function of this population were found to be minimal, but this could also be due to the small sample size which did not allow the researcher to draw a larger inference in the case of this objective. The treatment duration in days as well as race (p=0.479) were also found to be the statistically non-significant factors. With regards to gender, no statistical relationship between gender and hearing loss in the paediatric population with cancer was found in a study by Liberman et al. (2016), granted that it was reported by Yancey et al. (2012) that cumulative dose and gender are the most important clinical markers for ototoxicity. Even with these two sources of data, there still is limited evidence to indicate the effect gender might have on this population's hearing function. Additionally, there was no statistical relationship between race and hearing loss in the paediatric population with cancer, and there was no prior data to indicate that race has any effect on paediatric population with cancer.

With regards to the type of cancer and the hearing function, current findings revealed type of cancer to be the only factor that was true to the alternative hypothesis, with a p-value of 0.027. Thus, the most significant changes in hearing were found to be within this factor. Santucci et al. (2021), found that due to the proximity of the disease to the auditory system, head and neck cancer patients are more susceptible to ototoxic side effects due to the cochlea being extremely sensitive to radiation and cancer treatments, such as chemotherapy. The prevalence of hearing loss and the type of cancers which affect it the most, will be discussed further later in this chapter.

Regarding the treatment options in this study, it was found that each patient record had a combination of up to five treatment options to help treat their cancer. Doxorubicin and Vincristine were the most commonly used treatment options amongst this population in this

study, although the standard treatment in South Africa is platinum compounds such as cisplatin and carboplatin (Smith et al., 2017). Furthermore, according to Lambert et al. (2008), and Tillmanns et al. (2021), aminoglycosides, vinblastine, etoposide, loop diuretics, and vincristine are usually part of standard chemotherapy protocol of treatment due to their proven efficacy. However, a commonly reported complication of cancer treatment is hearing loss as a result of ototoxicity (Whelan et al., 2011). On the contrary, in this study it was found that the treatment options were statistically non-significant. The relationship between treatment options and hearing loss will be discussed later in this chapter.

An objective of this study was to investigate if overall age, race, and gender, would have a significant effect on the hearing function of this population. Findings on the relationship between these demographic factors and the hearing function findings in this study showed that there were statistically non-significant relationships, indicating that the effects of the age, race and gender of this population had minimal to no significant effect on the hearing function. With regards to age, these results are not consistent to previous findings. A study conducted by Konrad-Martin et al. (2005), reported that individuals may also be susceptible to ototoxicity based on their age. Furthermore, this is supported by Dillard et al. (2022), who highlighted that age may have a significant effect on the hearing function of patients. As discussed above Dillard et al. (2022) had found that children younger than 5-years old who were treated with carboplatin, had the lowest prevalence of hearing loss; comparatively, it was further found that, children under 5-years old who treated using cisplatin-based regimens had the highest prevalence of hearing loss, consistent with research indicating that young age is a risk factor for hearing loss. In this current study, it was found that the minimum age to be susceptible to hearing loss in this study was five years old, with the maximum age being 17 years old. In a study by Olgun et al. (2021), it was found that children under 5 years of age are 15-20 times at a higher risk of developing ototoxicity. With

regards to gender, the findings in this study support Liberman et al. (2016) who indicated the lack of a statistically significant relationship between gender and hearing function in this population. However, it was found that there was a higher incidence of hearing loss with males as compared to females. In terms of race, there was limited data on the effects race has on the hearing function of this population, and as indicated by Spector et al. (2015), the incidence of childhood cancer varies in race or ethnicity; therefore, it can be deduced that if cancer can vary, so can the hearing function of this population.

The findings of this current study and previous studies, more specifically the age of the population sample, are incongruent and this could be due to the sample size of this study, as the small sample size could have had a negative effect on drawing up comprehensive conclusions on this study. This could contribute significantly to the evidence base of the study as it can encourage future research to be conducted to establish well-rounded inferences on these factors using larger sample sizes. The inferences that could be drawn from future research could have important implications for the paediatric population with cancer as inequalities and disparities within the paediatric population with cancer could be identified, and therefore assist in the establishment of policies in areas of need that require attention, such as determining age-specific, gender-specific or race-specific treatment protocols or interventions, and therefore providing flexible age-appropriate assessments to the community, creating effective interventions and assessments which are both age appropriate and appeal to both genders, especially in a country such as South Africa that contains a diverse, multiracial population, with a healthcare system that is plagued by immense inequities when it comes to accessing it, which is largely divided by racial lines (Stuart et al., 2022).

Additionally, this study may have warranted further research to be done to understand the reasons for any discrepancies, as discrepancies can influence how the participants

responded to the medication and therefore how their hearing function could be affected. Incorporating demographic factors such as age, race and gender in a study such as this, enables the researcher and other researchers who choose to expand on the research study's main aim and objectives to understand the relationship between these variables and therefore they are able to emphasize how these relationships might differ across the different demographic groups, if any inferences can be drawn, however in the case of this study, none could be drawn due to the small sample size.

Current results on the relationship between diagnostic factors such as type of cancer and duration of cancer treatment and hearing function findings in this population revealed that the relationship between the type of cancer and the hearing function of this population were statistically significant, and these findings are not consistent with specific research that looks into the type of cancer being a direct cause or reason to the deterioration of hearing function in this specific population. Although, Santucci et al. (2021) reported that due to the proximity of the disease to the auditory system, head and neck cancer patients are more susceptible to ototoxic side effects from surgery and radiation, and we can assume chemotherapy, as the cochlea is extremely sensitive to radiation and ototoxic medication. Therefore, the findings in their study imply that the root cause of hearing impairment in the population of paediatric patients with head and neck cancer is medication, treatment options or the route that they receive their treatment. Silverman et al. (2021) found that the most common types of head and neck cancers globally include Lymphoma's, Nasopharyngeal Carcinoma, Thyroid Carcinoma and Rhabdomyosarcoma. Furthermore, medulloblastoma, retinoblastoma and craniopharyngioma have also been reported as the most common childhood cancers reported globally (Brooks & Knight, 2018; WHO Global Initiative for Childhood Cancer, 2021; Amayiri et al., 2023). In South Africa, lymphomas and brain tumours are found to be one of the highest prevalent childhood cancers amongst many other

cancers (Otoo et al., 2020; NICD, 2021). Medulloblastoma and rhabdomyosarcoma were found to be one of the least common cancers in this study; whereas nasopharyngeal carcinoma, brain cancer and Hodgkin's lymphoma were amongst the top five most common cancers found among this study's population sample. According to the results of this current study, the type of cancer that had the most hearing losses present was nasopharyngeal carcinoma with 100% of the patients who had this type of cancer acquiring a hearing loss. This was followed by rhabdomyosarcoma where 100% of the participants also acquired a hearing loss. Cancers such as medulloblastoma, brain cancer, and Hodgkin's lymphoma had a low occurrence of impaired hearing function. However, in a study by Zand et al. (2023), it was found that within two years after receiving cisplatin chemotherapy, that nearly 50% of paediatric patients who had medulloblastoma experienced some form of hearing loss.

According to Bass et al. (2016) and Robertson et al. (2019), head and neck cancer patients are likely to acquire a hearing loss six months to two years post-treatment. Furthermore, these patients are at an increased risk of developing an asymmetrical hearing loss or late onset hearing loss, which can be exacerbated if they received a combination of radiation and chemotherapy as their treatment protocol, which is the common treatment protocol used for head and neck cancer patients (Bass et al., 2016; Robertson et al., 2019). Due to the average diagnosis time of hearing loss being at least two years, coupled with the fact that this study assessed patient records over a five year period, it is possible that the patients who were diagnosed with medulloblastoma, brain cancer, and Hodgkin's lymphoma and had normal hearing at their initial sessions, could have presented with late onset hearing loss, if they were to be assessed at a later stage post-treatment. Nonetheless, the findings in this current study are supported by Santucci et al.'s (2021) study where it was found that head and neck paediatric cancer patients are more susceptible to hearing losses as compared to other types of cancers that affect different parts of the body or immune system. For example,

in this current study osteosarcoma was the most prevalent type of cancer that was diagnosed in this population, with a total number of 20 patients being diagnosed with a form of osteosarcoma, which is a type of bone cancer. The results in this study indicated that 75% of these patients presented with normal hearing as compared to the 25% who presented with a form of hearing loss. Therefore, it can be inferred that the location of the cancer, i.e., the head and neck, has an influence on whether a participant will present with a hearing loss or not, which can be assumed is a result of the route the treatment is administered. These finding are significant as they emphasise the importance of having screening programmes in place to monitor patients who have a diagnosis of cancer, especially that of the head and neck region

Additionally, current results on the relationship between the duration of cancer treatment and hearing function findings in this population revealed that there was no statistically significant relationship between the two variables. According to Yancey et al. (2012) various doses and dosing regimens seem to have varying susceptibilities that can cause ototoxicity. Implying that with differing treatment durations amongst participants, came differing susceptibilities to hearing impairments, therefore, inferences on the effect of the duration of treatment had on the hearing function of this population could not be assumed. It can therefore be concluded that the duration of the cancer treatment likely had no effect on the hearing function of this population.

In the current study, it was found that most of the participants underwent treatment with at least five types of medication in their treatment protocol. When the relationship between treatment factors such as different treatment options and hearing function findings was investigated, current findings indicated no statistically significant associations between treatment one through five. As discussed above, Doxorubicin and Vincristine were the two most preferred treatment options in this population, despite the standard treatment protocol in South Africa being platinum compounds such as cisplatin and carboplatin (Smith et al.,

2017). Doxorubicin is generally used to treat cancers such as soft tissue and bone sarcomas, as well as leukaemia and Hodgkin lymphoma to name a few (Johnson-Arbor & Dubey, 2023). There is limited literature that supports the ototoxicity of doxorubicin, and the lack of research on the ototoxicity of doxorubicin can be supported by the outcome of the incidence of hearing loss in this current study amongst the participants. Additionally, vincristine is also used to treat leukaemia, lymphoma, as well as neuroblastoma and Wilms tumour (Awosika et al., 2023); however, according to Strebel et al. (2023), vincristine is suspected to be a contributing risk factor to hearing loss when it is used in combination with platinum-based chemotherapy such as cisplatin and carboplatinum, but the incidence of hearing loss caused by vincristine, as well as carboplatinum, is low in this current study therefore it can be inferred that vincristine had no effect on the hearing function of this population. The results regarding doxorubicin and vincristine as treatment options, indicated a low incidence of hearing loss in the group of patients who were treated with these medications.

Conversely, although there was no significant statistical association, the results indicated that cisplatin, 5-Fluorouracil and MTX had the highest incidence of hearing loss in this population. There is limited evidence or research that speaks to the possibility of medications such as 5-Fluorouracil and MTX being ototoxic. However, as a known ototoxic agent, cisplatin is expected to have a high incidence rate of hearing loss (Al-Ali et al., 2023), and research supports the findings in this study that patients treated with cisplatin are at an increased risk of acquiring a hearing loss due to ototoxicity; furthermore, it can be assumed that patients who receive medication such as vincristine and doxorubicin as their main treatment protocol have a decreased risk of acquiring a hearing loss. However, with the findings from Strebel et al. (2023), where vincristine was found to be a possible contributing risk factor to hearing loss in combination with cisplatin and carboplatinum, there is a slight likelihood that if a patient was treated with both treatments at the same time, they could have

contributed to the small group of patients who acquired a hearing loss. Furthermore, Whelan et al. (2011), reported that carboplatinum is known to be the less toxic than cisplatin, however when used in combination, the consequences can be catastrophic in terms of hearing organ damage. Therefore, future research would need to be conducted to explore the severity of hearing loss in this population, and future interventions and implications would have to be raised to monitor individuals who are on a treatment protocol which combines treatments such as vincristine, cisplatin and carboplatinum. As inferred earlier, due to the lack of research on the ototoxicity of doxorubicin, the likelihood of hearing loss being caused by this treatment is low. But there is proven literature to support the effects cisplatin has on the hearing function of cancer patients (Al-Ali et al., 2023). This is also supported by the high incidence of hearing loss in patients treated with cisplatin in this current study. Therefore, the need for future research to expand on the findings of this current study, with both a larger sample size and a focus on different types of treatments is needed to aid in the establishments of policies and have programmes in place to monitor patients of this type of population.

The findings of this study revealed that the null hypothesis was proved true for majority of the objectives set out, except for the relationship between the type of cancer and hearing function in this population. The latter objective disproved the null hypothesis which stated that the objectives that were set out would not have any influence on the hearing function of the paediatric population with cancer.

CHAPTER FIVE

CONCLUSION, LIMITATIONS AND RECOMMENDATIONS

5.1. Summary of Main Findings

The prevalence of childhood cancer and its morbidity in this country is highlighted in this study. Furthermore, the hearing function of the paediatric population receiving cancer treatment in South Africa is presented and discussed in detail in this study.

Current findings revealed occurrence of hearing loss in this sample, with the prevalence rate of 23.5% at session one, which increased to 52.9% at session two. The most prevalent type, degree, laterality, configuration of the hearing loss in session one was found to be a conductive, mild, unilateral, asymmetrical high frequency hearing loss. Whereas the most prevalent type, degree, laterality, configuration of the hearing loss in session two was found to be a sensorineural, bilateral, mild to profound bilateral symmetrical high frequency hearing loss. The hearing function was found to be influenced by demographic and diagnostic factors. When establishing if a relationship existed between age of diagnosis, gender, race, type of cancer, treatment duration, and type of treatment and hearing function, only the type of cancer was found to have a statistically significant association. Furthermore, investigations on the relationship between diagnostic factors such as type of cancer, duration of cancer treatment, different treatment options and hearing function findings revealed that approximately 88.9% of the participants who presented with hearing losses were indicative ototoxic hearing losses in this population.

5.2. Implications of the study

Current findings, within the identified limitations, raise important implications. Current findings could possibly help guide future researchers, audiologists, pharmacists or

oncologists in developing treatment protocols, policies and interventions that could possibly help minimize the effects and risks of cancer treatments on the hearing function of this population without having to comprise the effectiveness of their treatment. Additionally, having these protocols in place may help researchers assess the impact different treatment protocols might have on the hearing function of this population and therefore determine the association between the treatments with the highest risk of causing a hearing loss, more specifically ototoxicity. Furthermore, this study may lead to the establishment of improved screening protocols and practices for the hearing function of this population, which will in turn ensure early detection or diagnosis and intervention. Counselling families and the patients about the potential risks of treatment and helping them understand and participate in preventive audiology initiatives. Furthermore, this study could help provide further input to researchers into creating preventive measures or interventions to prevent or delay hearing loss in the paediatric population with cancer.

5.3. Limitations of the Current Study

The aim of this current study was to investigate the hearing function of the paediatric population with cancer. The study was a retrospective record review study, which meant that the researcher was therefore limited to the information that was already available, leaving the study open to many limitations. Therefore, findings of this study need to be viewed in the context of the following identified limitations:

- The five-year range of longitudinal follow up limited the sample size of the study as some of the patient records had to be excluded due to not meeting the inclusion criteria. It would have been beneficial if the researcher extended the range to 10 years to allow for a larger and diverse sample size. Furthermore, extending the research to include data from the private healthcare sector, to allow for the expansion of a more diverse population output. These

limitations restrict generalisation of the results. Furthermore, a limitation found at CMJAH and CHBAH was that in the year 2020, when the COVID-19 pandemic hit worldwide, the patient load decreased substantially, which resulted in there being a decreased number of files reviewed from this year. Additionally, in the year 2021, a fire broke out at CMJAH which resulted in many of the patient's either defaulting or being referred to their catchment areas, resulting in a decreased number of available files to review from that year as well. These factors also contributed to the small sample size obtained.

- Initially the researcher wanted to investigate the relationship between the dosage of the treatment and the hearing function of this population, but due to each medication using different metric systems, this objective had to be amended, as converting the medications to be on the same scale would have been beyond the scope of the current study. For the sake of the reliability and validity of this study the researcher decided to remove this objective.
- Although many files were found at CHBAH, they did not keep files on record for more than five years, therefore some patient records who had been discharged from audiology for more than three to five years, might have not been available on hand as some files did not make it to archives, therefore limiting the records reviewed. This had an influence on the analysis of the longitudinal influence of cancer and its treatments in this population.

5.4. Conclusions

Less than half of the records reviewed in this study indicated an impairment in the hearing function of the paediatric population with cancer. The participants who were found to have a hearing impairment, the impairment was concluded to be ototoxic in nature, therefore these participants incurred damage to their inner ear structures due to the factors such as the type of

cancer they were diagnosed with. As evident from all the audiological assessments administered, there was an evident change in the hearing function of participants from session one to two, irrespective of age, gender or race as these objectives were found to have a statistically non-significant relationship with hearing function in the current sample. The researcher recommends that audiological monitoring as well as screening protocols be implemented in the oncology and audiology units of hospitals or clinics, especially for patients who have recently been diagnosed with a head or neck cancer as they are most at risk of acquiring a hearing impairment. Having screening and monitory systems in place will help identify changes in hearing function early, therefore preventing the deterioration in hearing through medical intervention such as motivating for a change in treatment or providing otoprotective measures to patients at risk. It is imperative that guidelines on the referral procedures and screening protocols be created and implemented in these units.

5.5. Recommendations for Future Studies

The current study findings raise implications for future studies, including studies that extend the timeline in which they will retrospectively be assessing the patient records. Additionally, the researcher recommends extending the age limit of the study protocol to include participants from at least the age of one, and with that include assessment results such as ABR and ASSR results. Furthermore, with an extended timeline and age limit, it will allow for a larger sample size to be drawn, therefore allowing inferences to be drawn for factors that were found to be statistically non-significant in the current sample. A similar study should be conducted prospectively, where the protocol and measures used can be controlled. It is also advised that future studies investigating the relationship between the dosages of the treatment and the hearing function find a reliable way to convert the metrics of the medication so that they may be statistically analysed correctly to obtain reliable results. Future studies should assess the relationship between the hearing function of the paediatric

population in South Africa and the effects of radiation treatment. Lastly, future research should assess the impact hearing loss has had on the quality of life of the surviving population of paediatric population with cancer, such as their communication, social interaction, educational outcomes, mental and emotional acuity.

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APPENDICES

Appendix A: Ethical Approval letter

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

R49 Ms T Chauke

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
CLEARANCE CERTIFICATE NO. M221128

NAME: (Principal Investigator)	Ms T Chauke
DEPARTMENT:	School of Community Development Department of Speech Pathology and Audiology University
PROJECT TITLE:	*Hearing function of paediatric patients with cancer in Johannesburg, South Africa: relationships and influences explored*
DATE CONSIDERED:	2022/11/25
DECISION:	Appproved unconditionally
CONDITIONS:	
NOTE:	If contact information regarding student study participants is required, please contact the Registrar's office - <Nicoleen.Potgieter@wits.ac.za>
SUPERVISOR:	Professor K Khoza-Shangase
APPROVED BY:	Dr CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	2023/04/14

This Clearance Certificate is valid for 5 years from the date of approval. An extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office secretariat on the 3rd floor, Phillip Tobias Building, Parktown, University of the Witwatersrand, Johannesburg.

I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated from the research protocol as approved, I/we undertake to submit details to the Committee. **I agree to submit a yearly progress report**. When a funder requires annual re-certification, the application date will be one year after the date when the study was initially reviewed. In this case, the study was initially reviewed in **November** and therefore reports and re-certification will be due in the month of **November** each year. Unreported changes to the study may invalidate the clearance given by the HREC (Medical).

Signature of Principal Investigator — Date: 13/04/2023

UNIVERSITY OF THE WITWATERSRAND JOHANNESBURG	HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

Office of the Deputy Vice-Chancellor (Research and Innovation)

TO: Ms T Chauke
School of Community Development
Department of Speech Pathology and Audiology
University

E-mail: tlangi.n.chauke@gmail.com

CC: Supervisor: Professor K Khoza-Shangase
<Katijah.Khoza-Shangase@wits.ac.za>
and <HREC-Medical Research Office@wits.ac.za>

FROM: Mr Iain Burns
Human Research Ethics Committee (Medical)
Tel: 011 717 1252

E-mail: Iain.Burns@wits.ac.za

DATE: 2023/04/14

REF: R14/49

PROTOCOL NO: **M221128** (This is your ethics application reference number. Please quote it in all enquiries, oral or written, relating to this study.)

PROJECT TITLE: *Hearing function of paediatric patients with cancer in Johannesburg, South Africa: relationships and influences explored*

Please find attached the Clearance Certificate for the above project. I hope it goes well and that an article in a recognized publication comes out of it. This will reflect well on your professional standing and contribute to Government funding of the University.

MSWorks2000/Iain0007/Clearscan.wps

Appendix B: Ethics Approval Amendment of Protocol

Amendments for PROTOCOL NO: M221128 (Miss Tlangelani Chauke) [Ref: R14149]

Title of Project:

Hearing Function of Paediatric Patients with Cancer in Johannesburg, South Africa: Relationships and Influences Explored.

Principal Investigator: Tlangelani Nyeleti Chauke

Supervisor: Professor Katijah Khoza-Shangase

Conditions:

- Amending the start date in section 6.4 of the ethics application form.
  - ✓ Completed
- Training:
  - Providing research ethics training certificate for supervisor.
    - ✓ Provided
- Permission(s):
  - Providing written permission to conduct the study from the Head of Paediatric
    - ✓ Provided
  - Oncology at CMJAH and CHBAH and MAC CHBAH and CEO CMJAH.
    - ✓ Provided
- Other:
  - Providing approval letter from the postgraduate forum.
    - ✓ Provided
  - Addressing POPIA in the SOP.
    - ✓ Completed



Appendix C: Ethical Approval Declaration form

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

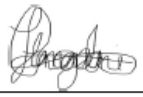
HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

DECLARATION:

Adherence to HREC (Medical) Ethics Application Terms and Conditions

I, the undersigned, hereby declare that I have not collected data/ done secondary data analysis or any other form of research, prior to obtaining clearance certificate from the HREC (Medical) for study no: M221128_____.

I have read and understood the terms and conditions on section 9 of HREC (Medical) application form. I confirm that it is my responsibility to ensure that I have received final HREC (Medical) Clearance before commencing any research.

Tlangelani Chauke 

Name, Surname and Signature

Student/Staff no if applicable: 1374860_____

Date: 28/02/2023

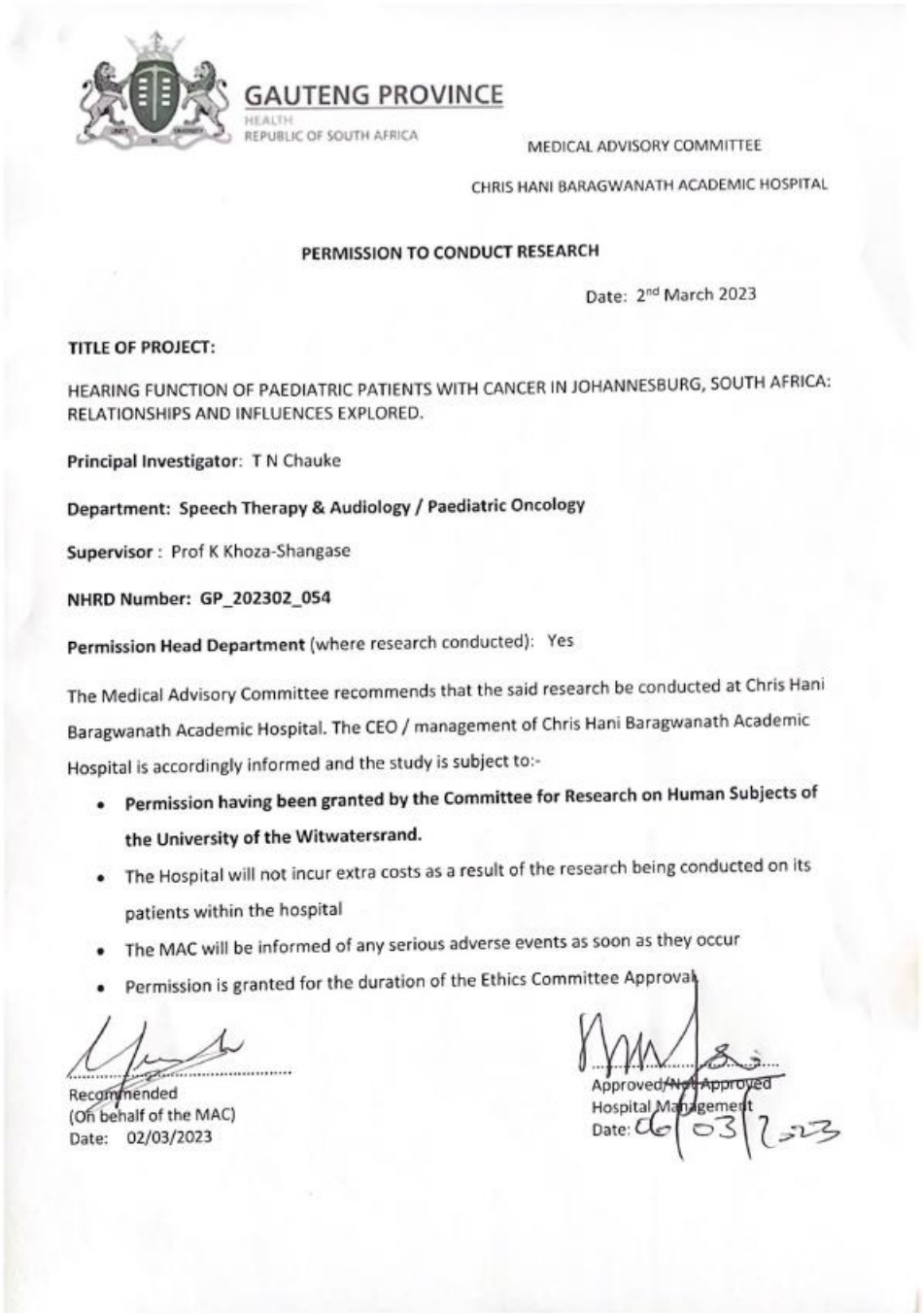
Prof Katijah Khoza-Shangase 

Name, Surname and Signature

Supervisor (if applicable)

Date: 01/03/2023

Appendix D: Chris Hani Baragwanath Academic Hospital Medical Advisory Committee Approval



GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

MEDICAL ADVISORY COMMITTEE

CHRIS HANI BARAGWANATH ACADEMIC HOSPITAL

PERMISSION TO CONDUCT RESEARCH

Date: 2nd March 2023

TITLE OF PROJECT:

HEARING FUNCTION OF PAEDIATRIC PATIENTS WITH CANCER IN JOHANNESBURG, SOUTH AFRICA: RELATIONSHIPS AND INFLUENCES EXPLORED.

Principal Investigator: T N Chauke

Department: Speech Therapy & Audiology / Paediatric Oncology

Supervisor : Prof K Khoza-Shangase

NHRD Number: GP_202302_054

Permission Head Department (where research conducted): Yes

The Medical Advisory Committee recommends that the said research be conducted at Chris Hani Baragwanath Academic Hospital. The CEO / management of Chris Hani Baragwanath Academic Hospital is accordingly informed and the study is subject to:-

- **Permission having been granted by the Committee for Research on Human Subjects of the University of the Witwatersrand.**
- The Hospital will not incur extra costs as a result of the research being conducted on its patients within the hospital
- The MAC will be informed of any serious adverse events as soon as they occur
- Permission is granted for the duration of the Ethics Committee Approval

Recommended
(On behalf of the MAC)
Date: 02/03/2023

Approved/~~Not Approved~~
Hospital Management
Date: 06/03/2023

Appendix E: Chris Hani Baragwanath Academic Hospital Head of Oncology Department Approval

Chris Hani Baragwanath Academic Hospital
Department of Paediatrics
PO Bertsham 2013
Tel: (011) 933-8416/8400
Fax: (011) 938-9074

health and social development
Department: Health and Social Development
GAUTENG PROVINCE

27 October 2022

Dear Sir/ Madam,

Human Research Ethics Committee,

University of the Witwatersrand

Re: **Ms Tlangelani Chauke**

Permission is granted for Ms Chauke to conduct the following study at the Paediatric Haematology Oncology Unit of Chris Hani Baragwanath Academic Hospital:

"Hearing function of paediatric patients with cancer in Johannesburg, South Africa: Relationships and influences explored".

The records of paediatric haematology oncology patients with childhood idiopathic thrombocytopenia who were managed at this facility will be reviewed for purposes of conducting this study, and confidentiality will be maintained as outlined in the study protocol.

Please contact me should you require further information.

With kind regards,

Gita Naidu

Gita Naidu
MBChB, FC (Paediatrics), MMed (Paediatrics), PhD
Professor and Head: Paediatric Oncology
Chris Hani Baragwanath Academic Hospital
Academic head: Paediatric Oncology
University of the Witwatersrand
Chair: South African Children's Cancer Study group

Appendix F: Chris Hani Baragwanath Academic Hospital Head of Audiology Department Approval

GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

Chris Hani Baragwanath Academic Hospital

Department of Speech Therapy & Audiology

PO Bertsham

2013

8/12/2022

Dear Sir/ Madam,

Human Research Ethics Committee,

University of the Witwatersrand

Re: Ms Tlangelani Chauke

Permission is granted for Ms Chauke to conduct the following study at the Speech Therapy & Audiology Department at Chris Hani Baragwanath Academic Hospital:

"Hearing function of paediatric patients with cancer in Johannesburg, South Africa: Relationships and influences explored".

The records of patients referred for hearing tests from the Paediatric Oncology unit will be reviewed for the purposes of conducting this study, confidentiality must be maintained as outlined in the study protocol. Note that audiologists will only be able to access records based on their availability on any day. Patient names must be submitted in advance to ensure a smooth process.

Please contact me should you require further information.

With kind regards,

Dr Sadna Balton

(Assistant Director Speech Therapy & Audiology)

Appendix G: Charlotte Maxeke Johannesburg Academic Hospital CEO Approval

GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

CHARLOTTE MAXEKE JOHANNESBURG
ACADEMIC HOSPITAL
OFFICE OF THE CLINICAL
DIRECTOR

Enquiries: Ms N. Mzila
Email: Nolwazi.Mzila@gauteng.gov.za
Tel: 011 488 3365
Ref: 1/7/2
Date: 18 April 2023

GP_202302_054

Dear Miss Tlangelani Chauke

RE: FINAL APPROVAL OF STUDY

TITLE: HEARING FUNCTION OF PAEDIATRIC PATIENTS WITH CANCER IN JOHANNESBURG, SOUTH AFRICA: RELATIONSHIPS AND INFLUENCES EXPLORED.

Permission is granted for you to conduct the above-mentioned study as described in your request provided:

1. Charlotte Maxeke Johannesburg Academic Hospital will not in any way incur or inherit costs as a result of the said study.
2. Your study shall not disrupt services at the study sites.
3. Strict confidentiality shall always be observed.
4. Informed consent shall be solicited from patients participating in your study.

Please liaise with the HOD and Unit Manager or Sister in charge to agree on the dates and time that would suit all parties.

Kindly forward this office with the results of your study on completion of the research.

Supported / ~~Not Supported~~

Signed by:Jayshree Punwasi
Signed at:2023-04-24 15:19:57 +02:00
Reason:Witnessing Jayshree Punwasi

Dr J. Punwasi
Clinical Director

Approved / ~~Not Approved~~

Signed by:Gladys Magugudi Bogoshi
Signed at:2023-04-25 11:53:41 +02:00
Reason:Witnessing Gladys Magugudi Bo

Ms G. Bogoshi
Chief Executive Officer: CMJAH

Appendix H: Charlotte Maxeke Johannesburg Academic Hospital Head of Oncology Department Approval

GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

WITS
UNIVERSITY

PAEDIATRIC HAEMATOLOGY/ONCOLOGY
CHARLOTTE MAXEKE JOHANNESBURG ACADEMIC HOSPITAL
WARD 294, YELLOW BLOCK, 9TH FLOOR

Tel: +27 11 488 3294/4619/3290 Address: Private Bag X 39, Johannesburg, 2000 Email: jennifer.geel@wits.ac.za

22 December 2022

Professor Clement Penny
Chair, Human Research Ethics Committee
University of the Witwatersrand

Dear Prof Penny

Re: Hearing function of paediatric patients with cancer in Johannesburg, South Africa: Relationships and influences explored.

Permission has been granted to Ms. Tlangelani Chauke to conduct the above-mentioned study at the Paediatric Oncology Unit of Charlotte Maxeke Johannesburg Academic Hospital. The proposed study will review the records of paediatric oncology patients retrospectively. All the activities and research administration will be done by the researcher, Ms. Chauke, and confidentiality will be maintained as outlined in the study protocol.

Please contact me should you require further information.

Yours sincerely,

Prof Jennifer Geel
HOU, Paediatric Haematology and Oncology
Charlotte Maxeke Johannesburg Academic Hospital

Appendix I: Charlotte Maxeke Johannesburg Academic Hospital Head of Audiology Department Approval

GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

CHARLOTTE MAXEKE JOHANNESBURG ACADEMIC HOPITAL

Enquiries: Ms. T. Radebe
Telephone: (011) 488 4228
Email: Thandeka.Radebe@gauteng.gov.za
Acting Assistant Director
CMJAH
14th October 2022

To: Whom It May Concern

Dear Sir/Madam

Re: Research proposal for Ms. Tlangelani Chauke

Topic: Hearing function of paediatric patients with cancer in Johannesburg, South Africa: Relationships and influences explored.

The above study will require retrospective medical records review within the Audiology department at CMJAH hospital. This proposed study will potentially contribute to the knowledge and practice in early hearing detection and intervention in childhood cancer.

The research proposed and activities thereof are supported. All research administration including location of the records will be done by the researcher. Ms. Tlangelani Chauke should ensure that service delivery is not compromised during the research process.

Regards

Ms. T. Radebe
Acting AD STA&A

Appendix J: Data Capture Form Adapted from (Khoza, 2007)

Demographic Information

Hospital:_____

Participant No.:_____ Age at diagnosis: _____ Gender: _____

Race: _____

Medical History:

Type of cancer participant was diagnosed with	

Participant's Health at	
Appointment 1	
Appointment 2	
Appointment 3	

Treatment protocol for diagnosed cancer:

Name of treatment	**Dosage**	**Duration of treatment (weeks/months/years)**

Administration of aminoglycoside antibiotic (gentamicin, tobramycin, and/or amikacin) at any time during treatment or other treatment administered other than chemotherapy:

Name of treatment	**Dosage**	**Duration of treatment (weeks/months/years)**

Did the participant suffer from any medical problems associated with hearing loss?

Medical Problem	**Treatment Given**	**When**
Ear Discharge		
Earache		
Trauma to the ear/s		

Did the participant ever receive treatment for any of the following?

Disease	**Was on treatment**	**Type of treatment**	**Length of time**
TB			
HIV			
Diabetes (Type: _____)			
Liver disease			
Renal disease			
Heart condition (Type: _____)			
Other (Specify: _____)			

Tinnitus:

Did the participant report ringing/buzzing/other sounds in their ears? [Yes(Y)=1; No(N)=2;

Not applicable(N/A) =0)

Ear	**Appointment 1**	**Appointment 2**	**Appointment 3**
Right			
Left			
Both			

Vertigo:

Did the participant experience dizziness/spinning? (Y=1; N=2; N/A=0)

Appointment 1	**Appointment 2**	**Appointment 3**

If yes, describe/explain:

_____

Hearing Status:

Does the participant have a family history of hearing loss?

Yes	
No	
Not applicable/Not noted	

If yes, explain:_____

How was the participant's hearing before their diagnosis with cancer?

Good	
Fair	
Bad/Poor	
Not applicable/Not noted	

Since the participant's diagnosis, was a change in their hearing noted?

	Appointment 1	**Appointment 2**	**Appointment 3**
Yes			
No			
Not applicable/Not noted			

Explain how their hearing changed:

_____

_____

If there was a change in the participant's hearing after treatment, what management was implemented? (Y=1; N=2; N/A=0)

Management	**(Y=1; N=2; N/A=0)**
Hearing Aids	
Cochlear Implant	
Aural Rehabilitation	
Referred elsewhere	
Other	

If referred elsewhere or other was selected, please explain:

_____

_____

Additional Comments:

_____

_____

_____

_____

Appendix K: Hearing Function Adapted from (Khoza, 2007)

Hospital:_____

Participant No.:_____

Otoscopy:

Otoscopy	Appointment 1	Appointment 2	Appointment 3
Right			
Left			

Acoustic Immittance:

Ear	Type			Canal Volume			Compliance			Pressure			Gradient		
Session	**1**	**2**	**3**	**1**	**2**	**3**	**1**	**2**	**3**	**1**	**2**	**3**	**1**	**2**	**3**
Right															
Left															

Audiometry-AC:

Hertz	250Hz			500Hz			1kHz			2kHz			3kHz			4kHz			6kHz			8kHz		
Session																								
Right																								
Left																								

Audiometry- BC:

Hertz	250Hz			500Hz			1kHz			2kHz			3kHz			4kHz			6kHz			8kHz		
Session																								
Right																								
Left																								

Otoacoustic Emissions Results (DPOAE):

Hertz	750Hz			1kHz			2kHz			3kHz			4kHz			6kHz			8kHz		
Session																					
Right																					
Left																					

Appendix L: Ethics Course Certificate



Certificate

October 20, 2022

This is to certify that Ms. Tlangelani Chauke has successfully completed the Macquarie University Human Research Ethics Online Training Module for the Social Sciences and Humanities.

Macquarie University